2017
2018

Memoria

Instituto de Investigaciones Biomédicas Alberto Sols

CSIC
Consejo Superior de Investigaciones Científicas

iibm

UAM

2017
2018

INFORMACIÓN GENERAL

DATOS BIBLIOMÉTRICOS

	2017	2018
TOTAL ARTICULOS	120	128
TOTAL REVISTAS	87	94

MEDIA DE PUBLICACIONES POR INVESTIGADOR

	2017	2018
ARTICULOS POR INVESTIGADOR	1,29	1,23

Citaciones en 2019 de las publicaciones 2017-18

Fuente: Web of Science

Número de citas en 2019:	2.169
Sin citas propias:	2.104
Artículos en que se citan:	2.048

REVISTAS MÁS UTILIZADAS

2017	2018
Scientific Reports (9)	Frontiers in Immunology (4)
Redox Biology (8)	Methods in molecular biology (4)
PLoS ONE (5)	PLoS ONE (4)
Stem Cells (3)	Thyroid (3)
	Stem Cell Research (3)
	Scientific Reports (3)
	Redox Biology (3)
	Nature Communications (3)
	Biochimica et Biophysica Acta (3)

2017
2018
CONGRESOS

1. **MCT8 Symposium 2017, Current Knowledge, Future Research on Treatment**
"Preliminary data from intranasal delivery of thyroid hormone to wild-type and Mct8 deficient mice".

Soledad Bárez-López; María Jesús Obregon; William H Frey 2nd; Samuel Refetoff; Ana Guadaño-Ferraz; Mari Carmen Grijota-Martínez.

Estados Unidos
4 de enero de 2017

2. **MCT8 Symposium 2017, Current Knowledge, Future Research on Treatment**
"The basal ganglia: a new possible therapeutic target in MCT8 deficiency".

Andrea Montero-Atalaya; Ángel García-Aldea; Juan Bernal; Estrella Rausell; Ana Guadaño-Ferraz.

Estados Unidos
4 de enero de 2017

3. **First Spanish Molecular Imaging Network (SMIN) Meeting**
"Neurological alterations in the brain of Kidins220 transgenic models".

Ana del Puerto; Eva Porlan; Beatriz Martí-Prado; Fabrizia Cesca; Giampietro Schiavo; Isabel Fariñas; Teresa Iglesias.

España
30 de enero de 2017

4. **First Spanish Molecular Imaging Network (SMIN) Meeting**
"PKD is regulated in excitotoxic conditions".

Lucía García-Guerra; Julia Pose-Utrilla; Noelia S.De León-Reyes; Abraham Martín; Ana Del Puerto; Andrea Gamir-Morralla; Christofer Ireson; Teresa Iglesias.

España
30 de enero de 2017

5. **Seminarios Centro Nacional de Biotecnología**
"Aneurysms: Novel mechanisms and therapies.".

Miguel R. Campanero.

España
1 de febrero de 2017

6. **40 Congreso SEI Mesa redonda Extracellular vesicles in immunity**
"Intracellular signals involved in the polarized traffic of multivesicular bodies and exosome secretion in T lymphocyes.".

Manuel Izquierdo.

Estados Unidos
2 de febrero de 2017

7. **61th Annual Biophysical Society Meeting**
"Trabectedin Re-Educates Resting Peritoneal Macrophages into M1 Subtype".

Diego A. Peraza; Marina Mojena; Alicia de la Cruz; Teresa Gonzalez; Lisardo Bosca; Carlos M. Galmarini; Carmen Valenzuela.

Estados Unidos
10 de febrero de 2017

8. **Association for research in otolaryngology**
"IGF-1 and APAF-1 LPT99 inhibitor promote survival of HEI-OC1 auditory cells".

Blanca Cervantes; Lourdes Rodríguez-de la Rosa; Marta Torrecilla-Parra,; Isabel Sánchez-Pérez; Carmen Herrero; Isabel Varela Nieto.

Estados Unidos
11 de febrero de 2017

9. **In the footsteps of Alberto Sols: a homage on the centennial of his birth**
"From yeast hexokinases to aminosugars metabolism. A long and winding road".

Gancedo C.

España
20 de febrero de 2017

10. **Seminarios Centro de Biología Molecular**
"Novel mediators and targets of therapy in aneurysm: NOS2 and ADAMTS1".

Miguel R Campanero.

España
21 de febrero de 2017

11. **Vitamina D y cáncer**
"Vitamina D y cáncer".

Muñoz A.

España
24 de febrero de 2017

12. **Receptores Nucleares**
"Receptores Nucleares".

Muñoz A.

España
1 de marzo de 2017

13. **Celebrate Brain Awareness Week: ¿Cómo estudian los científicos las enfermedades cerebrales?**
"Desarrollo de herramientas de diagnóstico en isquemia cerebral".

Gema Esteban.

España
16 de marzo de 2017

14. **COST action CA15203 MITOEAGLE, 2017**
"Adipocyte mitochondrial dysfunction in aging and diabetes. A redox proteomics approach".

Belén Peral.

España
22 de marzo de 2017

15. **X REUNION ANUAL CIBERER**
"La ablación del transportador de aminoácidos LAT2 (SLC7A8) causa hipoacusia asociada al envejecimiento en ratón".

Murillo-Cuesta S; Espino Guarch M; Font-Llitjós M; Celaya AM; Vilches C; Bodoy S; Sahún I; González L; Prat E; Dierssen M; Palacín M; Nunes V; Varela-Nieto I.

España
23 de marzo de 2017

16. **X REUNION ANUAL CIBERER**
"Modelos animales y celulares del déficit humano en la acción del IGF-1".

Lourdes Rodríguez-de la Rosa; Silvia Murillo-Cuesta; Ángela García Mato; Blanca Cervantes; Lluis Montoliu; Isabel Varela-Nieto.

España
23 de marzo de 2017

17. **Reunión Nacional de la Sociedad española de hipertensión liga española para la lucha contra la hipertensión arterial**
"FGF-23 altera la función contráctil e induce un fenotio proarritmogénico en el cardiomiocito adulto".

Navarro-García JA; Delgado C; Fernández-Velasco M; Val-blasco M; Rodriguez-Sánchez E; Aceves-Ripoll J; Segura J; Ruilope LM; Ruiz-Hurtado G.

España
29 de marzo de 2017

18. **13 th International Symposium on Insulin Receptor and Insulin action**
"A GLP-1R/GCGR dual agonist exhibits differential effects on metabolic control versus a single GLP-1R agonist by activation of BAT and browning in diet-induced obese mice".

P Valdecantos; L Ruiz; V Francisco; A Konkar; A Dos Santos; J Grimsby; C Rondinone; AM Valverde.

Francia
20 de abril de 2017

19. **13 th International Symposium on Insulin Receptor and Insulin action**
"Role of PTP1B in the progression of non-alcoholic fatty liver disease".

P Valdecantos; L Ruiz; V Francisco; A Konkar; A Dos Santos; J Grimsby; C Rondinone; AM Valverde.

Francia
20 de abril de 2017

20. **The Ins and Outs if cellular senescence**
"Isolation and characterization of senescence-associated exosomes".

S. Da Silva-Alvarez; A Ferreirós; P. Pedrosa-Lado; F. Triana-Martínez; P. Cabezas-Sainz; C. De Lope; G.N. Condezo; P. Ximénez-Embún; C. San Martín; J. Muñoz; M González-Barcia; L. Sánchez; I. Palmero; M. Collado.

Francia
16 de mayo de 2017

21. **CIBERDEM 8th ANNUAL MEETING**
"FUNCTIONAL ANALYSIS OF MODY2 MUTATIONS IN THE NUCLEAR EXPORT SIGNAL OF GLUCOKINASE".

Gutierrez-Nogués A; García-Herrero CM; Oriola J; Vincent O; Navas MA.

España
17 de mayo de 2017

22. **XXI Reunión Nacional de la Fundación Asociación Española de Coloproctología**
"La expresión del receptor de vitamina D y de una firma de expresión génica asociada a vitamina D en los fibroblastos estromales de cáncer colorrectal predice el pronóstico de los pacientes".

Ferrer-Mayorga G; Cantero R; Gutiérrez E; Asensio L; Díaz B; Peña C; Rojo F; Muñoz A; Larriba MJ.

Francia
17 de mayo de 2017

23. **19th European Congress of Endocrinology**
"The increase in unsaturated fatty acids is related with an anti-inflammatory profile in the hypothalamus of non-diabetic IRS2-deficient mice".

V Barrios; M Vinaixa; LM Frago; S Canelles; AM Valverde; J Argente; O Yanes.

Portugal
20 de mayo de 2017

24. **40 Congreso SEI MESA REDONDA EXTRACELLULAR VESICLES IN IMMUNITY**
"Intracellular signals involved in the polarized traffic of multivesicular bodies and exosome secretion in T lymphocyes".

Izquierdo, M.

España
25 de mayo de 2017

25. **Extracellular vesicles in Immunity**
"Intracellular Signals involved in the polarized traffic of multivesicular bodies and exosomes in T lymphocytes".

Manuel Izquierdo.

España
25 de mayo de 2017

26. **1st international conference on fatty liver**
"Role of PTP1B in the progression of non-alcoholic fatty liver disease".

A Gonzalez-Rodriguez; P Valdecantos; C Garcia-Monzon; P Rada; E Rey; V Pardo; L Ruiz Cañas; Angela M Valverde.

España
1 de junio de 2017

27. **EMBO Conference Cell Polarity and membrane dynamics**
"A NOVEL ROLE OF SYNTAXIN 3 AS A REGULATOR OF HUMAN CYTOMEGALOVIRUS GENE EXPRESSION".

Alberto Fraile-Ramos; Adrian Giovannone; Renato Aguiar; Manuel Izquierdo; Victor Calvo; Amilcar Tanuri; Wanderley de Souza; Thomas Weimbs.

España
4 de junio de 2017

28. **EMBO Conference Cell Polarity and membrane dynamics**
"PROTEIN KINASE C DELTA REGULATES THE CLEARANCE OF ACTIN AT THE IMMUNOLOGICAL SYNAPSE REQUIRED FOR POLARIZED EXOSOME SECRETION BY T CELLS".

Manuel Izquierdo.

España
4 de junio de 2017

29. **Tumour Microenvironment: Basic Science to Novel Therapies**
"1alpha,25-dihydroxyvitamin D3 inhibits the protumoural properties of colorectal cancer-associated fibroblasts and the expression of vitamin D receptor in these cells predicts patient clinical outcome".

Ferrer-Mayorga G; Gómez-López G; Cantero R; Rojo F; Muñoz A; Larriba MJ.

Gran Bretaña
14 de junio de 2017

30. **ITN-TREATMENT Kick-off meeting**
"Alterations of human adipose tissue in diabetes: a systems biology perspective".

PERAL B; GOMEZ-SERRANO M.

España
15 de junio de 2017

31. **EASD Eye Complications Study Group 26th Annual Meeting**
"Inhibition of protein tyrosine phosphatase 1B protects against inflammation-induced gliosis in the retina".

AM Valverde; AI Arroba.

Gran Bretaña
23 de junio de 2017

32. **XV Congreso Asociacion Osteogenesis imperfecta AMOI**
"Consideraciones Genéticas en OI".

Victor Luis Ruiz.

España
24 de junio de 2017

33. **Avances en Imagen Biomédica**
"Imagen de Difusión y Perfusión".

Lopez-Larrubia.

España
12 de julio de 2017

34. **Elastin, Elastic Fibers & Microfibrils Gordon Research Conference**
"Conditional Deletion of Rcan1 Promotes Aortic Intramural Hematoma that Progresses to Abdominal Aortic Aneurysm".

Juan Miguel Redondo; Miguel R Campanero.

Estados Unidos
3 de agosto de 2017

35. **Dicty 2017 (International Dictyostelium Conference)**
"Transmembrane transcription factors implicated in Dictyostelium ER-stress signaling".

DOMÍNGUEZ-MARTÍN E; DE PEDROSO A; VINCENT O; CORIA R; ESCALANTE R.

Suiza
20 de agosto de 2017

36. **42nd FEBS Congress From Molecules to Cells and Back**
"The role of dual phosphatase MKP1 in progressive hearing loss".

BERMUDEZ-MUÑOZ JM; CELAYA AM; VARELA-NIETO I.

Israel
11 de septiembre de 2017

37. **44th Computing in Cardiology Conference**
"IKs computational modeling to enforce the investigation of D242N, a Kv7.1 LQTS mutation".

Bartolucci C; Moreno C; Oliveras A; Muñoz C; de la Cruz A; Peraza DA; Gimeno JR; Martín-Martínez M; Severi S; Felipe A; Lambiase PD; Gonzalez T; Valenzuela C.

Francia
24 de septiembre de 2017

38. **17th National Congress SENC 2017**
"Physiological and pathophysiological implications of thyroid hormone transmembrane transport in the CNS.".

Guadaño Ferraz Ana.

España
27 de septiembre de 2017

39. **17th Congress of the Spanish Society for Neuroscience**
"Evaluation of synaptogenesis in MCT8 deficiency".

García-Aldea A; Grijota-Martínez C; Rausell E; Guadaño-Ferraz A.

España
27 de septiembre de 2017

40. **17th Congress of the Spanish Society for Neuroscience**
"Relative contributions of maternal hormones and fetal D2 to thyroid hormone economy during perinatal development in mice.".

S. Bárez-López; MJ. Obregon; J Bernal; A. Guadaño-Ferraz.

España
27 de septiembre de 2017

41. **IUNS, 21st International Congress of Nutrition**
"Cochlear homocysteine metabolism and related pathways in the Bhmt-/- mouse".

Teresa Partearroyo; Néstor Vallecillo; Lourdes Rodríguez de la Rosa; Steven H. Zeisel; María A. Pajares; Isabel Varela-Nieto; Gregorio Varela-Moreiras.

Argentina
15 de octubre de 2017

42. **IUBMB Focused Meeting on Molecular aspects of aging & longevity**
"THE ROLE OF INFLAMMATION MEDIATED BY MKP1 IN AGE-RELATED HEARING LOSS".

BERMUDEZ-MUÑOZ JM; Adelaida M. Celaya; Isabel Varela-Nieto.

España
16 de octubre de 2017

43. **XI Jornadas Jóvenes Investigadores**
"Efectos de la 1alpha,25-dihidroxivitamina D3 en fibroblastos estromales de cáncer de colon".

Ferrer-Mayorga G.

España
18 de octubre de 2017

44. **European Society for Magnetic Resonance In Medicine and Biology (ESMRMB). 34th Annual Meeting**
"Diffusion MRI to evaluate the role of the aquaporin 4 in the cerebral response to a feeding stimulus".

Irene Guadilla; María José Guillén; Sebastián Cerdán; Pilar López-Larrubia.

España
19 de octubre de 2017

45. **European Society for**

Magnetic Resonance In Medicine and Biology (ESMRMB). 34th Annual Meeting
"Anesthesia influence in magnetic susceptibility dependent MRI studies".

Daniel Calle; Irene Guadilla; Sebastián Cerdán; Pilar López-Larrubia.

España
19 de octubre de 2017

46. **European Society for Magnetic Resonance In Medicine and Biology (ESMRMB). 34th Annual Meeting**
"Diffusion MRI to assess the cerebral activation response to fasting status in a glioblastoma mouse model".

Irene Guadilla; María José Guillén; S. Cerdán; P. López-Larrubia.

España
19 de octubre de 2017

47. **European Society for Magnetic Resonance In Medicine and Biology (ESMRMB). 34th Annual Meeting**
"Diffusion MRI to detect the effects of a high-fat diet in the cerebral response to appetite stimulous in healthy mice".

Diffusion MRI to detect the effects of a high-fat diet in the cerebral response to appetite stimulous in healthy mice.

España
19 de octubre de 2017

48. **European Society for Magnetic Resonance In Medicine and Biology (ESMRMB). 34th Annual Meeting**
"Functional diffusion MRI in an animal model of paclitaxel induced-peripheral neuropathy".

Rita María Oliveira; Isabel Tavares; Pilar López-Larrubia.

España
19 de octubre de 2017

49. **European Society for Magnetic Resonance In Medicine and Biology (ESMRMB). 34th Annual Meeting**
"Functional MEMRI and HRMAS studies of brain regions in a mild depression model developed in female rats".

David Alcázar; María José Guillén; Teresa Navarro-Hernanz; Pilar López-Larrubia.

España
19 de octubre de 2017

50. **Diabetes**
"SEXUAL DIMORPHISM IN TYPE 2 DIABETES: A KEY ROLE OF ADIPOSE TISSUE".

Belén Peral.

España
19 de octubre de 2017

51. **15th Meeting of the International Bladder Cancer Network IBCN**
"CD49f labels an organoid-forming mouse urothelial cell population with stem cell features".

Santos CP; Lapi E; Álvaro L; Barbáchano A; Fernández-Barral A; Muñoz A; Real FX.

Portugal
21 de octubre de 2017

52. **FEBS3+ Barcelona 2017**
"MKP1 deficit causes hair cell loss, spiral ganglion degeneration and progressive hearing loss".

BERMUDEZ-MUÑOZ JM; Adelaida M. Celaya; Isabel Varela-Nieto.

España
23 de octubre de 2017

53. **The 1st FEBS3+ Joint Meeting of the French-Portuguese-Spanish Biochemical and Molecular Biology Societies Congress**
"Role of IGF-1 as an autophagy regulator during otic vesicle development".

SARA PULIDO; MARTA MAGARIÑOS; YOLANDA LEÓN; ISABEL VARELA-NIETO.

España
23 de octubre de 2017

54. **Joint Congress 2017 (organized by the Spanish Societies of Cell Biology, Developmental Biology and Genetics)**
"1ALPHA,25-DIHYDROXYVITAMIN D3 INHIBITS THE PROTUMORAL PROPERTIES OF COLORECTAL CANCER-ASSOCIATED FIBROBLASTS AND HIGH EXPRESSION OF VITAMIN D RECEPTOR IN THESE CELLS PREDICTS A BETTER CLINICAL OUTCOME".

Larriba MJ; Ferrer-Mayorga G; Gómez-López G; Peña C; Pisano DG; Cantero R; Rojo F; Muñoz A.

España
24 de octubre de 2017

55. **1st International Symposium on Inner Ear Therapies**
"Resveratrol and N-acetylcysteine combined treatment modulates the expression of oxidative stress response genes and ameliorate cochlear damage in a ototoxicity rat model".

S. Murillo; S. Pulido; JM. Bermúdez-Muñoz; F. García-Alcántara; R. Martínez-Vega; L. Rodríguez-de la Rosa; T. Rivera; M. Milo; I. Varela-Nieto.

Marruecos
1 de noviembre de 2017

56. **10th Conference of African Society of Human Genetics**
"Ellis-van Creveld syndrome: a ciliopathy directly implicated in hedgehog signaling"".

Victor L Ruiz-Perez.

Egipto
16 de noviembre de 2017

57. **XX Jornada Científica del IIBM**
"Vitamina D y cáncer de colon".

Larriba MJ.

España
1 de noviembre de 2017

54. **XXXVIII Congreso del Grupo Español de Neurotransmisión y Neuroprotección (GENN-38)**
"Neurogenic inducers based on the chromone scaffold, a new family of multitarget directed ligands for Alzheimer's disease".

Neurogenic inducers based on the chromone scaffold, a new family of multitarget directed ligands for Alzheimer's disease.

España
13 de diciembre de 2017

AÑO
2017

1. **41st Annual MidWinter Meeting**
"Genetic defects in progressive hearing loss".

Hannie Kremer; Mieke Wesdorp; Jeroen Smits; Silvia Murillo-Cuesta; Theo Peters; Adelaida Celaya; Margit Schraders; Jaap Oostrik; Martijn Huynen; Pia; de Koning-Gans; Ignacio Del Castillo; Pau Serra; Ronald Admiraal; Lies Hoefsloot; Helger Yntema; Isabel Varela-Nieto; Ronald Pennings.

Estados Unidos
9 de febrero de 2018

2. **41st Annual MidWinter Meeting**
"Resveratrol and N-acetylcysteine Combined Treatment Modulates the Expression of Oxidative Stress Response Genes and Ameliorate Cochlear Damage in a Ototoxicity Rat Model".

Ignacio Palmero.

Estados Unidos
9 de febrero de 2018

3. **REUNION ANUAL CIBERER**
"El déficit en la proteína similar a la mielina P0 tipo 2 causa hipoacusia prematura progresiva".

F.J. Ortega; J.M. Moreno-Navarrete; M. Gómez-Serrano; E. García-Santos; J. Latorre, M. Sabater; E. Caballano-Infantes, R. Guzmán; A. Vidal-Puig; M.M. Malagón; B. Peral; A. Zorzano; J.M. Fernández-Real.

España
21 de febrero de 2018

4. **62nd Annual Meeting Biophysical Society**
"D242N, a KV7.1 LQTS mutation uncovers a key residue for IKs voltage dependence".

Gema Ferrer Mayorga.

Estados Unidos
17 de febrero de 2018

5. **Second Spanish Molecular Imaging Network (SMIN) Meeting**
"Neuroprotective role of PKD1 against ischemic and kainic acid-induced brain injury".

Victor Luis Ruiz Perez.

Estados Unidos
26 de febrero de 2018

6. **Second Spanish Molecular Imaging Network (SMIN) Meeting**
"The role of PKD1 in aging-related neurodegeneration: Structural and functional imaging studies".

Muñoz A.

España
26 de febrero de 2018

7. **I Congreso Nacional de Estudiantes de Farmacia**
"Cáncer de colon: Wnt, vitamina D y organoides".

Isabel Cordova; Raquel García; Maite Bayo; Eduardo Ferrero-Herrero; María Monsalve.

España
1 de marzo de 2018

8. **XI Reunión Anual CIBERER**
"Análogos de Hormonas Tiroideas con Acciones Tiromiméticas en el Sistema Nervioso Central en Condiciones de Deficiencia del Transportador de Monocarboxilatos Mct8".

Maria Asuncion Fernandez Barral.

España
12 de marzo de 2018

9. **Workshop "Metabolic Reprogramming as a Target for Cancer and Other Diseases"**
"El proceso de carcinogenesis".

Barbáchano A; Fernández-Barral A; Costales-Carrera A; Muñoz A.

España
15 de marzo de 2018

10. **5th Symposium on Biomedical Research Advances and Perspectives in Pharmacology, Drug Toxicity and Pharmacogenetics**
"A cell-permeable peptide corresponding to the calmodulin-binding domain of Grb7 inhibits proliferation and migration of A431 cells".

Vincent O.

España
15 de marzo de 2018

11. **IV Simposio Nacional de Genómica Aplicada en Oncología**
"Organoides en cáncer colorrectal: estado y posible uso clínico".

Muñoz A.

España
20 de marzo de 2018

12. **9th International Meeting on Neuroacanthocytosis Syndromes**
"The role of VPS13A in the endo-lysosomal and autophagic pathways".

María Monsalve.

Alemania
23 de marzo de 2018

13. **Transcription factor NRF2: New opportunities for pharmaceutical innovations in chronic diseases**
"Targeting Nrf2 in metabolic diseases".

Muñoz A.

España
11 de abril de 2018

14. **University of Brescia Seminary Lesson**
"Mitochondrial oxidative stress: causes and consequences".

María Monsalve; Ramazan Yildiz; Gaurangkumar Patel.

Italia
16 de abril de 2018

15. **XXIII Congreso Nacional sobre Osteogénesis Imperfecta de AHUCE**
"El paciente con OI en el Laboratorio de Genética".

Soledad Bárez-López; Carmen Grijota-Martínez; Meredith D. Hartley; Thomas S. Scanlan; Ana Guadaño-Ferraz.

España
20 de abril de 2018

16. **Redox biology as a major drive to the understanding of pathophysiology: Contributions from the CONSOLREDOX network**
"Role of mitochondrial dysfunction in NAFL. Macrovascular alterations in PGC-1alfa knock-out mice".

Guadaño Ferraz A.

España
23 de abril de 2018

17. **Cáncer de colon: Wnt, vitamina D y organoides**
"Cáncer de colon: Wnt, vitamina D y organoides".

Angela M Valverde.

España
25 de abril de 2018

18. **Seminarios científicos del Instituto de Investigación Sanitaria Princesa (IIS-IP)**
"Implicacion de miembros de la familia de los factores asociados a los receptores de TNF (TRAFs) en el desarrollo de displasias y neoplasias linfoides".

Muñoz-Braceras; Tornero A; Vincent O; Escalante R.

España
26 de abril de 2018

19. **21st Workshop on Vitamin D**
"Mechanisms of action of vitamin D in colon cancer".

Tamayo M; Martin L; García-Piedras MJ; Lage E; Val-Blasco A; Fernández-Velasco M; Delgado C.

España
16 de mayo de 2018

20. **21st Workshop on Vitamin D**
"Beneficial effects of paricalcitol in a setting of cardiac dysfunction induced by transverse aortic constriction in mice.".

Muñoz A.

España
16 de mayo de 2018

21. **21st Workshop on Vitamin D**
"Calcitriol inhibits the protumoral properties of colorectal cancer-associated fibroblasts and high VDR expression in these cells predicts a better patient clinical outcome".

Muñoz A.

España
16 de mayo de 2018

22. **10th Cajal Winter Conferences on ¿Translational Neuroscience: Bridges in the Valley of Death?**
"Evaluation of neuropathology in the MCT8 deficient human brain. New insights into the neuroglial cells.".

Victor L Ruiz Perez.

España
16 de mayo de 2018

23. **21st Workshop on Vitamin D**
"The effect of vitamin D on the expression of the calcium-sensing receptor in colonic organoids".

Irene Guadilla; María José Guillén; Sebastián Cerdán García-Esteller; Pilar López-Larrubia.

España
16 de mayo de 2018

24. **II MEETING FOR YOUNG INVESTIGATORS OF MECHANISM OF TUMOR PROGRESSION PROGRAM OF CIBERONC**
"Human colorectal organoids: response to chemotherapy and effect of calcitriol".

Julia Pose Utrilla; Teresa Iglesias.

España
18 de mayo de 2018

25. **1st PhD Research Symposium in Health Sciences and Biomedicine. Facultad de Medicina, Universidad Autónoma de Madrid**
"Evaluation of the physiopathology of the Allan-Herndon-Dudley syndrome. A characterization of double knock-out mice model of the disease.

Evaluation of the physiopathology of the Allan-Herndon-Dudley syndrome. A characterization of double knock-out mice model of the disease.

España
18 de mayo de 2018

26. **Caracterización genética y fisiopatologica de un nuevo tipo de miopatía**
"Conferencia invitada. Instituto de Biomedicina de Valencia (CSIC)".

Hannie Kremer; Mieke Wesdorp; Jeroen Smits; Silvia Murillo-Cuesta; Theo Peters; Adelaida Celaya; Margit Schraders; Jaap Oostrik; Martijn Huynen; Pia; de Koning-Gans; Ignacio Del Castillo; Pau Serra; Ronald Admiraal; Lies Hoefsloot; Helger Yntema; Isabel Varela-Nieto; Ronald Pennings.

España
23 de mayo de 2018

27. **19th biennial meeting for the Society for Free Radical Research International (SFRRI)**
"Early induction of senescence and immortalization in PGC-1¿-deficient mouse embryonic fibroblasts".

Zapata JM.

Portugal
4 de junio de 2018

28. **Joint Annual Meeting ISMRM-ESMRMB**
"Effects of a high-fat diet in the mouse cerebral response to appetite detected by functional diffusion MRI and HRMAS studies".

Pedro Lorenzo; Felipe Atienza; Juan Manuel Zapata; Isabel Varela-Nieto.

Francia
16 de junio de 2018

29. **Joint Annual Meeting ISMRM-ESMRMB**
"Functional and metabolic magnetic resonance evaluation of the role of the aquaporin-4 in the cerebral response to appetite".

Irene Guadilla; María José Guillén; Sebastián Cerdan García-Esteller; Pilar López-Larrubia.

Francia
16 de junio de 2018

30. **Joint Annual Meeting ISMRM-ESMRMB**
"Magnetic resonance to

characterize the cerebral response to fasting status in a glioblastoma mouse model".

Teresa Navarro-Hernanz; David Alcázar; Fátima Sanchís; Pilar López-Larrubia.

Francia
16 de junio de 2018

31. Joint Annual Meeting ISMRM-ESMRMB

"Multiparametric magnetic resonance and phenotypic characgterization of a mild depression rat model".

González-Hedström D; Amor S; García-Quintans N; García R; Tejera-Muñoz; García-Villalón AL; Monsalve M; Granado M.

Francia
16 de junio de 2018

32. Meeting of the European Society for Clinical Investigation (ESCI)

"Cytoskeletal TAGLN2 is associated with sex-dependent adipose tissue expandability".

Teresa Iglesias Vacas.

España
21 de junio de 2018

33. SMETS2. 2nd small meeting on endocytic trafficking and signaling

"Mechanisms and regulation of autophagy in yeast".

ALCALDE J; GONZÁLEZ-MUÑOZ M; MADROÑAL I; VILLALOBO A.

Portugal
11 de julio de 2018

34. Yeast Genetics Meeting

"Construction and characterization of a strain of Saccharomyces cerevisiae able to grow on glucosamine as carbon and nitrogen source".

Bárez López S; Martínez Grijota; Thomas Scanlan; Meredith D. Hartley,; Guadaño Ferraz.

Estados Unidos
22 de agosto de 2018

35. Yeast Genetics Meeting

"Evidence for a moonlighting role of the N-acetylglucosamine kinase from Yarrowia lipolytica".

Navarro-García, J.A.; Delgado, C.; Fernández-Velasco, M.; Val-Blasco, A.; Rodríguez-Sánchez, E.; Aceves-Ripoll, J.; Gómez-Hurtado, N.; Praga, M.; Hernández, E.; Salguero, R.; Arribas, F.; Ruilope, L.M.; Ruiz-Hurtado, G.

Estados Unidos
22 de agosto de 2018

36. European Society of Cardiology (ESC) Annual Meeting

"Pro-resolving mediators prevent miocarditis-induced calcium mishandling and cardiac dysfunction: involvement of Nfr2".

BUENO ARRIBAS M; CERVERO GARCIA MP; ESCALANTE R; VINCENT O.

Alemania
25 de agosto de 2018

37. European Society of Cardiology (ESC) Annual Meeting

"Fibroblast growth factor (FGF)-23 induces ventricular arrhytmogenesis through Ca2+ handling dysregulation".

Silvia Murillo-Cuesta; Lourdes Rodríguez-de la Rosa; Stephan Zeisel; María A. Pajares; Gregorio Varela-Moreiras; Isabel Varela-Nieto.

España
26 de agosto de 2018

38. ESC CONGRESS

"The deficiency of NOD1 improves beta-adrenergic regulation of Ca2+ handling in experimental heart failure".

Ferrer-Mayorga G; Gómez-López G; Peña C; Pisano DG; Cantero R; Rojo F; Muñoz A; Larriba MJ.

España
25 de agosto de 2018

39. 55th Inner Ear Biology 2018

"G6PD overexpression protects from oxidative stress and ameliorates ARHL progression".

Ferrer-Mayorga G; Gómez-López G; Cantero R; Rojo F; Muñoz A; Larriba MJ.

Alemania
25 de septiembre de 2018

40. 41 Congreso SEBBM

Santander
"Total or partial PGC-1¿ deficiency is associated with alterations in vascular function in mice".

Gancedo C; Flores CL.

España
10 de septiembre de 2018

41. 41 Congreso de la Sociedad Española de Bioquímica y Biología Molecular (SEBBM)

"Calcitriol inhibits the protumoural properties of colorectal cancer-associated fibroblasts and the expression of its receptor in these cells predicts patient clinical outcome".

Motiño, Omar; Francés, Daniel E.; Casanova, Natalia; Cucarella, Carme; Fuertes-Agudo, Marina; Flores, Juana M.; Olmedilla, Luis; Pérez Peña, José; Bañares, Rafael; Boscá, Lisardo; Casado Pinna, Marta; Martin-Sanz, Paloma.

España
10 de septiembre de 2018

42. XLI Congreso de la SEBBM

"Cyclooxygenase-2 expression in hepatocytes protects against hepatic ischemia-reperfusion injury in mice".

Motiño O; Frances DE; Casanova N; Cucarella C; Fuertes-Agudo M; Bosca L; Casado M: Martin-Sanz P.

España
10 de septiembre de 2018

43. 41 Congreso de la Sociedad Española de Bioquimica y Biología Molecular

"Cyclooxygenase-2 expression in hepatocytes protects against hepatic ischemia/reperfusion injury in mice".

Ortega, F; Moreno-Navarrete, J; Gomez-Serrano, M; Garcia-Santos, E; Latorre, J; Sabater, M; Caballano-Infantes, E; Guzman, R; Vidal-Puig, A; Malagon, M; Peral, B; Zorzano, A; Fernandez-Real, J.

España
10 de septiembre de 2018

44. FASEB Science Research Conferences. Fundamental Biology and Pathophysiology of the Liver

"Protective role of hepatocyte cyclooxygenase-2 expression against liver ischemia-reperfusion injury in mice".

Moreno C; Oliveras A; Bartolucci C; Muñoz C; de la Cruz A; Peraza DA; Gimeno JR; Martin-Martinez M; Severi S; Felipe A; Lambiase PD; Gonzalez T; Valenzuela C.

Estados Unidos
10 de septiembre de 2018

45. 13th International Workshop on Resistance to Thyroid Hormone

"Searching for strategies to overcome the lack of MCT8 in the brain".

Ignacio Prieto; Alberto Zambrano; Javier Laso; Enrique Samper; Ana Aranda; María Monsalve.

Países Bajos
11 de septiembre de 2018

46. 41 Congreso de la SEBBM

"Cell senescence in cancer and development".

Murillo-Cuesta S; Celaya AM; del Castillo I; Serra P; Kremer H; Varela-Nieto I.

España
12 de septiembre de 2018

47. XXXIX Congreso de la Sociedad Española de Ciencias Fisiológicas (SECF)

"Human Normal and Tumor Colorectal Organoids: Gene Expression Studies".

García-Aldea A; Guillén-Yunta M; Grijota-Martínez C; Rausell E; Guadaño-Ferraz A.

España
18 de septiembre de 2018

48. Sociedad ESpañola de Ciencias Fisiológicas (SECF). Reunión anual.

"A novel role of fibroblast growth factor (FGF)-23 in ventricular arrhythmogenesis".

García-Aldea A; Grijota-Martínez C; Rausell E; Guadaño-Ferraz A; Marina Guillén Yunta.

España
18 de septiembre de 2018

49. VI International Congress on Research and Innovation in Neurodegenerative Diseases (CIIIEN)

"Molecular Mechanism involved in short Kidins220 isoform degradation in Huntington´s Disease".

Navarro-García, J.A.; Delgado, C.; Fernández-Velasco, M.; Bada-Bosch, T.; Mérida, E.; Hernández, E.; Salguero, R.; Praga, M.; Ruilope, L.M.; Ruiz-Hurtado, G.

España
19 de septiembre de 2018

50. VI International Congress on Research and Innovation in Neurodegenerative Diseases (CIIIEN)

"Molecular Mechanism involved in short Kidins220 isoform degradation in Huntington´s Disease".

Navarro-García, J.A.; Delgado, C.; Fernández-Velasco, M.; Bada-Bosch, T.; Mérida, E.; Hernández, E.; Salguero, R.; Praga, M.; Ruilope, L.M.; Ruiz-Hurtado, G.

España
19 de septiembre de 2018

51. VI International Congress on Research and Innovation in Neurodegenerative Diseases (CIIIEN)

"The Loss of Neuronal PKD1 activity causes an early onset of Phenotypes associated with brain aging-related neurodegeneration".

JNavarro-Garcia A; Delgado C; Fernandez-Velasco M; Val-Blasco A; Rodriguez-Sanchez E; Aceves-Ripoll J; Hernandez E; Bada-Bosch T; Arribas F; Salguero R; Solis J; Prag M; Bueno H; Ruilope LM; Ruiz-Hurtado G.

Alemania
19 de septiembre de 2018

52. 54th Annual Meeting of the European-Association-for-the-Study-of-Diabetes (EASD)

"Cytoskeletal transgelin 2 (TAGLN2) is associated with sex-dependent adipose tissue expandability".

BERMUDEZ-MUÑOZ JM; Adelaida M. Celaya; Isabel Varela-Nieto.

Alemania
1 de octubre de 2018

53. "Ciclo de Charlas en Biomedicina CENTRO DE INVESTIGACIONES BIOLOGICAS-CSIC (Depto. Biomedicina Molecular. CIB; Depto. Biología Molecular y Celular. CIB; Red de Inflamación y Enfermedades Reumáticas)"

"Una nueva ruta de detoxificación de estrés oxidativo neuronal confiere neuroprotección".

Navarro-García, J.A.; Fernández-Velasco, M.; Delgado, C.; Val-Blasco, A.; González-Lafuente, L.; Rodríguez-Sánchez, E.; Aceves-Ripoll, J.; Ruilope, L.M.; Ruiz-Hurtado, G.

España
8 de octubre de 2018

54. IV World Congress of Public Health Nutrition y el XII Congreso de la Sociedad Española de Nutrición Comunitaria (SENC) NUTRIMAD 2018

"BETAINE HOMOCYSTEINE S-METHYLTRANSFERASE DEFICIENCY INCREASES SUSCEPTIBILITY TO NOISE-INDUCED HEARING LOSS CORRELATING WITH PLASMA HYPERHOMOCYSTEINEMIA".

Álvaro Sebastián-Serrano; Ana Simón-García; Alicia Belmonte-Alfaro; Julia Pose-Utrilla; Lucía García-Guerra; Ana M. Del Puerto; María Santos; José J. Lucas; Teresa Iglesias.

España
24 de octubre de 2018

55. 2018 Focus Program on Translational Neuroscience Seminar Series SummerUniversity Medical Center of the Johannes Gutenberg-Universität Mainz

"Searching for therapeutic targets and strategies to overcome the lack of the specific thyroid hormone transporter MCT8 in the brain".

L. García-Guerra; J. Pose-Utrilla; A. Del Puerto; A. Martín-Muñoz; J. Jurado-Arjona; N.S. De León-Reyes; A. Gamir-Morralla; A. Sebastián-Serrano; J. Fielitz; I. Ferrer; F. Hernández; J. Ávila; M.R. Campanero; T. Iglesias.

Alemania
6 de noviembre de 2018

56. **SEFAGIA 2018**
"Association of the Atg1 kinase complex with the lipidation machinery in yeast".

Fernández-Velasco, M.; Val-Blasco, A.; Delgado, C.; Ruiz-Hurtado, G.; Tamayo, M.; Navarro-García, J.A.; Terrón, V.; Zaragoza, C.; Gil-Fernández, M.; Boscá, L.; Prieto, P.

España
14 de noviembre de 2018

57. **SEFAGIA 2018**
"VPS13A is required for endo-lysosomal trafficking and autophagy".

O Motiño, D Francés, M Casado, P Martín-Sanz.

España
14 de noviembre de 2018

58. **Spanish Society of Nephrology (SEN) Anual Meeting.**
"FGF-23 a novel pro-arrhythmogenic factor: clinical approach in dialysis patients and experimental approach in the adult isolated cardiomyocyte".

Silvia Murillo-Cuesta; Sara Pulido; Bermúdez-Muñoz; Fernando García-Alcántara; Raquel Martínez-Vega; Teresa Rivera; Marta Milo; Isabel Varela-Nieto.

España
16 de noviembre de 2018

59. **XLVIII Congreso Nacinal de la SEN y IX Congreso Iberoamericano de Nefrología**
"Klotho prevents Ca2+ mishandling in the adult cardiomyocyte asociated with arrhythmogenic activity in an experimental model of chronic kidney disease".

Fuertes Agudo, Marina; Casanova, Natalia; Cucarella, Carme; Boscá, Lisardo; Martin-Sanz, Paloma; Casado, Marta.

España
16 de noviembre de 2018

60. **I REUNIÓN NURCAMEIN 2**
"Efecto de vitamina D y Wnt en fibroblastos colónicos humanos".

Val-Blasco A; Navarro-García A; Tamayo M, Piedras MJ; Prieto P,; Delgado C; Ruiz-Hurtado G, Terrón V; Mesa JM; Blazquez JA; Bosca L; Fernández-Velasco M.

España
21 de noviembre de 2018

61. **Cáncer de colon: Wnt, vitamina D y organoides**
"Cáncer de colon: Wnt, vitamina D y organoides".

Iamartino L; Barbáchano A; Muñoz A; Kallay E.

España
23 de noviembre de 2018

62. **XII Jornadas Científicas del Ciberehd**
"Role of COX-2 in liver mitochondrial function".

Julia Pose Utrilla; Lucía García-Guerra; Judith Hernández; Ana Del Puerto; Álvaro Sebastián Serrano; Rubén Fernández de la Rosa; Luis García-García; Miguel Ángel Pozo; Jens Fielitz; Miguel R. Campanero; Teresa Iglesias.

España
26 de noviembre de 2018

63. **La investigación biomédica, multidisciplinar y translacional**
"Introducción a la investigación de los animales modificados genéticamente".

J. Pose-Utrilla; L. García-Guerra; J. Hernández; A. Del Puerto; A. Sebastián-Serrano; R. Fernández de la Rosa; L. García-García; M.A. Pozo; J. Fielitz; M.R. Campanero; T. Iglesias.

España
30 de noviembre de 2018

64. **2018 ASCB | EMBO Meeting**
"Evaluation of circulating mtDNA as biomarker of metabolic alterations in thyroid cancer".

MUÑOZ-BRACERAS S; TORNERO-ECIJA AR; VINCENT O; ESCALANTE R.

Estados Unidos
8 de diciembre de 2018

2017
2018
SEMINARIOS

1. **Giampietro Schiavo**
"Modulation of axonal transport in neurodegeneration".

University College London, Institute of Neurology.

18 de enero de 2017

2. **Ascensión Marcos y Sonia García**
"Inmunonutrición: una materia interdisciplinar".

Instituto de Ciencia y Tecnología de Alimentos y Nutrición (ICTAN) Madrid, CSIC.

20 de enero de 2017

3. **Bergazyn Liberman, Gabriel**
"Estudio del efecto pro-apoptótico de los diterpenos derivados del labdano en células tumorales".

Centro Nacional de Investigaciones Oncológicas (CNIO).

25 de enero de 2017

4. **Alfonso Valencia**
"Cancer genomes at big nd small scale ".

Centro Nacional de Investigaciones Oncológicas (CNIO).

25 de enero de 2017

5. **Carmelo Bernabeu**
"Nuevas funciones de endoglina en el endotelio vascular".

Centro de Investigaciones Biológicas (CIB).

3 de febrero de 2017

6. **María Molina**
"Fibrosis pulmonar en la era de la medicina personalizada".

Hospital Universitari de Bellvitge.

8 de febrero de 2017

7. **Francisco Martín**
"What flies can teach us about hormones and behavior".

Instituto Cajal, CSIC.

17 de febrero de 2017

8. **Celia López**
"Papel de las proteínas E2A en la progresión tumoral y la metástasis de carcinomas de mama".

Departamento de Biología del Cáncer, Instituto de Investigaciones Biomédicas "Alberto Sols".

20 de febrero de 2017

9. **José A. Cancelas**
"Inflammation recruits innate immune bone marrow progenitors into lymphatic circulation".

Cancer & Blood Diseases Institute, Cincinnati Children's Hospital Medical Center.

22 de febrero de 2017

10. **Ana María Falcón**
"¿Qué le hace letal a un virus de la gripe?".

Centro Nacional de Biotecnología (CNB), CSIC.

22 de febrero de 2017

11. **María de los Ángeles Balboa**
"Regulación del inflamasoma por enzimas del metabolismo lipídico".

Instituto de Biología y Genética Molecular (IBGM).

3 de marzo de 2017

12. **José María Delgado García**
"Hablando de lo que entiende: el cerebro en vivo y en directo".

Universidad Pablo Olavide.

8 de marzo de 2017

13. **Daniel Granados**
"Micro and Nanofabrication at the CEI UAM+CSIC".

Centro de micro y nanofabricación, IMDEA-Nanociencia.

10 de marzo de 2017

14. **Nuno Sousa**
"The stressed brain".

Cancer & Blood Diseases Institute, Cincinnati Children's Hospital Medical Center.

22 de marzo de 2017

15. **Roger Gomis**
"¿Mechanisms of tissue specific metastasis?".

Institut de Recerca Biomèdica (IRB)

24 de marzo de 2017

16. **Silvia Martín Puig**
"The Heart of Hypoxia: Exploring HIF/VHL signaling in Cardiovascular Development & Disease".

Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC)

31 de marzo de 2017

17. **Borja Ibáñez**
"Bloqueo de sistema beta-adrenérgico como diana terapéutica en isquemia/reperfusión miocárdica".

Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC).

5 de abril de 2017

18. **María de los Ángeles Pajares**
"Contribuciones clave al conocimiento del ciclo de la metionina y su regulación desde el IIBM".

Centro de Investigaciones Biológicas (CIB).

7 de abril de 2017

19. **José Luis Lanciego**
"Mutaciones de glucocerebrosidasa y agregación de alfa-sinucleína: Cruce de caminos entre las enfermedades de Gaucher y Parkinson".

Centro de Investigación Médica Aplicada (CIMA) - Universidad de Navarra

19 de abril de 2017

20. **Jing Wang**
"DNA damage and mitochondrial dysfunction in cochlear cell degeneration: towards hearing rescue".

Institute for Neuroscience of Montpellier.

24 de abril de 2017

21. **Ignacio Flores Hernández**
"Telomere control of heart regeneration".

Centro Nacional de Investigaciones Cardiovasculares (CNIC).

28 de abril de 2017

22. **Javier Benítez**
"Descifrando la complejidad genética del cáncer de mama hereditario".
Centro Nacional de Investigaciones Oncológicas (CNIO).
3 de mayo de 2017

23. **Miguel Morales**
"Espinogénesis regulada por PI3K".
Universidad de Barcelona (UB).
12 de mayo de 2017

24. **Antonio Cuadrado**
"Nuevas estrategias terapéuticas en enfermedades neurodegenerativas basadas en el factor de transcripción NRF-2".
Investigaciones Biomédicas "Alberto Sols", Universidad Autónoma de Madrid (UAM), Madrid
17 de mayo de 2017

25. **Laura Sánchez Piñón**
"El pez cebra: un nuevo compañero en la investigación biomédica".
Universidade de Santiago de Compostela (USC).
26 de mayo de 2017

26. **Hana Algül**
"Stat3 and its signaling components in pancreatic cancer development".
Molecular Medicine & Oncology, Medicine Faculty, Technische Universität München.
31 de mayo de 2017

27. **Jacqueline A. Wilce**
"Las variantes sin lisinas de las proteínas SMN y SMNΔ7, implicadas en atrofia muscular espinal, se degradan por la vía del proteasoma".
Monash University.
9 de junio de 2017

28. **Flavio Maina**
"Tracking RTK cooperative mechanisms during tumour initiation and evolution".
Institut de Biologie du Développement de Marseille (IBDM).
16 de junio de 2017

29. **Enrique Martín-Blanco**
"The mechanics of morphogenesis in Drosophila and zebrafish".
Instituto de Biología Molecular de Barcelona (IBMB), CSIC, Parc Científic de Barcelona.
23 de junio de 2017

30. **Inés Pineda-Torra**
"Liver X Receptor as modulators of lipid metabolism and fibrosis: lessons from a knock in mutant mouse model".
Metabolism & Experimental Therapeutics, UCL.
28 de junio de 2017

31. **Markus Schober**
"Tumor Propagating Cancer Cells: Opportunities and Challenges for Therapy Design".
The Helen and Martin Kimmel Center for Stem Cell Biology. NYU Langone Medical Center.
30 de junio de 2017

32. **Cristina García-Cáceres**
"Papel de los astrocitos en el control metabólico".
Instituto de Diabetes y Obesidad de Helmholtz Zentrum Muenchen, Munich.
5 de julio de 2017

33. **Alessandra Stacchiotti**
"Sirtuin 1 heterozygous- mice model to study obesity".
Università delgi Studi di Brescia.
6 de julio de 2017

34. **Javier Calvo Garrido**
"SQSTM1/p62-directed metabolic reprogramming is required to prevent neurodegenerative disease".
Karolinska Institutet, Stockholm.
13 de julio de 2017

35. **José María Sánchez Puelles**
"Nuevos y viejos fármacos: estrategia académica de reposicionamiento".
Centro de Investigaciones Biológicas (CIB, CSIC).
21 de julio de 2017

36. **David Mayo**
"¿Te previenen tus células contaminadas de publicar tus resultados?".
IDEXX Bioresearch.
8 de septiembre de 2017

37. **Edgar Gonzalo Fdez. Malave**
"El TCR como regulador de la diferenciación de los linfocitos Tyð efectores en el timo".
Facultad de Medicina, Universidad Complutense de Madrid (UCM).
13 de septiembre de 2017

38. **Felipe X. Pimentel**
"Unconventional forms of autophagy and their role in health and disease".
Departamento de Metabolismo y Señalización Celular, Instituto de Investigaciones Biomédicas "Alberto Sols".
6 de octubre de 2017

39. **James Yang**
"Digital Human Modeling and Simulation for Engineering and Spine Biomechanics".
Texas Tech University.
16 de octubre de 2017

40. **Paola Martinelli**
"Epithelial differentiation is a GATA and FOXA family business".
Institute for Cancer Research, Medical University of Vienna
20 de octubre de 2017

41. **Javier Fontecha**
"Fosfo- y esfingolípidos de la dieta y su impacto en la salud humana".
Instituto de Investigación en Ciencias de la Alimentación (CIAL), CSIC-UAM.
25 de octubre de 2017

42. **Virginia Amador**
"The role of SOX11 in mantle cell lymphoma protective microenvironment".
Institut D'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS).
3 de noviembre de 2017

43. **Joan Isern**
"Nuevas herramientas genéticas para el estudio de la formación y remodelación de vasos coronarios".
Área de Biología Celular y del Desarrollo / Fisiopatología Vascular - CNIC (Carlos III).
8 de noviembre de 2017

44. **Sebastián Pons**
"The multiple actions of β-Catenin along the development of the nervous system".
Instituto de Biología Molecular de Barcelona (IBMB).
17 de noviembre de 2017

45. **Marisa Toribio**
"Modeling human T-cell acute lymphoblastic leukemogenesis in vivo: Therapeutic implications".
Centro de Biología Molecular Severo Ochoa (CBMSO).
22 de noviembre de 2017

46. **Susana Guerra**
"Papel de ISG15 en la infección por el virus Vaccinia".
Dto. Medicina Preventiva, Salud Pública y Microbiología. Facultad de Medicina. Universidad Autónoma de Madrid (UAM).
13 de diciembre de 2017

47. **Antonio Oliviero**
"Efectos de los campos magnéticos estáticos sobre la corteza cerebral humana".
Hospital Nacional de Parapléjicos de Toledo.
20 de diciembre de 2017

48. **María José Dueñas DeCamp**
"Understanding the structural changes in HIV-1 trimer and their effects on tropism and vaccine development".
University of Massachusetts Medical School (UMMS).
10 de enero de 2018

49. **Jesús Balsinde**
"Mitochondrial function and its role in the pathophysiology of metabolic disorders".
Instituto de Biologia y Genetica Molecular, CSIC.
19 de enero de 2018

50. **Antonio Zorzano**
"Mitochondrial function and its role in the pathophysiology of metabolic disorders".
Institute for Research in Biomedicine (IRB).
24 de enero de 2018

51. **Miguel Ángel Salinero Fort**
"Complicaciones Microvasculares en la Diabetes Tipo 2: Resultados de la cohorte MADIABETES".
Servicio General de Investigación Sanitaria. Consejería de Sanidad.
2 de febrero de 2018

52. **Vicente Andrés**
"Mecanismos moleculares y celulares de enfermedad cardiovascular en progeria".
Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC).
7 de febrero de 2018

53. **David Reverter**
"Structural insights into the SUMO/ubiquitin modification pathway".
Institut de Biotecnologia i Biomedicina-Universitat Autònoma de Barcelona (UAB).
16 de febrero de 2018

54. **Joan Seoane**
"Dealing with intra-tumor heterogeneity in brain cancer".
Vall D'Hebron Institut d'Oncologia (VHIO).
21 de febrero de 2018

55. **Juan Manuel Encinas**
"Reactive Neural Stem Cells in the Adult Hippocampus".
Achucarro Basque Center for Neuroscience e Ikerbasque, the Basque Science Foundation.
2 de marzo de 2018

56. **Baldo Oliva**
"La enfermedad desde una perspectiva de medicina de sistemas".
Dept. Ciencias Experimentales y de la Salud. Universitat Pompeu i Fabra (UPF).
7 de marzo de 2018

57. **Ricardo Sanchez Prieto**
"Bases de la radio- y quimorresistencia".
Departamento Biología del Cáncer, Instituto de Investigaciones Biomédicas "Alberto Sols".
20 de marzo de 2018

58. **Salvador Martínez**
"Terapia celular en ELA: experiencia científica y clínica después de diez años".
Instituto de Neurociencias (IN), CSIC-UMH.
21 de marzo de 2018

59. **Zafira Castaño**
"Innate immune response to primary breast cancer prevents metastasis-initiating cell colonization".
Brigham and Women's Hospital (BWH).
4 de abril de 2018

60. **Guillermo Velasco**
"Towards the utilization of cannabinoids as anticancer agents...and other stories inspired by cannabis".
Universidad Complutense de Madrid (UCM).
18 de abril de 2018

61. **Luis Angel Fernández**
"Engineering E. coli for the injection of therapeutic proteins into tumor cells".
Centro Nacional de Biotecnología (CNB), CSIC.
20 de abril de 2018

62. **Marta Mendiola Sabio**
"Identificación de biomarcadores relacionados con la transición epitelio-mesénquima en cáncer de ovario avanzado".

Grupo Patología Molecular del Cáncer y Dianas Terapáuticas, IdiPAZ.

25 de abril de 2018

63. **Jesús Gil**
" The senescence-associated secretory phenotype: linking senescence with inflammation".

London Institute of Medical Sciences.

27 de abril de 2018

64. **Luis M. Rodríguez-Alcalá**
"Lipobonomic studies in food & health research".

Centre for Biotechnology and Fine Chemistry (CBQF), Universidade Católica Portuguesa, Porto.

11 de mayo de 2018

65. **Arkaitz Carracedo**
"Fuel and oil for the cancer engine".

University of the Basque Country. CIC BIOGUNE.

16 de mayo de 2018

66. **Malu Martínez-Chantar**
"Papel de la mitocondria en la enfermedad hepática".

CIC bioGUNE, Parque Científico Tecnológico de Bizkaia.

30 de mayo de 2018

67. **Mónica García Alloza**
"Diabetes mellitus y enfermedad de Alzheimer: modelos preclínicos e implicaciones translacionales".

Universidad de Cádiz.

8 de junio de 2018

68. **Mahmood Reza Amiry-Moghaddam**
"Pathophysiology of astrocytic loss of polarity: The case of Aquaporin-4 (AQP4)".

Institute of Basic Medical Sciences, University of Oslo.

13 de junio de 2018

69. **Shobha Ghosh**
"Macrophage cholesterol homeostasis: Central to the regulation of inflammation and metabolic diseases".

VCU Medical Center, Richmond.

13 de julio de 2018

70. **Aránzazu Cruz**
"Anti-tumor properties of bacteria-trained lymphocytes".

Centro Nacional de Biotecnología(CNB), CSIC.

19 de septiembre de 2018

71. **Francisco José Iborra**
"Mitochondria: more is different".

Centro Nacional de Biotecnología (CNB-CSIC).

28 de septiembre de 2018

72. **Juan Bernal**
"Thyroid hormone action in brain in the absence of thyroid hormone transporters".

Instituto de Investigaciones Biomédicas "Alberto Sols".

3 de octubre de 2018

73. **Miguel Ángel Formoso Roura**
"Take your research to the next dimension: Cellular Imaging Seminar and Workshop".

Izasa Scientific.

5 de octubre de 2018

74. **Salvador Moncada**
"Inflamación, hiperglucemia y enfermedad vascular".

The University of Manchester.

17 de octubre de 2018

75. **Modesto Redrejo**
"New models and new mechanisms of DNA replication initiation".

Instituto de Investigaciones Biomédicas "Alberto Sols".

24 de octubre de 2018

76. **Manuel Collado**
"Stem cells in cancer and aging".

Instituto de Investigación Sanitaria de Santiago de Compostela (IDIS) & Complejo Hospitalario Universitario de Santiago (CHUS).

26 de octubre de 2018

77. **Patricia Boya**
"Autophagy as a cytoprotective response in neurons during aging and disease".

Centro de Investigaciones Biológicas (CIB), CSIC.

31 de octubre de 2018

78. **María Yáñez-Mó**
"Tetraspaninas, exosomas y SAMHD1. Como ayudar a la cura de enfermedades investigando sobre aspectos básicos en biología celular".

Centro de Biología Molecular Severo Ochoa (CBMSO), UAM.

14 de noviembre de 2018

79. **Elisa Martí**
"A centrosomal view of CNS growth".

Instituto de Biología Molecular de Barcelona (IBMB), CSIC.

23 de noviembre de 2018

80. **Inés Antón**
"Understanding the dual role of WIP as oncogene and tumor suppressor".

Centro Nacional de Biotecnología (CNB-CSIC) & CIBERNED.

28 de noviembre de 2018

81. **Pilar Sánchez Gómez**
"Tumor microenvironment, friend or foe for glioma growth".

Chronicity, Digital Health and Systems (CROSADIS), ISCIII.

12 de diciembre de 2018

2017
2018

TESIS DOCTORALES

1. **Elvira Alonso Medina**
"Inhibición de la ruta del TGFβ por las hormonas tiroideas y sus efectos en fibrosis e inflamación".

Directora:
Ana Aranda Iriarte

13 de enero de 2017

2. **Soledad Bárez López**
"Thyroid hormone homeostasis in the perinatal mouse brain: implications for MCT8 transport defect".

Directores:
Ana Guadaño y Juan Bernal

30 de enero de 2017

3. **Jone Bargiela Iparraguirre**
"Estudio de biomarcadores de pronóstico y respuesta a terapia en Cáncer Gástrico".

Directora:
Isabel Sánchez Pérez

1 de marzo de 2017

4. **Teresa Galera Monge**
"Síndrome de Leigh: Estudio fisiopatológico en neuronas y cardiomiocitos derivados de iPSc".

Director:
Rafael Garesse

21 de abril de 2017

5. **Sara Ayuso Dolado**
"Desarrollo de péptidos neuroprotectores frente a la isquemia cerebral basados en el receptor de glutamato de tipo NMDA y su proteína interaccionante PSD-95".

Directora:
Margarita Díaz-Guerra

27 de abril de 2017

6. **Laura Pintado Berninches**
"Uso de los péptidos GSE24.2 Y GSE4 como posible tratamiento de células de pacientes de Ataxia Telangiectasia".

Directora:
Rosario Perona

11 de mayo de 2011

7. **María Gómez Serrano**
"Aplicación de técnicas proteómicas de alta resolución al estudio de la obesidad y la diabetes tipo 2: análisis de la disfunción mitocondrial en el tejido adiposo humano".

Directora:
Belén Peral Fuentes

23 de mayo de 2017

8. **Yuri Chiodo**
"Cell death, cell growth and cell cycle regulation by the Retinoblastoma family".

Director:
Miguel R. Campanero García

2 de julio de 2017

9. **Javier Rodríguez Centeno**
"Estudio de los telómeros en Dictyostelium discoideum. Desarrollo de un modelo celular de disqueratosis congénita".

Director:
Leandro Sastre

8 de julio de 2017

10. **Alicia de la Cruz Fernández**
"Physiological and pharmacological modulation of Kv7 channels".

Directoras:
Carmen Valenzuela y Teresa González

29 de julio de 2017

11. **Ester García-Casarrubios Pimentel**
"Efectos adversos de la rapamicina en las acciones de la insulina y la norepinefrina en los adipocitos marrones".

Directoras:
Angela M. Valverde y María Jesús Obregón

3 de julio de 2017

12. **Ángela Prieto Folgado**
"Regulación de canales Kv4 por subunidades beta accesorias".

Directoras:
Carmen Valenzuela y Teresa González

10 de julio de 2017

13. **Sandra Muñoz Braceras**
"The role of VPS13 proteinsin autophagy".

Director:
Ricardo Escalante

12 de julio de 2017

14. **Arístides López Márquez**
"Expresión y función de los factores de transcripción FoxE1 y Sox9 en la célula folicular tiroidea.".

Directora:
Pilar Santisteban

14 de julio de 2017

15. **Ania Benítez Sánchez del Campo**
"Intelligent Analysis of Cerebral Magnetic Resonance Images: Extracting Relevant Information from Small Datasets".

Directores:
Manuel Sánchez-Montañés Isla y Sebastián Cerdán García-Esteller.

21 de septiembre de 2017

16. **Ignacio Prieto Arroyo**
"Estudio del Papel de PGC-1α en Senescencia Celular y Transformación Tumoral".

Directora:
María Monsalve Pérez

6 de abril de 2018

17. **Luis Carlos Tábara Rodríguez**
"Role of VMP1 in Membrane trafficking".

Director:
Ricardo Escalante

19 de julio de 2018

18. **Eunice Alejandra Domínguez Martín**
"La respuesta al estrés de retículo endoplásmico en Dictyostelium discoideum".

Directores:
Ricardo Escalante y Roberto Coria

17 de octubre de 2018

19. **Irene Francisco Recuero**
"Papel de la Aurora quinasa B en la regulación epigenética

inducida por el virus de la hepatitis C".

Directores:
Javier García-Samaniego y Aurora Sánchez

25 de octubre de 2018

20. **Adelaida Celaya**

"Bases genéticas y moleculares de la sordera progresiva C".

Directora:
Isabel Varela

12 de noviembre de 2018

Departamentos de Investigación

Introduction

This report summarizes the activities of the Institute of Biomedical Research Alberto Sols (IIBM) during the last two years. The Institute is organized into four departments aimed to tackle relevant problems in biomedicine. They are focused in the study of cell communication, metabolism regulation and its impact in the immune response, as well as in the cancer field and the nervous system associated pathologies. During 2017-18, we elaborated a new strategic plan identifying our strengths, but certainly more importantly, our weaknesses and threats. The IIBM is a research center that integrates professionals and students supported by the Autonomous University of Madrid (from the Department of Biochemistry and Molecular Biology, Faculty of Medicine) and the Spanish National Research Council. This combination of members from both organizations provides a significant capacity to adapt to changing administrative circumstances, in a synergistic way. The IIBM is a member of the Campus of International Excellence UAM+CSIC, which provided support to locate in our Institute the facilities for research, using biomedical imaging.

Regarding our internal structure, one of the topics of discussion from the last years was the necessity to enhance the collaboration between groups of the four departments. This analysis may help to reorganize the research activity, from the present structure of departments and mainly individual groups, to an intermediate level of coordination incorporating these individual groups into larger teams that can add value to this internal collaboration as well as to set common objectives of interest in the immediate years.

In addition to the researchers of the IIBM, I will express the recognition to the administration team, coordinated by Isabel Ocaña, the executive manager of the Institute. I will also recognize the dedication of the personnel in charge of the different scientific core facilities of the Institute that have shown a deep professionalism in their activities, with a positive collaboration spirit with all the researchers, especially the young recruited scientists.

We are also happy for our recent young incorporations to the Institute that have shown a commitment with the Institute, both from the University and from CSIC.

Finally, I would like to express my gratitude and recognition to the Vice-director of the Institute, Dr Aurora Sánchez Pacheco that has contributed greatly to both the cohesion of the groups and the collaboration in the management activities.

1 Biología del Cáncer

2017
2018

1 Biología del Cáncer

Cancer Biology

Malignant tumors develop from normal cells through complex processes with multiple stages. The laboratories of the Cancer Biology Department investigate the genes and molecular mechanisms involved in the initiation, development and progression of malignant tumors. In order to discover new biomarkers for diagnosis, prevention and therapeutic intervention in cancer, it is necessary to identify the molecular alterations by which normal cells acquire the tumor phenotype and the biological principles underlying tumor metastasis. The research conducted in the department has a strong translational vocation, as it is aimed to produce effective treatment and prevention strategies for many different types of cancer, one of the leading causes of death in developed countries.

Our researchers study of the main types of tumors affecting our society, including colon, breast, prostate, pancreatic and lung cancers. In addition, they also investigate key oncogenic processes such as epithelial-mesenchymal transition and angiogenesis. A great deal of effort is also devoted to understanding the molecular mechanisms by which tumor cells develop resistance to anti-tumor drugs with the ultimate aim of developing new, more effective treatments. This research requires a multidisciplinary approach that combines the use of animal models, cellular and molecular biology and computational biology. Lastly, there are numerous scientific collaborations between IIBM researchers and clinical investigators that facilitate the transfer of the basic knowledge generated into clinical practice.

Our department has incorporated new researchers during these past two years (Ricardo Sánchez, María Jesús Larriba, Wolfgang Link, Guillermo de Cárcer and Pilar Santisteban) and, currently, different research groups working on common themes are being structured to optimize coordination between laboratories with the aim of tackling more complex and ambitious projects. Among these research topics are the following:

Vitamin D and colon cancer: Alberto Muñoz, María Jesús Larriba y José Manuel González.

Cell Signaling and Cancer Therapy: Wolfgang Link, Guillermo de Cárcer, Ricardo Sánchez. Borja Belandia.

Tumor microenvironment and metastasis: Amparo Cano, Miguel Quintanilla, Bruno Sainz, Luis del Peso , Benilde Jiménez, Jorge Martín

Molecular Oncology: Gema Moreno, Gemma Domínguez

In the following pages, we describe some of the projects developed in the Cancer Biology Department during the years 2017-18.

2017
2018

Role of cellular signaling in transformation

Investigador Principal
Sánchez Prieto, Ricardo

Co-Investigador Principal
Belandia Gómez, Borja

Investigadores Asociados
Sarabia Ochoa, Ignacia Rosalía.
Universidad Castilla-La Mancha
Romero Macías, Juan Ramón.
Universidad Castilla-La Mancha

Predoctoral
Ortega Muelas, Marta

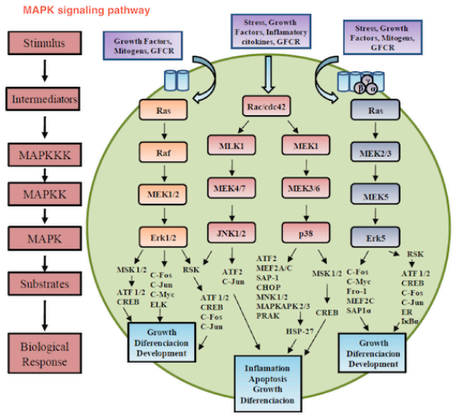
Estudiantes de Master
Tortosa Domenech, Andrea
Muñoz Martínez, Ismael

Investigador Visitante
Roche Losada, Olga.

Keywords: MAPK, AKT, Chemotherapy, Radiotherapy, Kinase Inhibitors, p53.
Palabras clave: MAPK, AKT, Quimioterapia, Radioterapia, Inhibidores de quinasas, p53.

Role of cellular signaling in transformation

Our group is interested in studying how cellular signaling (vg. MAPK, AKT) can affect the process of cellular transformation. To this end, we have developed several lines of research including chemical and genetic approaches applied to in vitro models of cancer cell lines and in vivo mouse models. For example, in the case of MAPK we have been able to uncover the implication of erk1/2 in the process of viral oncogenesis. We are currently focusing on the study of the role of MAPK-dependent signaling in human sarcoma, a poorly studied pathology but with high incidence in childhood. By using an experimental mouse model based on chemical carcinogenesis we expect to clarify MAPK´s role in the development of soft tissue sarcomas.



Role of cellular signaling in cancer therapy

Role of cellular signaling in the response to chemotherapy.
Our study encompasses conventional chemotherapy as well as novel compounds used in targeted therapy, such as Imatinib, Palbociclib or Sorafenib, among others. The main goal is to understand how cellular signaling can affect the response to cancer therapy and its involvement in the development of resistant phenotypes. On this subject, our group has great expertise in the study of how p38 MAPK or ERK1/2 modulate the cellular responses to several antitumor agents including Cisplatin, 5-FU, Sorafenib or Imatinib.

Role of cellular signaling in the response to radiotherapy.

In the case of ionizing radiation, we are focused on elucidating the role of cellular signaling in the development of cancer cell radioresistance. Also, our group has great interest in the role of cellular signaling in the radiosensitizer potential of several chemotherapeutics agents such as 5-FU or Palbociclib. In addition, our laboratory is also studying the interplay between key proteins in DNA damage response (vg. ATM, p53) and cellular signaling.

Role of autophagy in cancer therapy.

Finally, our group is also interested in the role of autophagy in the cellular responses to different antitumor treatments. In this sense, Autophagy has become a key player in the development of chemo and radioresistance. On the other side, Autophagy induction could be an alternative mechanism for treating tumors resistant to apoptotic responses induced by chemo and radiotherapy, suggesting a novel therapeutic potential for the modulation of this interesting biological process.

Publicaciones

Serrano-Oviedo, L., Ortega-Muelas, M., García-Cano, J., Valero, ML., Cimas, FJ., Pascual-Serra, R., Fernandez-Aroca, DM., Roche, O., Ruiz-Hidalgo, MJ., Belandia, B., Giménez-Bachs, JM., Salinas, AS., Sánchez, R. (2018). *Autophagic cell death associated to Sorafenib in renal cell carcinoma is mediated through Akt inhibition in an ERK1/2 independent fashion.* PLoS ONE. 13(7): e0200878.

Meléndez-Rodríguez, F., Roche, O., Sánchez, R., Aragones, J. (2018). *Hypoxia-Inducible Factor 2-Dependent Pathways Driving Von Hippel-Lindau-Deficient Renal Cancer.* Front Oncol. 8: 214.

Salinas-Sánchez, AS., Serrano-Oviedo, L., Nam-Cha, SY., Roche-Losada, O., Sánchez, R., Giménez-Bachs, JM. (2017). *Prognostic Value of the VHL, HIF-1α, and VEGF Signaling Pathway and Associated MAPK (ERK1/2 and ERK5) Pathways in Clear-Cell Renal Cell Carcinoma. A Long-Term Study.* Clin Genitourin Cancer. 15(6): e923-e933.

Cimas, FJ., Callejas-Valera, JL., García-Olmo, DC., Hernández-Losa, J., Melgar-Rojas, P., Ruiz-Hidalgo, MJ., Pascual-Serra, R., Ortega-Muelas, M., Roche, O., Marcos, P., Garcia-Gil, E., Fernandez-Aroca, DM., Ramón Y Cajal, S., Gutkind, JS., Sánchez, R. (2017). *E1a is an exogenous in vivo tumour suppressor.* Cancer Lett. 399: 74-81.

Serrano-Oviedo, L., Giménez-Bachs, JM., Nam-Cha, SY., Cimas, FJ., García-Cano, J., Sánchez, R., Salinas-Sánchez, AS. (2017). *Implication of VHL, ERK5, and HIF-1alpha in clear cell renal cell carcinoma: Molecular basis.* Urol. Oncol. 35(3): 114.e15-114.e22.

Labrousse-Arias, D., Martínez-Alonso, E., Corral-Escariz, M., Bienes-Martínez, R., Berridy, J., Serrano-Oviedo, L., Conde, E., García-Bermejo, M., Giménez-Bachs, JM., Salinas-Sánchez, AS., Sánchez, R., Yao, M., Lasa, M., Calzada, MJ. (2017). *VHL promotes immune response against renal cell carcinoma via NF-κB-dependent regulation of VCAM-1.* J. Cell Biol. 216(3): 835-847.

Cheray, M., Bessette, B., Lacroix, A., Mélin, C., Jawhari, S., Pinet, S., Deluche, E., Clavère, P., Durand, K., Sánchez, R., Jauberteau, M., Battu, S., Lalloué, F. (2017). *KLRC3, a Natural Killer receptor gene, is a key factor involved in glioblastoma tumourigenesis and aggressiveness.* J. Cell. Mol. Med. 21(2): 244-253.

Tesis Doctoral y otros trabajos

Juan Ramón Romero Macías

"Papel de la autofagia en Leucemia Linfatica Crónica B". Universidad de Castilla- La Mancha. Medicina. 2018. Director/es: Ricardo Sánchez . Calificación: Sobresaliente cum laude

Ignacia Rosalía Sarabia Ochoa

"Evaluación de biomarcadores en carcinoma ductal in situ de mama: expresión inmunohistoquímica y correlación clinicopatológica". Universidad de Castilla-La Mancha. Medicina. 2018. Director/es: Ricardo Sánchez . Calificación: Sobresaliente cum laude

Molecular basis of tumorigenesis and vascular pathogenesis

Investigador Principal
Miguel Campanero García

Investigadores Contratados
Sierra Cruz, Marta
Punzón Jiménez, Paula

Predoctorales
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Kourani Méndez, Omar
Martín Cortázar, Carla
Hernández Alcántara, Alberto

Personal de Apoyo
Martínez Nuñez, Patricia

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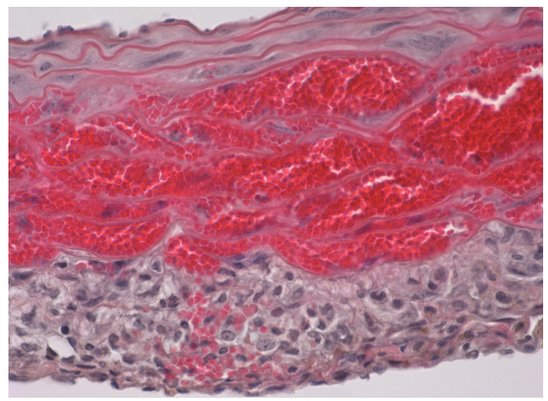
Medina Dome, Gonzalo Antonio. Bioquímica, Universidad Autónoma de Madrid
Fuentenebro Navas, David. Bioquímica, Universidad Autónoma de Madrid
Chica Pineda, Manuela. Tecnológico de Costa Rica

Estudiante de Master
Murzakhmetova -, Sabina. Biomedicina Molecular; Universidad Autónoma de Madrid

Lineas de Investigación

We are interested in uncovering novel mediators of tumorigenesis and cardiovascular pathogenesis, the two major causes of death worldwide, because these mediators might become novel targets for therapeutic intervention. To this end, we use a combination of in vitro and in vivo experimental approaches involving cellular and molecular analysis, mouse models, and advanced imaging techniques.

We had thus uncovered a critical role for E2F1 and E2F4 in Burkitt lymphoma (Cancer Res 2009; Leukemia 2012) and now discovered that members of the MAZ family of transcription factors are essential for the transcriptional induction of the MYB oncogene (Nucleic Acids Res 2017). By using transcriptomics to compare gene expression profiles of lymphoma cells and immortal, but non-tumoral lymphocytes, we have recently identified >1,600 differentially expressed genes. We used a combination of in vivo and in vitro experimental approaches to demonstrate that one of these genes, CDCA7, is essential for lymphoma cell migration and invasion (Haematologica 2019) and for anchorage-independent growth and lymphomagenesis (Haemtatologica 2018). These results therefore urge to evaluate the potential of CDCA7 as a therapeutic target for lymphoid tumors. We are currently assessing the



Microscopic image of an intramural hematoma

contribution of additional differentially expressed genes to lymphomagenesis. We are also investigating the molecular mechanisms underlying anchorage-independent growth of lymphoid tumors, a treat almost exclusive to tumor cells rarely investigated with lymphoid cells.

In collaboration with the group of Dr. J.M. Redondo (CNIC), we also search for genes mediating pathological vascular wall remodeling, a key process in the development of hypertension and arterial diseases such as atherosclerosis and aneurysm. We had determined that calcineurin and its downstream effector Rcan1 are essential mediators of abdominal aorta aneurysm, atherosclerosis, and restenosis (J Exp Med 2011; EMBO Mol Med 2013). Much of our recent effort focused on the identification of novel genes that mediate aortic diseases. Our studies allowed the identification of new pathophysiological mechanisms and new therapeutic targets in aortic diseases.

Using tissue-specific inducible knockout mice, we have uncovered a homeostatic role for Rcan1 in the aorta and that its genetic inactivation in the adult mouse predisposes to hypertension-induced intramural hematoma and subsequent aneurysm through mechanisms involving GSK-3b, ROCK and smooth muscle Myosin (Nat Commun 2018). These results have opened new exciting avenues of research into the pathogenesis of aortic diseases.

Our studies showing that deficiency of the metalloproteinase Adamts1 leads to thoracic aorta aneurysm (TAA) in mice due to increased Nos2-dependent NO production (Nat Med 2017) are particularly pioneering. We also showed that TAA was reversed using pharmacological NOS2 inhibition in mouse models, raising the possibility that blocking NO signaling could be a novel treatment for TAA. Indeed, we are pursuing clinical trials with NOS2 inhibitors in Marfan syndrome, a heritable life-threatening disease in which TAA accounts for over 90% of its mortality. These findings changed our view of the pathophysiology of TAA and prompted us to further explore the molecular and biomechanical mechanisms of TAA and identify additional mediators of these aortic diseases.

Publicaciones

Villahoz, S., Yunes-Leites, PS., Méndez-Barbero, N., Urso, K., Bonzon-Kulichenko, E., Ortega, S., Nistal, JF., Vazquez, J., Offermanns, S., Redondo, JM., Campanero, M. (2018). *Conditional deletion of Rcan1 predisposes to hypertension-mediated intramural hematoma and subsequent aneurysm and aortic rupture.* Nat Commun. 9(1): 4795.

Alfranca, A., Campanero, M., Redondo, JM. (2018). *New Methods for Disease Modeling Using Lentiviral Vectors.* Trends Mol Med. 24(10): 825-837.

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Jiménez, R., Martín, C., Kourani, O., Chiodo, Y., Cordoba, R., Domínguez-Franjo, MP., Redondo, JMM., Iglesias, T., Campanero, M. (2018). *CDCA7 is a critical mediator of lymphomagenesis that selectively regulates anchorage-independent growth.* Haematologica. 103(10): 1669-1678.

Pose, J., García, L., del Puerto, AM., Martín, A., Jurado-Arjona, J., de León, NS., Gamir, A., Sebastián, Á., García-Gallo, M, Kremer, L., Fielitz, J., Ireson, C., Pérez-Álvarez, MJ., Ferrer, I., Hernández, F., Ávila, J., Lasa, M., Campanero, M., Iglesias, T. (2018). *Author Correction: Excitotoxic inactivation of constitutive oxidative stress detoxification pathway in neurons can be rescued by PKD1.* Nat Commun. 9(1): 473.

Pose, J., García, L., del Puerto, AM., Martín, A., Jurado-Arjona, J., de León, NS., Gamir, A., Sebastián, Á., García-Gallo, M, Kremer, L., Fielitz, J., Ireson, C., Pérez-Álvarez, MJ., Ferrer, I., Hernández, F., Ávila, J., Lasa, M., Campanero, M., Iglesias, T. (2017). *Excitotoxic inactivation of constitutive oxidative stress detoxification pathway in neurons can be rescued by PKD1.* Nat Commun. 8(1): 2275.

Álvaro-Blanco, J., Urso, K., Chiodo, Y., Martín, C., Kourani, O., Arco, PG., Rodríguez, M., Calonge, E., Alcamí, J., Redondo, JM., Iglesias, T., Campanero, M. (2017). *MAZ induces MYB expression during the exit from quiescence via the E2F site in the MYB promoter.* Nucleic Acids Res. 45(17): 9960-9975.

Oller, J., Méndez-Barbero, N., Ruiz, EJ., Villahoz, S., Renard, M., Canelas, LI., Briones, AM., Alberca, R., Lozano-Vidal, N., Hurlé, MA., Milewicz, D., Evangelista, A., Salaices, M., Nistal, JF., Jiménez-Borreguero, LJ., De Backer, J., Campanero, M., Redondo, JM. (2017). *Nitric oxide mediates aortic disease in mice deficient in the metalloprotease Adamts1 and in a mouse model of Marfan syndrome.* Nat. Med. 23(2): 200-212 .

Tesis Doctoral y otros trabajos

Yuri Chiodo

"Cell death, cell growth and cell cycle regulation by the Retinoblastoma family.". Universidad Autónoma de Madrid. Facultad de Medicina. 2017. Director/es: Calificación: Sobresaliente Cum Laude. Director/es: Miguel R. Campanero y Juan Miguel Redondo

Jorge Oller Pedrosao

"Identification of the metalloproteinase Adamts1 and Nitric Oxide as new therapeutic targets in aortic diseases". Universidad Autónoma de Madrid. Facultad de Ciencias. 2017. Director/es: Calificación: Sobresaliente Cum Laude. Directores: Miguel R. Campanero y Juan Miguel Redondo

Silvia Villahoz Lázaro

"Effects of conditional deficiency of Rcan1 in pathological vascular wall remodeling (Tesis Europea)". Universidad Autónoma de Madrid. Facultad de Ciencias. 2018. Director/es: Calificación: Sobresaliente Cum Laude. Directores: Miguel R. Campanero y Juan Miguel Redondo

Financiación

"Identificación y evaluación de nuevas dianas terapéuticas en cáncer." Financiado por: Ministerio de Economía y Competitividad. Año 2014-2017

"Regulación de la linfomagénesis, el crecimiento independiente de anclaje y la invasividad de los tumores linfoides por CDCA7." Financiado por: Ministerio de Ciencia, Innovación y Universidades. Año 2018-2020

"Mediadores y mecanismos moleculares de patologías aórticas y valvulares." Financiado por: Comunidad de Madrid. Año 2018-2021

Patentes

"IN VITRO METHOD FOR IDENTIFYING THORACIC AORTIC ANEURYSMS (TAA) IN A SUBJECT." Año 2017

Role of EMT-TFs and Lysyl Oxidase-like 2 and 3 (LOXL2/LOXL3) in tumour progression and metastasis

Investigadora Principal
Amparo Cano García

Co-Investigador Principal
Portillo Pérez, Francisco

Investigadoras Asociadas
Eraso Mazmela, Pilar.
Mazón Calpena, María Jesús
López Menéndez, Celia

Investigador Contratado
González Santamaría, Patricia

Postdoctorales
González Santamaría, Patricia
Majuelos Melguizo, Jara . UAM (hasta marzo 2019)

Predoctorales
Bustos Tauler, José
Vázquez Naharro, Alberto

Personal de Apoyo
Santos Fernández, Vanesa
Yuste Pérez, Lourdes. UAM (hasta diciembre 2018)

Estudiantes de Grado
Spoljaric -, Valentina
Barahona Santervás, Henar
Mínguez Toral, Irene
Estudiante de Master
González Masa, Andrea
Vázquez Naharro, Alberto

Lineas de Investigación

Role of EMT-TFs and Lysyl Oxidase-like 2 and 3 (LOXL2/LOXL3) in tumour progression and metastasis

LOXL2 and LOXL3 proteins belong to the lysyl oxidase family, constituted by lysyl oxidase (LOX) and four lysyl oxidase-like paralogs (LOXL1 to LOXL4). LOX family members are lysine-tyrosylquinone-dependent copper amine oxidases that catalyze the oxidative de-amination of the ε-amino group in certain peptidyl lysine residues promoting covalent cross-linkages. Accumulating evidence indicates the participation of lysyl oxidases in a plethora of biological extra- and intra-cellular functions ranging from extracellular matrix maturation to tumorigenesis and metastasis,. Our previous studies described that intracellular LOXL2 and LOXL3 regulate Snail1 stability and functionality being in the case of LOXL2 independent of its catalytic activity, and further studies indicated that LOXL2 plays also Snail1-independent roles in EMT and cooperates with other EMT-TFs, like E47/TCF3. LOXL2 perinuclear localization is a poor prognosis factor in human squamous cell carcinomas and it is associated to metastatic basal breast carcinomas (BBC). Regarding LOXL3, our studies identified LOXL3 overexpression in a broad cohort of human melanoma samples and an essential role for LOXL3 in melanoma cell survival. Our main research interest focus on a deep understanding of the role of LOXL2 and LOXL3 in tumorigenesis and metastasis, in particular we aim to dissect the contribution of their intra and extracellular functions to initiation and/or progression of breast carcinoma and melanoma, respectively. To this end, we have develop genetically modified mouse models (GEMs) for conditional deletion of Loxl2 and Loxl3, as well as conditional overexpression of

Loxl2 in specific mouse cancer model, as breast and melanoma, together with a broad range of mouse and human tumor-derived cell lines manipulated for Loxl2 or Loxl3 expression. We have also generated and characterized GEM with conditional deletion of E2A gene (coding for E47/E12 EMT-TF) in the context of PyMT breast cancer.

During the last two years (2017 and 2018), the main objectives addressed are summarized as:

1. Characterization of LOXL2 action in breast tumors. In vivo and in vitro studies have allowed identify the prominent action of Loxl2 in lung breast cancer metastasis. Mechanistically, Loxl2 induces invasion by regulating Snail1 stability and favors the generation of the lung pre-metastatic niche.

2. Characterization of LOXL3 action in melanoma. In vitro analyses in human melanoma cell lines identified LOXL3 pro-survival action mediated by regulation of DNA repair and mitotic exit contributing to maintain the high genetic instability of melanoma. Further studies on GEM of melanoma support a role for Loxl3 in melanoma initiation and lymph node metastatic dissemination

3. Characterization of E47/E12 action in breast cancer initiation and metastasis. The GEM of E2A KO gene in the PyMT breast cancer model has provided strong evidence for the participation of E47 EMT-TF in breast cancer initiation and lung metastasis. At least, some of the E47 actions are mediated by functional interaction with Snail1 as well as with Loxl2.

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Financiación

"Contribution of LOXL3 to melanomagenesis." Financiado por: Worldwide Cancer Research (UK). Año 2016-2018

"Contribution of LOXL2 and LOXL3 to tumour progression and metastasis ." Financiado por: Subdirección General de Investigación. Ministerio de Economía y Competititvidad. Año 2017-2019

"Consorcio Ciber. Area temática de cáncer (CIBERONC)." Financiado por: Fondo de Investigaciones Sanitarias (FIS). Instituto de Salud Carlos III. Año 2017-202

Premios

"Premio Internacional de Investigación Oncológica Ramiro Carregal. VII Edición." Año 2018

"Premio Honorífico a la mejor trayectoria investigadora. IdiPAZ ." Año 2017

"Tercer premio. Revisiones mas citadas publicadas ultimos 5 años. IdiPAZ." Año 2018

Cell cycle and cancer biomarkers

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Key words: Cancer, oncology biomarkers, kinases, cell cycle, mitosis, kinases, genetic mouse models, cancer, Therapy, drugs.
Palabras clave: Cáncer, biomarcadores oncológicos, quinasas, mitosis, ciclo celular, terapia oncologica, farmacos.

Lineas de Investigación

El cáncer no es una sola enfermedad, sino más de 200 diferentes. El incremento en el conocimiento de los mecanismos geneticos del cáncer nos ha permitido llegar a nuevas estrategias clínicas y acercarnos al concepto de "medicina personalizada" dependiendo de cada paciente.

La desregulación del ciclo celular es una característica común en procesos tumorales. Las células tumorales anulan los mecanismos de control del ciclo celular resultando en la acumulación de aberraciones genéticas. La manipulación de estos mecanismos de control ofrece nuevas vías para el diseño de estrategias terapéuticas contra el cáncer. En la actualidad hay varias estrategias terapéuticas que están dirigidas a inhibir el ciclo celular. La mayoría de los esfuerzos se han dirigido contra quinasas del ciclo celular, como las quinasas dependientes de ciclinas (CDKs) y quinasas mitóticas (Auroras, Plk1, etc.) En la actualidad hay aproximadamente 14 moléculas en ensayos clínicos. Las de primera generación son a menudo inhibidores pan-CDK (Flavopiridol) y las nuevas tienden a centrarse en CDK específicos (Palbociclib y Abemaciclib contra CDK4/6). Esta tendencia a concentrarse en una quinasa específica también puede observarse para las quinasas Aurora, donde la mayoría de los ensayos clínicos se han enfocado en los inhibidores selectivos para Aurora A (Alisertib y Danusertib) en comparación con Aurora B (Barasertib). Más recientemente, están apareciendo inhibidores específicos de la quinasa Plk1 (Volasertib y Rigosertib). En la actualidad hay más de un centenar de ensayos clínicos activos con estas drogas en un amplio espectro de cánceres humanos, y los datos disponibles sugieren que los inhibidores de ciclo celular pueden tener efecto terapéutico en algunos tipos de tumores. Aunque los mecanismos moleculares de estas quinasas son bien conocidos, algunos de los nuevos fármacos específicos de mitosis no ven traducida su eficacia preclínica a la respuesta clínica en ensayos con seres humanos. Una explicación a esto, es el hecho de que los tumores son muy heterogéneos en su origen genético, y los ensayos preclínicos no se centran en el perfil genético de los tumores.

Por lo tanto, poder definir mecanismos de sensibilidad y resistencia a estos inhibidores de nueva generación puede ayudar a determinar las estrategias terapéuticas específicas para cada inhibidor. El objetivo del laboratorio CCCB es usar las últimas tecnologías de editado genético para poder definir cuáles son los posibles mecanismos genéticos de resistencia y sensibilidad a las nuevas drogas específicas para el ciclo celular, específicamente en células tumorales de mama. Nuestra intención es definir biomarcadores terapéuticos que ayuden a saber qué pacientes pueden o no beneficiarse de un tratamiento en concreto, de tal forma que podamos avanzar en establecer nuevos tratamientos de "medicina personalizada".

Financiación

"Dentificación De Nuevos Biomarcadores Para Cancer De Mama: Mecanismos De Sensibilidad Y Resistencia A Drogas De Ciclo Celuar". Financiado Por: Fundacion De La Asociacion Española Contra El Cancer -Aecc. Año 2017-2020

"Identificación De Los Mecanismos Oncogénicos Asociados A La Quinasa Mitótica Plk1.." Financiado Por: Consejo Superior De Investigaciones Cientificas. Año 2018-2019

"Identificacion De Los Mecanismos Oncogenicos Asociados A La Quinasa Mitotica Plk1.." Financiado Por: Ministerio De Ciencia, Investigación Y Universidades (Mciyu). Año 2019-2021

Bioinformatics and computational biology

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Keywords: statistics, computational biology, bioinformatics, evolution, ecology, cancer, cancer progression models, computer simulation.
Palabras clave: estadística, biología computacional, bioinformática, evolución, ecología, cáncer, modelos de progresión del cáncer, simulación por computadora.

Lineas de Investigación

Our main research area is bioinformatics, computational biology, computational statistics and evolutonary biology applied to the analysis of "high-throughput" data, mainly in cancer. Part of our work ranges from the application of standard techniques to the development of new statistical approaches, with special emphasis in their implementation using high performance computing. Our main current work focuses on trying to understand the sequence of driver genetic events and predict tumor evolution using methods that take ideas from phylogenetic methods and probabilistic graphical models which has also led us to develop software for simulating clonal evolution processes. This area is actually our main major focus: cancer progression models and evolutionary models of cancer (applying ecology and evolutionary biology to cancer).

Publicaciones

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Financiación

"Identificacion de restricciones en el orden de acumulacion de mutaciones durante la progresion tumoral: metodos de inferencia y software de simulacion." Financiado por: MINECO. Año 2015-2019

Hypoxia and angiogenesis

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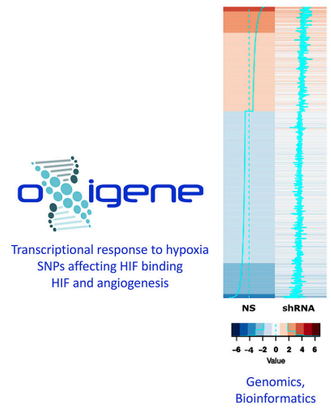
Keywords: Hypoxia, Angiogenesis, Genomics, Bioinformatics.
Palabras clave: hipoxia, angiogénesis, genómica, bioinformática.

The elucidation of the cellular and molecular responses to hypoxia constitutes an important research topic due to the relevance of this process in cellular physiology and high-incidence pathologies such as cancer and cardiovascular diseases. The Hypoxia Inducible Transcription Factor (HIF) plays a pivotal role in this response by controlling the expression of most of the genes involved in adaptation to hypoxia. The aim of our group is to contribute to the understanding of the transcriptional response to hypoxia and the cellular and molecular mechanisms underlying central adaptation responses like angiogenesis. Our long term goal is to exploit this knowledge to improve clinical management of pathologies in which development of tissue hypoxia is a common feature.

Characterization of the transcriptional response to hypoxia

Ablation of HIF prevents both gene upregulation and repression triggered by hypoxia. However, genome-wide profiling of HIF-binding sites indicates that only gene induction is directly regulated by HIF. To identify the mechanisms responsible for gene repression during hypoxia, we developed a computational approach that, exploiting the vast amount of publicly available ChIP-seq datasets, identified enriched transcriptional regulators. This approach revealed that several subunits of the SIN3A corepressor complex had a significant association to hypoxia-repressed genes. (Tiana et al., Nucleic Acids Res. 2018).



Identification of polymorphisms affecting HIF binding sites and their contribution to disease inter-individual variability

The vast majority of human genetic variation lies in non-coding regions of the genome, but its functional impact in phenotype and disease is almost unknown. We have described that several common SNPs affect the transcriptional response to hypoxia (Ortiz-Barahona et al., Nucleic Acids Res. 2010 and Roche et al., Nucleic Acids Res. 2016). However, a global analysis of comon genetic variability on the response to hypoxia is still lacking. Aiming to fill this gap, we designed an unbiased approach to identify SNPs having a functional impact on HIF binding to chromatin. Using this strategy we have identified over 300 variants conferring allele-specific binding, most of them outside HREs.

Understanding the role of HIFs in endothelial cells during angiogenesis induced by hypoxia

Angiogenesis is the main mechanism of vascular remodeling and a fundamental adaptive response to hypoxia in physiology and disease. Cancer relies on chronic activation of angiogenesis to support unlimited growth and dissemination; therefore halting this process could allow for new therapeutic developments for cancer patients. The role of Hypoxia Inducible Factors (HIFs) in the control of angiogenesis is still incomplete. Our group has revealed that hypoxia imposes an anti-proliferative gene expression signature in endothelial cells. Using angiogenesis models based on the differentiation of embryoid bodies generated from murine stem cells and loss/gain of function genetic approaches for HIFs we are currently elucidating the molecular mechanism involved and its role in the induction of angiogenesis by hypoxia. Our long term goal is to exploit this knowledge to identify molecular targets for the inhibition of hypoxia driven angiogenesis in cancer.

Publicaciones

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Financiación

"Genomic, Bioinformatic and Functional study of the role of hypoxia in angiogenesis and von Hippel-Lindau síndrome." Financiado por: Ministerio de Ciencia e Innovación. Año 2014-2017

"Hypoxia and angiogenesis: basic mechsnisms in physiology ad disease." Financiado por: Ministerio de Ciencia, Innovación y Universidad . Año 2017-2020

Cancer Signalling and Therapy

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Lineas de Investigación

The focus of our research has been the PI3K/AKT/FOXO signaling which is considered as the most frequently activated pathway in cancer. FOXO is the major transcriptional effector of this signaling pathway and inactivated in many tumours[1]. FOXO3a is the second most replicated gene associated with extreme human longevity (Figure1)[2].

Figure 1. *The key components of the PI3K signal transduction pathway are we conserved throughout evolution. It is important to note, that there is a single gen for many components, in Hydra, C. elegans and D. melanogaster whereas mammals have several isoforms of these components with the exception of PTEN Figure adapted from [2].*

FOXO activating compounds

Our Team is unique in the world because we have a collection of over 300 previously identified FOXO activator molecules[3,4]. Among these compounds are several kinase inhibitors[1,4,5], nuclear export inhibitors[4,5,6,7]and orphan natural products[8]. These molecules have great potential to be developed as drugs against cancer and aging.

Mechanisms of therapy resistance

Resistance to therapy is the fundamental reason for treatment failure and represents the major barrier to improve survival of cancer patients. Understanding how cancer cells manage to escape treatment is essential to develop therapies that block escape routes. A major breakthrough has been accomplished with the discovery of the FOXO repressor protein TRIB2 as a novel oncogene in melanoma[9]. TRIB2 is overexpressed in melanoma and correlate with poor response to treatment[10]. Our research group has discovered a novel, clinically relevant TRIB2-mediated mechanism of drug resistance. Therapy resistance is mediated by direct interaction of TRIB2 with AKT. TRIB2/AKT-interaction promotes AKT activation resulting in FOXO inhibition and p53degradation[11]. As a consequence, the expression of FOXO and p53 target genes which lead to drug-induced

apoptosis, is attenuated by TRIB2 (Figure2). We plan to translate our results into clinically useful tools, namely TRIB2 inhibitors to overcome therapy resistance and TRIB2-based biomarkers to predict treatment response and therefore to stratify patients into responders and non-responders.

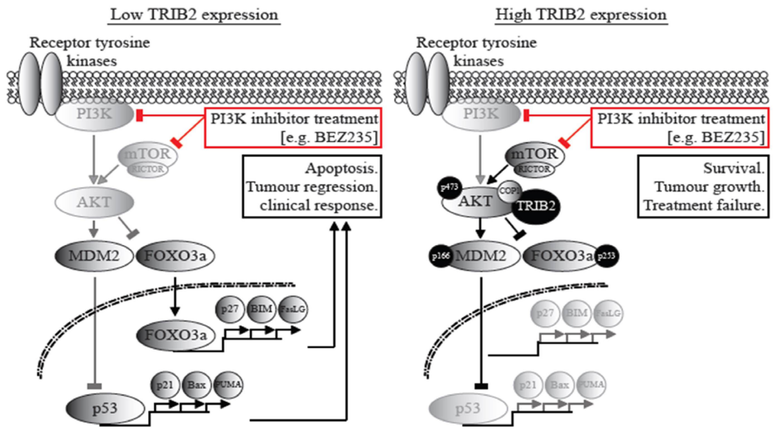

Figure 2. *Cell model of TRIB2-mediated drug resistance adapted from [11]. TRIB2-mediated AKT activation leads to the inactivation of FOXO and p53, well-known tumour suppressors, and effectors of anti-cancer drug action*

Private appropriation of publicly financed research

The way new medicines are discovered has changed dramatically over the past few decades[12]. Modern drug development relies on the molecular understanding of the disease which is often the result of decades of publicly financed research (Figure3).

In an environment of shrinking science funding and increasing knowledge-dependence of drug discovery, private appropriation of publicly financed research without efficient return mechanisms threatens the pace of discovery and generation of future medicines[13]. In addition, novel therapeutic options including targeted therapy and immunotherapy are extremely expensive and broad access to them won´t be sustainable for the public health care systems within the near future in many countries. We are collaborating with economists to measure the contribution of public funding to innovative drugs.

Figure 3. *Flow chart of past and present drug discovery and development process. In the past, a drug was found before its molecular target was identified. Modern drug discovery is based on the molecular understanding of the disease and starts out with a validated molecular target. Figure adapted from [12].*

Publicaciones

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Src Family of Kinases and Breast Cancer: The functional role of Src kinases in breast cancer: contribution of the adapter and catalytic domains

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Lineas de Investigación

The proto-oncogene c-Src, the prototype of the Src Family of non-receptor tyrosine kinases (SFKs), contains three major functional domains, the adapters SH2 and SH3, and the catalytic domains, which in turns determine the cellular role of c-Src. Its expression and/or its kinase activity is increased in a variety of tumors, including breast cancer. This proto-oncogene is associated with and activated by, receptors for growth factors and cytokine, which are relevant in human breast cancer. Thus, the goal of this project is to define the relevance of the SH2, SH3 and catalytic functional domains in metastatic human breast cancer. To this end, we are analyzing the conditional expression (Tet-On System) of c-Src variants with point-mutations that inactivate each of these three mayor domains in human metastatic breast cancer cell lines MDA-MB-231 or SUM159PT. We have evaluated them for their effects in cellular functionality by testing for proliferation, migration, invasion, anchorage-independent growth, the capability to generate mammospheres, exosomal production, etc. Several scientific pieces of evidence show that c-Src is associated with the composition and functionality of exosome, suggesting its possible role in intercellular communication. In cancer, exosomes can facilitate the pre-metastatic niche where circulating tumor cells will finally nest. We have previously shown that c-Src can modulate the expression of certain proteins in exosomes. In addition, c-Src can facilitate the production and secretion of exosomes. The question raised as to whether the adapter domains of c-Src will modulate the number of exosomes, their composition, and consequently, the pre-metastatic niche of the triple negative breast cancer cells.

Presently, c-Src catalytic inhibitors are used in clinical oncology, if the c-Src adapter SH2 and/or SH3 domains are also crucial for metastatic breast cancer, the generation of inhibitors for the SH2 and/or SH3 could be employed in combination with those for the catalytic to completely block c-Src functionality in metastatic breast cancer. Moreover, since c-Src is also involved in other metastatic tumors such as colorectal, prostatic, and pancreatic, the results obtained in this study could eventually be extrapolated to other human cancers.

Publicaciones

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Financiación

"Role of the SH2 and SH3 adapter domains of c-Src in breast cancer metastasis ."
Financiado por: MINECO. Año 2016-2019

Translational research in breast cancer and gynecological cancer (ovarian and endometrial cancer)

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Investigadore Visitante
Cordani -, Marco

Key words: breast and gynecological cancer, prognosis, molecular classification, immunotherapy, targeted therapies.
Palabras clave: cáncer de mama y ginecológico, pronóstico, clasificación molecular, inmunoterapia, terapias dirigidas.

Lineas de Investigación

During the last years, the main objective of the group has been the study of the mechanisms underlying tumor progression and metastasis together with the identification of new targets related to the response to treatment, using an approach based on pharmacogenomics and methods of analysis. mass, gene expression profiles and high-performance sequencing techniques.

Our group has deepened in the study of the molecular mechanisms of the Mesenchymal Epithelium Transition (TEM) as crucial events in tumor progression. Specifically, we have focused on the analysis of basal phenotype breast tumors as well as endometrial carcinomas and high grade ovarian serous.

Another line of research of the group has focused on advancing the molecular mechanisms that lead to failures. On the other hand, from a clinical point of view one of the failures in the treatment in breast cancer is the innate or acquired chemoresistance that patients develop. Studies carried out in the laboratory have revealed the existence of possible markers involved in resistance to Trastuzumab. In this line of work, new markers are searched with predictive and prognostic capacity, markers of alternative therapies in ovarian cancer and endometrial carcinomas.

The concrete objectives are:

a) Analysis of the gene expression profile in tumor and cell samples, related to TEM processes.

b) Identification of breast carcinomas of basal phenotype and/or carcinosarcomas as candidates to undergo TEM processes.

c) Identification of tumor markers in breast and gynecological cancer through high-throughput mass sequencing.

d) Pharmacogenomic study in breast cancer. Identification of drug resistance mechanisms.

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Tesis Doctoral y otros trabajos

Alba Mota Jiménez

"DECIPHERING INTRATUMOR MOLECULAR HETEROGENEITY IN GYNECOLOGICAL CANCER PROGRESSION". Universidad Autónoma de Madrid. Facultad de Medicina. 2017. Director/es: Gema Moreno. Calificación: Sobresaliente Cum Laude

Ángela Molina Crespo

"ANÁLISIS DE GASDERMINA B COMO MARCADOR DE RESPUESTA A TRATAMIENTO Y NUEVA DIANA TERAPÉUTICA EN TUMORES HER2+". Universidad Autónoma de Madrid. Facultad de Medicina. 2017. Director/es: Gema Moreno, José David Sarrió. Calificación: Sobresaliente Cum Laude

Financiación

"Gasdermina B: mediador de respuesta inflamatoria y terapéutica en cáncer de mama y digestivo. Referencia: PI16/00134. IP: Gema Moreno Bueno." Financiado por: Instituto de Salud Carlos III. Año 2017-2019

"Consorcio CIBERONC. Área Cáncer de mama. Referencia: CB16/12/00295. IP: Amparo Cano García; Co-IP: Gema Moreno Bueno." Financiado por: Instituto de Salud Carlos III. Año 2017-2019

Cáncer de colon y vitamina D

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Investigadore Visitante
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Keywords: Colon cancer, organoids, stromal fibroblasts, vitamin D, Wnt
Palabras clave: Cáncer de colon, organoides, fibroblastos estromales, vitamina D, Wnt

Lineas de Investigación

Colon/colorectal cancer (CRC) is a leading neoplasia worldwide in terms of incidence and mortality. In Spain, CRC is the most frequent cancer both genders considered. Many epidemiological studies associate vitamin D deficiency with high risk and poor prognosis of CRC. In the last two decades, our group and others have shown that the active vitamin D metabolite 1alpha,25-dihydroxyvitamin D3 (calcitriol) inhibits proliferation, promotes differentiation and attenuates the invasive and proangiogenic phenotype of colon carcinoma cells. We were first to report that part of these effects was due to the antagonism of the Wnt/beta-catenin signaling pathway whose abnormal activation is an initial and crucial event in CRC.

Today it is well accepted that tumor microenvironment or stroma plays a crucial role in colon tumorigenesis. Fibroblasts are the major cellular component of tumor stroma. Recently, we have described that calcitriol exerts its antitumor action in CRC not only by acting on carcinoma cells but also through the inhibition of the protumoral capacities of cancer-associated fibroblasts (CAFs). Thus, high expression of vitamin D receptor (VDR) and of a calcitriol-associated gene signature in tumor stromal fibroblasts is significantly associated with longer patient survival. These findings have a clear clinical impact as indicate that the therapeutic action of calcitriol can extend to CRC patients who express VDR in CAFs even in the absence of VDR expression in carcinoma cells, which occurs in a relevant percentage of patients.

Based on these data, we have studied the effects of calcitriol and the canonical Wnt3A factor, alone and in combination, on CCD-18Co human colon myofibroblasts. Our data show that calcitriol and Wnt3A have additive and partially overlapping modulatory effects on gene expression and phenotype of colon fibroblasts. Both agents inhibit fibroblast proliferation and migration, while calcitriol reduces but Wnt3A increases their "activated" phenotype.

Organoids are a novel technology of three-dimensional culture of stem cells (adult/aSC, induced/iPSC, pluripotent/PSC or cancer stem cells/CSC) and their progeny that allows the generation of structures resembling the organ they derive from and, thus, reproduces the in vivo situation better than classical two-dimensional cell cultures. We have established

a living biobank of colon normal and tumor organoids from surgical biopsies of CRC patients. In these organoids we are studying the effects of calcitriol on cell gene expression, proliferation and phenotype. In addition, we are optimizing an assay to test the activity of antitumor drugs against CRC in these patient-derived organoids. Finally, we are also establishing a living biobank of normal and tumor rectum tissue from endoscopic biopsies to compare: a) normal colon and normal rectum stem cells, b) tumor colon and tumor rectal stem cells, and c) their respective response to calcitriol.

Our group collaborates with numerous colleagues from different scientific institutions: Drs. Prieto, Cantero, Burgos and Guerra (Hospital Universitario La Paz), García-Olmo and Rojo (Fundación Jiménez Díaz), Peña (Hospital Universitario Ramón y Cajal), Rojas (ISCIII), del Peso and Delgado (our Institute).

Publicaciones

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Financiación

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"Estudio de la posible acción protectora de la vitamina D en pacientes con cáncer de colon tratados con quimioterapia." Alberto Muñoz Terol. Financiado por: Grupo Farmasierra, S.L.. Año 2017-2018

"Efectos de la vitamina D sobre el microentorno tumoral en cáncer de colon." María Jesús Larriba Muñoz. Financiado por: Consejo Superior de Investigaciones Científicas. Año 2018-2019

"Red Temática de Investigación Cooperativa en Cáncer (RTICC)." Alberto Muñoz Terol. Financiado por: Instituto de Salud Carlos III. Año 2013-2017

"CIBER de Cáncer (CIBERONC)." Alberto Muñoz Terol. Financiado por: Instituto de Salud Carlos III. Año 2017-2019

"Red Temática de Receptores Nucleares en Cáncer, Metabolismo e Inflamación (NURCAMEIN)." Alberto Muñoz Terol. Financiado por: Ministerio de Economía y Competitividad. Año 2016-2017

"Red Temática de Receptores Nucleares en Cáncer, Metabolismo e Inflamación (NURCAMEIN 2)." Alberto Muñoz Terol. Financiado por: Ministerio de Economía y Competitividad. Año 2018-2019

Cell senescence in physiology and disease

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Lineas de Investigación

SIX1 and senescence in cancer

We have recently shown that the SIX1 homeoprotein is an essential repressor of cellular senescence, mainly via the regulation of the senescence effector p16INK4A (Adrados et al, Oncogene, 2016. PMID 26500063). SIX1 is also an oncogene, frequently activated in different types of human tumors such as lung and brain cancer or sarcomas. We have explored the role of senescence in the protumorigenic role of SIX1, studying mouse fibrosarcoma tumors derived from transformed fibroblasts. Our results show that SIX1 has a protumorigenic effect in this model, which is accompanied by the blunting of the expression signature associated to SIX1 in senescence. This is consistent with the role of cell senescence as a tumor barrier and suggests that opposing senescence plays a role in the oncogenic role of SIX1. These studies have also shown that SIX1 promotes an undifferentiated phenotype in these tumors, mainly mediated by the transcrptional activation of the stemness regulator SOX2. Our results have identified new mechanisms that may underpin the oncogenic role of SIX1: blocking the tumor suppressive action of senescence and promoting stem-cell features via SOX2 (De Lope et al, Scientific Reports, 2019. PMID 30723235).

SIX1 and senescence in development

Developmental senescence is a form of programmed, physiological senescence that occurs transiently in specific embryo locations and contributes to patterning during embryonic development. SIX1 is a key transcriptional regulator of development, essential for the formation of organs such as inner ear, kidney, muscle and thymus, among others. Interestingly, alterations in the SIX/EYA pathway are linked to the Branquio-Oto-Renal (BOR) syndrome, a human rare congenital disorder with defects in the ear and kidney and branchial arch anomalies. Based on our recent finding that SIX1 is a senescence regulator, we are currently testing the hypothesis that aberrant activation of senescence can underpin the developmental defects associated with SIX1 deficiency in mice and humans.

Senescence and cell plasticity

One of our interests is to understand the link between cell senescence and plasticity. Emerging evidence has uncovered a complex connection between senescence, differentiation and regeneration in different contexts, with examples of both inhibitory and activating effects of senescence. In this context, our recent results have identified a gene signature related

to differentiation in cellular models of senescence triggered either by oncogenic stress or SIX1 loss (Adrados et al, Oncogene, 2016. PMID 26500063). To investigate further this link, we are currently exploring the impact of senescence on the potential of primary fibroblasts to transdifferentiate to different cell types. We hope that this work will shed light on the connection between cell senescence and differentiation.

Financiación

"Senescencia celular: Mecanismos de regulación y conexión con plasticidad celular." Financiado por: MINECO. Año 2016-2018

"Red Temática de Excelencia "Senescencia celular: de mecanismos a terapias". Financiado por: MINECO. Año 2017-2019

Carcinogénesis epitelial

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Lineas de Investigación

Relevance of podoplanin-CD44 interaction for invasiveness of squamous cell carcinomas (SCCs)

Podoplanin (PDPN) is a small mucin-like transmembrane glycoprotein that plays a crucial role in malignant progression of carcinomas. We have found that:

1. Podoplanin is a component of ventral membrane protrusions with proteolytic activity called invadopodia, which are involved in tumor cell invasion and metastasis.

2. It promotes invadopodium stability and an efficient degradation of the extracellular matrix.

3. It interacts with the standard isoform of the hyaluronan receptor, CD44s, on the surface of SCC cells in order to stimulate directional migration. CD44 is also an integral component of invadopodia, and its transcription is regulated by alternative splicing giving rise to different variable (CD44v) isoforms in addition to CD44s.

We have characterized the expression of CD44 isoforms in human and mice SCC cell lines, and found that all CD44v isoforms expressed in these cells interact with podoplanin. Podoplanin co-localizes with CD44s and CD44v in the adhesion ring of invadopodia.

Knockdown and rescue experiments point to an important role of podoplanin-CD44 association for invadopodia-mediated invasion through the basement membrane. Both molecules cooperate to promote invesion, but differ in their specific contribution.

Involvement of podoplanin in epidermal homeostasis and carcinogenesis

The epidermis is a self-renewing stratified epithelium that forms the outer barrier of the skin. It is maintained by stem cells (ESCs) located in different compartments, including the hair follicle (HF) and the interfollicular epidermis (IFE). Podoplanin is absent from the normal adult epidermis, but its expression is induced in epidermal keratinocytes of the basal layer and outer root sheet (ORS) of HFs during wound healing, psoriasis, and after a pro-inflammatory stimulus with TPA.

We have developed three conditional podoplanin knockout mouse models in the epidermis: one constitutive (K5Cre. PDPN), and two inducible (K14Cre-ERT2.PDPN and K15Cre-PR1.PDPN), in which silencing of podoplanin occurs either in the basal layer of IFE and ORS of HFs or in the HF bulge region, where a key population of ESCs reside.

Preliminary studies suggest a role for podoplanin in the maintenance of epidermal architecture and terminal differentiation in conditions of hyperproliferation, and its involvement in the hair growth cycle. Furthermore, podoplanin silencing in the epidermis reduces tumor incidence and burden after chemical carcinogenesis.

Role of the non-classical MHC-I complex Qa-2 in malignancy of breast carcinoma cells

Qa-2 was proposed as the murine homolog of the human non-classical major histocompatibility complex (MHC), or MHC class 1b, HLA-G, which are involved in immunosurveillance during embryogenesis and cancer.

Nevertheless, while both HLA-G and Qa-2 appear to be involved in immune tolerance during pregnancy, our studies in vitro and in vivo on 4T1-induced mouse mammary carcinomas in a syngeneic host suggest that they play opposite roles in cancer.

Qa-2 acts as a tumor suppressor, attenuating epithelial-mesenchymal transition and inhibiting tumor-initiating, invasive, and metastatic capabilities of tumor cells.

In contrast, HLA-G has been found by other authors to promote tumor progression.

Tesis Doctoral y otros trabajos

Istéfani Luciene Dayse da Silva null

"Expressão de Qa-2 e sua relação com o infiltrado linfocítico e a diferenciação celular em dois modelos murinos de adenocarcinoma mamário". Universidad Federal de Minas Gerais, Belo Horizonte (Brasil). Medicina. 2017. Director/es: Miguel Quintanilla . Calificación: Aprobado por unanimidad (máxima)

Financiación

"Role of the cell-surface glycoproteins podoplanin and endoglin in skin homeostasis and carcinogenesis." Financiado por: MINECO. Año 2014-2017

"A role of podoplanin in malignant progression of epithelial cancer. Relevance of podoplanin-CD44 interaction." Financiado por: Ministerio de Ciencia, Innovación y Universidades. Año 2018-2020

Cancer stem cells and Tumor microenvironment

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Palabras clave: Células madre de cáncer, Cáncer de páncreas, Microambiente Tumoral

Lineas de Investigación

Cancer stem cells (CSCs), also known as tumor-initiating cells or tumor-propagating cells, constitute a biologically unique subset of stem-like cells within the bulk tumor cell population. These cells are believed to be important in metastasis and chemoresistance, and they are hypothesized to be key drivers of the multistep process of oncogenesis, giving rise to the clonogenic core of tumor tissues. In my laboratory, we study CSCs in the context of pancreatic ductal adenocarcinoma (PDAC), the 4th leading cause of cancer related deaths in developed countries. I am running a combined basic and translation research program, which synergistically combines studies on the biology of mouse and human CSCs, including their in vivo microenvironment, in order to enhance our understanding of the regulatory machinery of CSCs. Specifically, the avenues of research that my laboratory is pursuing are:

1) The identification and characterization of new biomarkers for the detection of CSCs from different solid tumors. We have recently discovered a new inherent biomarker present in CSCs across several solid tumors. This biomarker, known as autofluorescence, is the result of riboflavin accumulation in ABCG2-coated intracellular vesicles exclusively found in CSCs. We are currently using autofluorescence as a means of isolating CSCs for in depth biological and molecular characterization studies.

2) The identification of proteins that govern key CSC phenotypes, such as stemness", epithelial to mesenchymal transition (EMT), oxidative phosphorylation (i.e. mitochondrial respiration) and chemoresistance. We have discovered that the Interferon Stimulated Gene 15 (ISG15) is not only up-regulated in CSCs, but its function as a Ubiquitin-like modifier is necessary for many CSCs biological processes.

3) Comprehensively understand the cellular make-up of the CSC niche and the larger more complex tumor microenvironment, specifically the role of tumor-associated macrophages (TAMs) in "activating" CSCs, with respect to the different environmental proteins they can secrete in response to cues from the tumor and how these proteins alter the function of the CSCs at the level of EMT and chemoresistance.

Publicaciones

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Tesis Doctoral y otros trabajos

Laura Lerma Martínez

"Expresión de la proteína IE180 del virus de la Pseudorrabia bajo de control de promotores tumorales humanos (hTERT y CEA): Implicación en la inducción de apoptosis". Universidad Autónoma de Madrid. Ciencias. 2018. Director/es: Bruno Sainz . Calificación: Cum Laude

Financiación

"Dotación Ramón y Cajal." Financiado por: ISCIII & Ministerio de Economía y Competividad. Año 2014-2019

"Role of the innate immune system in promoting cancer stem cells." Financiado por: Cancer Research Institute (CRI). Año 2014-2017

"Development of a liquid biopsy assay to isolate circulating cancer stem cells in the blood for their characterization and validation as a biomarker for early detection of pancreatic cancer." Financiado por: ISCIII & Ministerio de Economía y Competividad. Año 2015-2019

"Citotoxicidad de Compuestos Anti-tumorales en ratones." Financiado por: VALORALIA I MAS D SL. Año 2016-2017

"Targeting mitochondrial respiration, an Achilles' heel of cancer stem cells." Financiado por: Concern Foundation. Año 2016-2019

"A multi-faceted approach to treating pancreatic cancer (Grupos Coordinados Estables 2016)." Financiado por: Asociación Española Contra el Cáncer (AECC). Año 2016-2021

"Identifying pancreatic cancer stem cell immune escape receptors." Financiado por: Asociación Cáncer de Páncreas (ACANPAN). Año 2017-2020

"The basal subtype of pancreatic cancer as a new tool towards personalized medicine: cellular and molecular characterization for the development of new therapies." Financiado por: ISCII & Ministerio de Ciencia, Innovación y Universidades. Año 2019-2022

"Photoactivable nanoparticles to immunostimulate the tumour microenvironment in pancreatic cancer (PANIPAC)." Financiado por: ISCII & Ministerio de Ciencia, Innovación y Universidades. Año 2019-2022

"Combating Pancreatic Cancer by Identifying Those Genes Essential for Cancer Stem Cell-Mediated Tumorigenicity." Financiado por: Fundación Fero. Año 2019-2021

"Direccionamiento selectivo y eliminación de células madre cancerosas con complejos sinteticos de polipiridil de rutenio." Financiado por: Universidad de Santiago de Compostela y Universidad Autónoma de Madrid. Año 2019-2021

Patentes

"Complejos de Rutenio para el tratamiento del cancer." Año 2017

2 Fisiopatología Endocrina y del Sistema Nervioso

2017
2018

2 Fisiopatología Endocrina y del Sistema Nervioso

Endocrine and Nervous System Pathophysiology

The research carried out by the Department of Endocrine and Nervous Systems Pathophysiology focuses on the study of these two key systems which control a great number of physiological processes and that will very often act together to regulate animal physiology.

To study how these systems operates in physiological as well as in pathological conditions, its research groups apply multidisciplinary research from molecules and cells to whole organisms providing the right expertise needed for both fundamental and translational research through the following specific research topics:

- thyroid hormones in the Central Nervous System during development and adult life;
- pathophysiology of the thyroid gland and nuclear receptors;
- regulation of the development, differentiation and function of pancreatic islets;
- signaling cascades modulated by neurotrophins and myelin formation,
- molecular basis of hearing function and the pathophysiology of hearing loss;
- mechanisms of neurodegeneration and neuroprotection taking place in the Nervous System including the identification of diagnostic markers and target molecules that will help developing new and efficient therapeutic drugs.

These topics are extremely relevant from a biomedical point of view, since they deal with fundamental physiological processes and highly prevalent pathologies with a strong social and health impact.

Thyroid hormone action in the brain

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Keywords: Hypothyroidism, transporters, deiodinases, blood-brain-barrier, radial glia, Allan-Herndon-Dudley syndrome .
Palabras clave: Hipotiroidismo, transportadores, desyodasas, barrera hematoencefalica, glia radial, sindrome de Allan-Herndon-Dudley

Lineas de Investigación

Relative role of thyroid hormone transporters and deiodinases in the brain action of thyroid hormones

Thyroid hormones cross the blood-brain barrier through integral membrane transporter proteins, the monocarboxylate 8 (MCT8) transporter and the organic anion transporter polypeptide 1C1 (OATP1C1). MCT8 is encoded by the SLC16A2 gene located in the X crhomosome. It is specific for T3, T4, and other thyroid hormone derivatives. Disruption of the gene causes an X-linked syndrome with altered thyroid hormone metabolism and action, and profound neuromotor and cognitive impairement (Allan-Herndon-Dudley syndrome, or AHDS). It is thought that the syndrome is due to deficient transport of T4 and T3 through the blood-brain barrier from fetal stages. OATP1C1 is encoded by the SLCO1C1 gene, located in chromosome 12, with high affinity for T4 but very low for T3. A neurodegenerative syndrome has recently been described caused by mutation in this gene, and the relationship with lack of T4 transport is suspected but not demonstrated.

The active thyroid hormone is T3, which binds to nuclear receptors and regulates gene expression. T4, the main hormone produced by the thyroid gland, is a prohormone which generates T3 in tissues by the action of deiodinases. These are selenoenzymes which remove iodine atoms from the iodothyronine molecule generating the active product T3, from T4 (types 1 and 3 deiodinases, or DIO1 and DIO2), or inactive metabolites from T4 or T3 (Type 3 dedinase, or DIO3). Brain T3 derives in part from the circulation, and in part from DIO2-catalyzed, T4 deiodination in the astrocytes. During early development, most brain T3 is derived from T4 which, as stated above, enters the brain through MCT8 and OATP1C1.

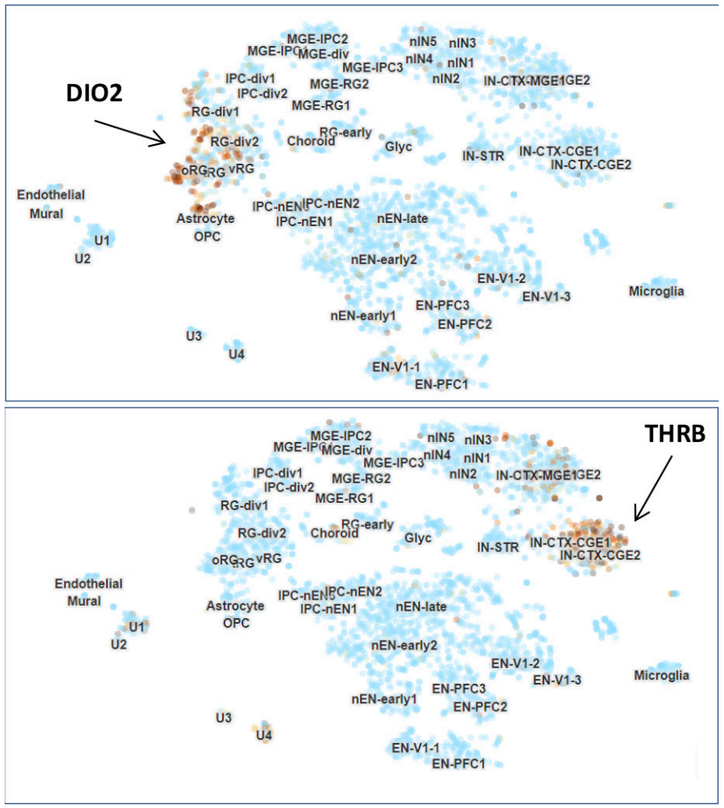

Fig 1: DIO2 and THRB expression (brown color) in single cells of the developing human cerebral cortex. DIO2 is the enzyme that generates the active thyroid hormone T3 from the T4 precursor by deiodination. It is expressed in clusters of cells with the identitity of radial glia cells and astrocytes. THRB is the thyroid hormone nuclear receptor beta subtype, and is specifically expressed in a cluster of cells with the identity of interneurons. The data were extracted from the databases generated by Novakowski et al. (Science 358, 1318–1323, 2017). The cell clusters were generated by unbiased clustering and weighted gene coexpression network analysis after RNA-Seq of 4261 individual cells. Our analysis indicates that the radial glia is a local source of the active thyroid hormone, and that the thyroid hornone receptor beta subtype is involved in differentiation of interneurons. (RG: Radial glia; IN, Interneurons; NE, excitatory neurons).

OATP1C1 is expressed at very low levels in the human blood-brain barrier, and therefore the human brain is strictly dependent on MCT8. In contrast, the rodent brain expresses similarly MCT8 and OATP1C1 so that MCT8 knock out mice do not have neurological phenotype, because lack of MCT8 is compensated by OATP1C1.

Alternative mdels of AHDS have been generated. One, the MCT8 and DIO2 double KO (dKO), in which T3 transport and T3 generation from T4 are compromised. Another, the MCT8 and OATP1C1 dKO, in which T4 and T3 transport is abolished. In either case similar T3 deficiency and brain hypothyroidism should occur. However, a series of theoretical and experimental considerations cast doubts on this model. We compared the effects of the dKO models, and systemic hypothyroidism on gene expression in the cerebral cortex and the striatum using RNA-Seq. We analyzed the following groups: wild type mice, systemic hypothyroid mice after chemical thyroidectomy, MCT8 and DIO2 dKO, and MCT8 and OATP1C1 dKO. The two dKO cause hypothyrodism limited to the cerebrum, whereas systemic hypothyroidism affects all tissues.The results show that the impact of systemic hypothyroidism is much more profound in terms of gene expression than cerebral hypothyroidism. In addition, there is only a partial overlap between the two models of cerebral hypothyroidism. The results obtained by us strongly question current hypothesis on the mechanisms of disease in AHDS.

Analysis of the cellular coexpression of thyroid hormone transporters, deiodinases and receptors in single cells of the human brain

Our research interest is the mechanisms of action of thyroid hormones in the human brain during development. Along this line we are interested in the identification of the thyroid hormone sensitive cells during cortex development. Recently, the accumulation of transcriptomics datasets on single cells isolated from human samples makes it possible to perform in silico studies to analyze the co-expression of thyroid hormone transporters, thyroid hormone receptors, and thyroid hormone activating and inactivating enzymes in single cells, as a mean to identify the sensitive cells. One of these databases was generated recently by Tomasz J. Nowakowski and coworkers (Nowakowski et al, Spatiotemporal gene expression trajectories reveal developmental hierarchies of the human cortex, Science 358: 1318-1323, 2017). This database contains transcriptomics data of 4260 single cortical cells from 73 human fetal subjects, and is deposited in the database on Genotypes and Phenotypes (dbGaP) (https://dbgap.ncbi.nlm.nih.gov/gap/) under the label “STUDIES OF HUMAN DEVELOPMENTAL NEUROGENESIS phs000989.v3.p1.”

We are performing in silico analysis of this dataset. Clustering and differential expression analysis will enable to identify groups of cells showing evidence of regulation by thyroid hormones. For this we will focus on genes involved in thyroid hormone production and transport, their nuclear receptors and genes known to be regulated by thyroid hormones in humans and mice. Some preliminary data indicate that DIO2 is present in radial glia cells that also express OATP1C1. The MCT8 transporter is associated with the thyroid hormone receptor alpha and with many of the T3 target genes. Interestingly the TRbeta is present in a cluster containing interneurons (Fig 1). The data will shed light as to the specific role of thyroid hormones on cortical development and the mechanisms involved.

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(2018). *Thyroid Hormone Economy in the Perinatal Mouse Brain: Implications for Cerebral Cortex Development.* Cereb Cortex. 28: 1783-1793.

(2018). *Regulation of Gene Expression by Thyroid Hormone in Primary Astrocytes: Factors Influencing the Genomic Response.* Endocrinology. 159: 2083-2092.

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(2018). *New insights on thyroid hormone and the brain.* Current Opinion in Endocrine and Metabolic Research. 2: 24-28.

(2017). *Thyroid hormone regulated genes in cerebral cortex development.* J Endocrinol. 232: R83-R97.

(2017). *Transcriptome Analysis of Primary Cerebrocortical Cells: Identification of Genes Regulated by Triiodothyronine in Specific Cell Types.* Cereb Cortex. 27: 706-717.

(2017). *Is the Intrinsic Genomic Activity of Thyroxine Relevant In Vivo? Effects on Gene Expression in Primary Cerebrocortical and Neuroblastoma Cells.* Thyroid. 27: 1092-1098.

(2017). *Deiodinases. En: Reference Module in Neuroscience and Biobehavioral Psychology.* Elsevier. .

(2017). *Thyroid Hormones and Brain Development.* En: Hormones, Brain, and Behavior 3rd edition. (Pfaff, D.W and Joëls, M eds.). Academic Press. vol 5.

Financiación

Juan Bernal Carrasco

“Mecanismos patogénicos en la deficiencia de MCT8: Un enfoque multidisciplinar hacia tratamientos basados en el conociemiento.” Financiado por: AGENCIA ESTATAL CONSEJO SUPERIOR DE INVESTIGACIONES CIENTIFICAS (CSIC). Año 2018-2020

“Thyroid Physiology Studies of Inherited Disorders.” Financiado por: National Institutes of Health. Año 2018-2019

Beatriz Morte Molina

“Allan-Herndon-Dudley Syndrome: Mechanisms of Disease and Therapeutic Approaches in Model Organisms.” Financiado por: Fundación Inocente, Inocente. Año 2017-2018

Physiology of neurotrophins and nuclear receptors in the Nervous system

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Regulation of the peripheral myelination process by neurotrophic factors.

Besides neurotrophins, the main group of neurotrophic factors capable of affecting sensory neurons is constituted by GFLs, growth factors originally identified as trophic factors involved in the survival and morphological differentiation of dopaminergic neurons, of which four members have been described to date: the glia-derived neurotrophic factor (GDNF), neurturin (NRTN), artemin (ARTN) and persephin (PSPN).

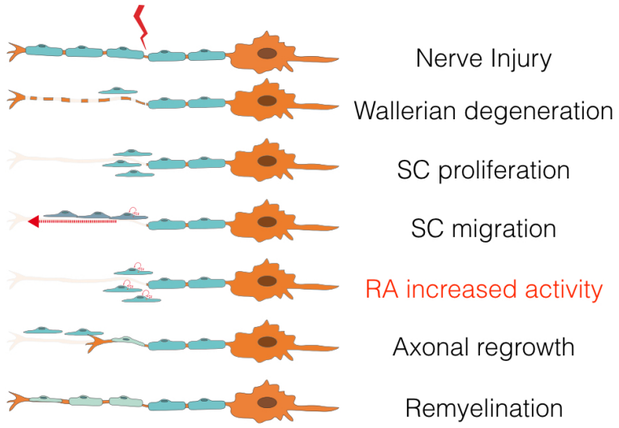
GFLs act through specific binding to the family of glycosylphosphatidylinositol receptors (GFR) α1-4. All of them interact with RET, a tyrosine kinase receptor that is the mediator of transmembrane signaling and is only activated if the ligand is previously attached to its corresponding GFRα co-receptor. Furthermore, GFLs can also use NCAM as a signaling receptor, an adhesion molecule that can act as a receptor activating different signal transduction pathways, such as Fyn kinase, or indirectly through the transactivation of the FGF receptor.

Previous laboratory data confirmed in the literature indicate that GDNF acts on the peripheral myelination process by stimulating myelin formation. Our work has allowed us to extend these studies to other members of this family of neurotrophic factors, as well as to identify the molecular mechanisms by which this effect occurs.

In addition, we have also studied the effect of this family of neurotrophic factors on Schwann cell migration, identifying the receptors and signal transduction pathways involved in the regulation of this process.

Regulation of the peripheral myelination process by retinoic acid.

Several evidences indicate that hormonal agents that act through the superfamily of nuclear receptors are implicated in the regulation of the myelinization process. In the Peripheral Nervous System, studies have so far focused mainly on the effect of steroid hormones, although there are different indications that members of the thyroid hormone/retinoid/vitamin D3 receptor family may also be involved in the myelination process.
Our studies have focused on the regulation of peripheral myelin formation by retinoic acid (RA). Using both in vitro



models of Schwann cell cocultures with dorsal ganglion root neurons and in vivo during sciatic nerve development, we have been able to demonstrate a regulatory effect of retinoic acid on peripheral myelination by acting through a double mechanism. On the one hand RA inhibits the expression of MAG, a minority myelin protein for which a signaling role in the interaction between neurons and Schwann cells has been postulated. On the other hand RA is able to produce an increase in the levels of Krox20, a transcription factor that plays a central role in the development and functionality of the Schwann cell. This increase in Krox20 levels results in an increase in the accumulation of myelin proteins such as MBP or P0. As is the case in major human peripheral myelinopathies, this disproportionate increase in the expression of various myelin proteins produces a saturation of the system resulting in a blockage in normal myelin formation. As a side effect, this increase in the accumulation of myelin proteins is accompanied by reticulum stress.

We have continued the studies about the actions of RA focusing in other aspects of the myelination process, namely SC migration and differentiation.

During nerve regeneration, there is an increase in endogenous RA production and signaling. RA produces an up-regulation of NEDD9, a member of the CAS family of scaffold proteins previously implicated in migratory and invasive behavior in gliomas, melanomas and the neural crest cells from which Schwann cells derive. This RA-induced NEDD9 accumulation is due to augmented mRNA levels, as well as an increase of NEDD9 protein stability. Although all NEDD9 phospho-isoforms present in Schwann cells are induced by the retinoid, the hormone also changes its phosphorylation status, thus altering the ratio between the different isoforms.

As a consequence, RA increases Schwann cell migration, while silencing NEDD9 had no effect on basal migratory ability, but completely abrogated RA-induced enhanced migration. Collectively, our results indicate that RA could be a major regulator of Schwann cell migration after nerve injury, thus offering a new insight into peripheral nerve repair.

Currently, we are interesting in elucidating other actions of RA on the physiology of the Schwann cell, basically:
* Schwann cell de-differentiation and re-differentiation during nerve repair.
* Interaction of RA with the Notch signaling pathway in Schwann cells.
* RA-dependent miRNA-mediated regulation of gene expression.

Peripheral neuropathies: Innate immune system and the acute inflammatory demyelinating polyneuropathy (AIDP) Gillain-Barré Syndrome (GBS) variant.

The importance of myelin is showed by the harmful effects that its loss or failure has on the correct function of the nervous system. Examples of diseases that affect proper myelin function in the PNS are Guillain-Barré syndrome (GBS), with one-two cases every 100,000 people or the much more common Charcot-Marie-Tooth disease (CMT) that affects one in every 3,500 people, and multiple sclerosis that is suffered by approximately one in a thousand people in the CNS.

Since the virtually disappearance of poliomyelitis, GBS is the main cause of acute disabling paralysis. GBS is a severe neurological disorder characterized by inflammatory demyelination of peripheral nerves. Patients with GBS develop a rapidly ascending neuromuscular paralysis followed by a loss in sensitivity and pain perception. Many patients have a good recovery, but in severe cases patients need months of intensive care and are left with severe weakness, sensory disorder and pain. Moreover, 5% of patients die due to complications, making GBS a medical emergency with a high morbidity and significant mortality.

Acute inflammatory demyelinating polyneuropathy (AIDP), acute motor axonal neuropathy (AMAN), and acute motor sensory axonal neuropathy (AMSAN) are clinical variants of GBS, principally defined through electrophysiological studies and supported by pathological findings.

While AMAN and ASMAN variants are clearly linked to a loss of immunological tolerance to self-antigens and probably constitute the best example of antigen mimicry with the occurrence of anti-ganglioside antibodies able to bind to some constituents of the outer myelin membrane or the nodes of Ranvier, the same does not hold true for AIDP.

Most of AIDP cases are preceded by viral infection, such as CMV or EBV and, more recently, it was also described an increase of GBS cases after ZIKV outbreaks in French Polynesia, Brazil and Colombia.

We are currently interested in analyzing the implication of the intrinsic Schwann cell antiviral response mediated by the innate immune system in AIDP etiology hoping that this knowledge could provide a starting point for therapeutic intervention in AIDP.

Crosstalk between retinoids and innate immune signaling in cancer

The search for therapies to manage breast cancer constitutes an area of intensive research. Due to its ability to regulate the growth, differentiation and apoptosis of cancer cells, retinoic acid (RA) is considered a signaling molecule with promising therapeutic potential in oncology. Transcriptome analysis using microarrays from breast cancer cell lines treated with RA has revealed a striking regulation of different transcription programs. Among them, Toll-like Receptor 3 (TLR3) arises as a interesting target for RA. We found that RA is able to induce the intrinsic ability of breast cancer cells to recognize double-stranded RNA (dsRNA) through the upregulation of TLR3 expression. RA, co-administered with the dsRNA mimicker polyinosinic-polycytidylic acid (poly(I:C)), synergizes to mount a specific response program able to sense dsRNA through the concurrent upregulation of TLR3, the dsRNA helicases Melanoma Differentiation-Associated Antigen-5 (MDA-5) and Retinoic acid-Inducible Gene-1 (RIG-1), and the dsRNA-activated Protein Kinase (PKR) expression, driving ultimately breast cancer cells to die by a TRAIL (Tumor-Necrosis-Factor Related Apoptosis-Inducing Ligand)- dependent apoptotic program (Cell Death Dis. 2013 Jan 31;4:e479. doi: 10.1038/cddis.2013.5. PMID: 23370279).

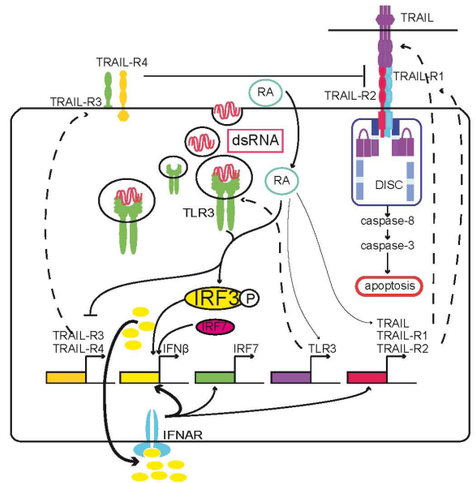


Figure 1. Schematic representation of a proposed model for RA/dsRNA-induced cell death. RA and dsRNA synergize to induce the activation of IRF3, which drives IFNβ expression upregulation. IFNβ triggers autocrine an paracrine circuitries that result in TRAIL death pathways upregulation and cell death

In addition, we also found that RA/poly(I:C) co-treatment, synergically, induce the activation of Interferon Regulatory Factor-3 (IRF3) in breast cancer cells. IRF3 activation is mediated by TLR3, since its depletion abrogates IRF3 activation by RA/poly(I:C) co-treatment. Besides induction of TRAIL, apoptosis induced by RA/poly(I:C) correlates with the increased expression of pro-apoptotic TRAIL receptors, TRAIL-R1/2, and the inhibition of the antagonistic receptors TRAIL-R3/4. IRF3 plays an important role in RA/poly(I:C)-induced apoptosis since IRF3 depletion suppresses caspase-8 and caspase-3 activation, TRAIL expression upregulation and apoptosis. Interestingly, RA/poly(I:C) combination synergizes to induce a bioactive autocrine/paracrine loop of type-I Interferons (IFNs) which is ultimately responsible for TRAIL and TRAIL-R1/2 expression upregulation, while inhibition of TRAIL-R3/4 expression is type-I IFN-independent (Apoptosis. 2017 Jul;22(7):920-932. doi: 10.1007/s10495-017-1377-z. PMID: 28409399). Our findings reveal important links among RA, TLR3, IRF3, type-I IFNs and TRAIL and highlight the combined use of RA and poly(I:C) as a potential effective tumor therapy by improving the apoptotic response of cancer cells with low sensitivity to the action of synthetic dsRNA.

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Bernardo, AR, Cosgaya, JM, Aranda, A, Jiménez-Lara, AM. (2017). *Pro-apoptotic signaling induced by Retinoic acid and dsRNA is under the control of Interferon Regulatory Factor-3 in breast cancer.* Apoptosis. 22(7): 920-932.

Neuroprotective strategies for neuroderegenative diseases

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Neuroprotective strategies for neurodegenerative diseases

Aging is the main factor contributing towards both Parkinson's (PD) and Alzheimer's (AD) diseases. These chronic diseases are incurable and their disabling effects may continue for years or even decades. Studies on animal models of AD and PD and on human postmortem brain tissues, indicate that many pathological changes in the brain derive from a network of local stresses, like oxidative stress, tightly connected to inflammatory and proteotoxic stresses. Local stressful conditions are probably challenged by pathologically modified proteins, and, through a vicious cycle, may further trigger alteration of key molecules. Our team has been studying protective mechanisms used to maintain homeostatic respones and how these mechanims coudl be targeted pharmacologically to provide superior defense.

We are currently studying the role of transcription factor NRF2 in protection against stimuli that induce neurodegeneration. NRF2 is a protein that regulates the expression of about 250 genes. These genes possess the antioxidant response element (ARE) in their promoters. The genes participate in adaptive responses to oxidative, inflammatory and proteotoxic stress and in the regulation of enzymes involved in biotransformation and glutathione metabolism.

Using genetically modified rodent models as well as pharmacological approaches, we are studying the contribution of this transcription factor to the protection against oxidative damage and neuroinflammation in toxic (MPTP and 6-OHDA) and genetic (alpha-synuclein) models of Parkinson's disease and in transgenic mice possessing amyloidopathy (APPV717I) and tauopathy (TauP301L) , which are characteristic of Alzheimer's disease. Objectives:

• Generation of knowledge: Understanding the mechanisms that regulate NRF2 is fundamental to determine its physiological role and its pathological alterations as well as to design new pharmacological strategies. We are currently studying the regulation of NRF2 by signaling pathways. We have already described its regulation by the GSK-3/beta-TrCP pathway. We are now analyzing its participation in cell signaling by primary cilium and proliferative stimuli.

• Low-grade chronic inflammation is a key element of neurodegenerative diseases. We are studying the crosstalk between NF-kB and NRF2, key elements in the pro and anti-inflammatory phenotypes of microglia.

• Applicability: in collaboration with several companies, we are looking for novel mechanisms of regulation of NRF2 in the brain that could serve to reinforce its activity against neurotoxic stimuli. In preclinical models of Parkinson's disease, we are focusing on repurposing of dimethyl fumarate, a compound already used in clinical practice for multiple sclerosis.

Tesis Doctoral y otros trabajos

Marta Pajares Cabetas

"Transcription factor NRF2 regulates de expression of autophagy genes". Universidad Autónoma de Madrid. Medicina. 2018. Director/es: Antonio Cuadrado . Calificación: Cum Laude

Financiación

"Papel de NRF2 en la función y el destino del cerebro con Alzheimer." Financiado por: MINECO. Año 2017-2019

"Knowledge transfer in redox biology for developing advanced molecular tools in neurodegenerative diseases – focus on the signature of NRF2 transcription factor in diagnosis and therapy." Financiado por: Competitiveness Operational Programme (COP). European Union. Año 2016-2020

"Developing preclinical and clinical biomarkers of NRF2 pathway activation for therapeutic application in neurodegenerative diseases." Financiado por: COEN/JPND. Año 2018-2020

"Advanced theranostic approach in cancer combining photodynamic therapy and nanoparticles." Financiado por: M.ERA-NET. Año 2016-2019

"Glial dysfunction in Alzheimer's disease: pathologic implications and clinical potential ." Financiado por: Ciberned. Año 2018-2020

"Development of new NRF2-activating drugs for innovative therapiy of Alzheimer's disease." Financiado por: CAM. Año 2018-2022

Neuroprotective peptides for exocitotoxicity and cerebral ischemia

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Keywords: neuroprotection, neurodegeneration, stroke, excitotoxicity, cell-penetrating peptides, glutamate/NMDAR, BDNF/TrkB, calpain, CREB/MEF2, PSD-95
Palabras clave: neuroprotección, neurodegeneración, ictus, excitotoxicidad, péptidos penetrantes, glutamato/ NMDAR, BDNF/TrkB, calpaína, CREB/MEF2, PSD-95

Lineas de Investigación

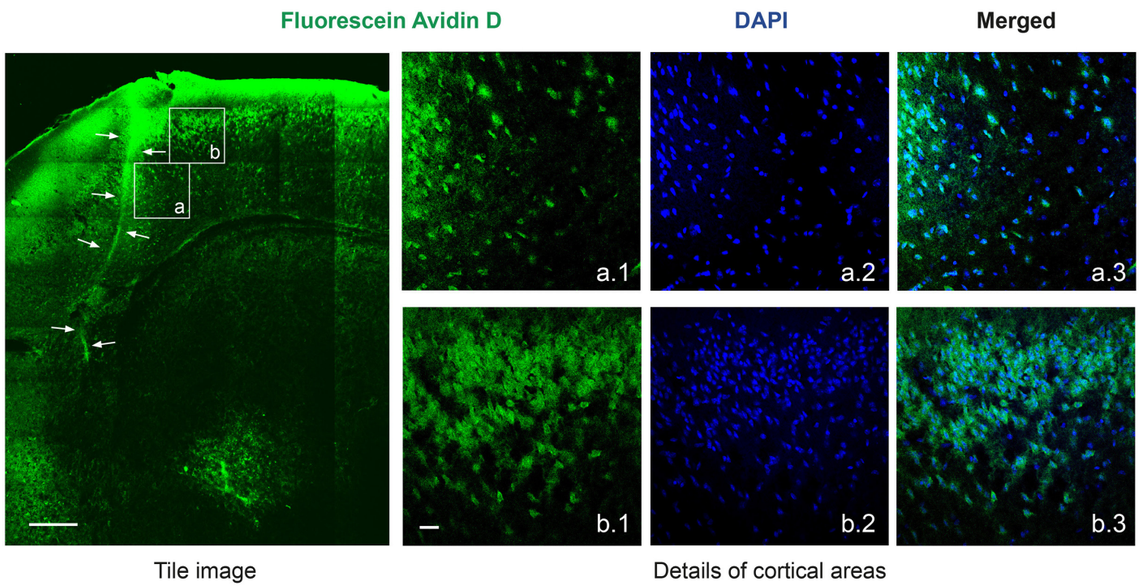
Stroke is the second cause of death worldwide and leading cause of adult disability and dementia. Pharmacological therapies for ischemic stroke (85% of cases) are still limited to thrombolytic drugs, which can be only administered to very few patients.

Cerebrovascular accidents are unpredictable and, therefore, primary death of neurons in the ischemic core cannot be avoided. However, secondary neuronal death progressively affecting the ischemic penumbra might be potentially prevented to reduce brain damage. In order to develop neuroprotective drugs for stroke therapy, we propose:

·A comprehensive characterization of the pathological processes induced by excitotoxicity, main mechanism of the secondary neuronal death, which subvert pro-survival pathways such as those regulated by neurotrophins and neurotrasmitters.
·Selection of rational targets for stroke neuroprotection such as increased endocytosis/processing of BDNF receptor

TrkB or dephosphorylation/calpain processing of CREB transcription factor, both induced in excitotoxicity.

·Development and refinement of cell-penetrating peptides (CPPs) able to cross the blood-brain barrier and preserve functioning of those critical survival pathways in pathological conditions.

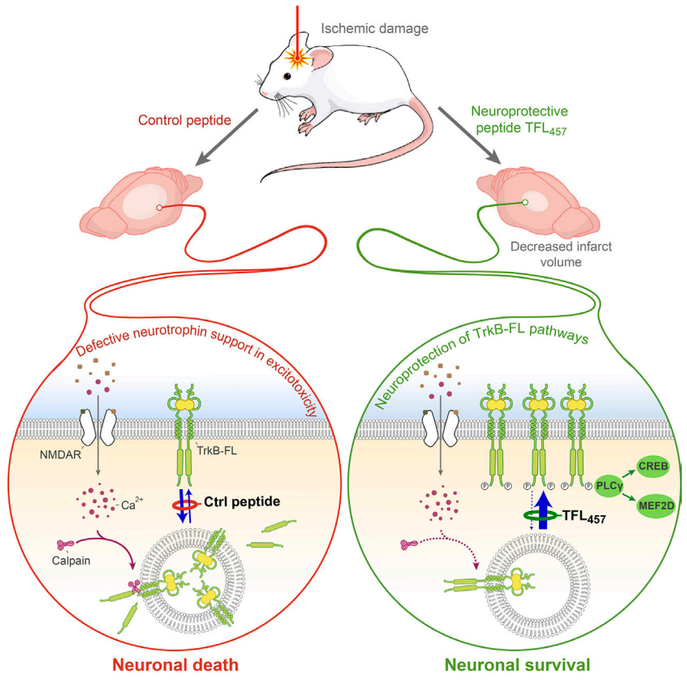


Tile image of mice cortical and sub-cortical areas showing entry of an intravenously injected biotinylated-CPP into brain

·In depth characterization of these CPPs' mechanisms of action in neurons and/or astrocytes.

·Test of these neuroprotective peptides in pre-clinical models of stroke and neurodegenerative diseases associated to excitotoxicity. The complexity of these pathologies instructs us to combine peptides having different targets or those CPPs with BDNF, TrkB agonists or certain NMDAR antagonists.

To accomplish these objectives, we are using primary cultures of cortical neurons and/or astrocytes, animal models of brain ischemia and human samples from stroke patients (plasma and brain necropsias).



Model explaining the mechanism of action of neuroprotective peptide TFL457 which prevents excitotoxicity-induced processing of BDNF receptor TrkB-FL

Publicaciones

Tejeda, GS. , Díaz-Guerra, M. (2017). *Integral Characterization of Defective BDNF/TrkB Signalling in Neurological and Psychiatric Disorders Leads the Way to New Therapies.* Int J Mol Sci. 18(2).

Tesis Doctoral y otros trabajos

Sara Ayuso Dolado

"Desarrollo de péptidos neuroprotectores frente a la isquemia cerebral basados en el receptor de glutamato de tipo NMDA y su proteína interaccionante PSD-95". Autónoma de Madrid. Medicina. 2017. Director/es: Margarita Díaz-Guerra . Calificación: Sobresaliente

Financiación

"Optimización de péptidos neuroprotectores frente al ictus que atenúan la inactivación en excitotoxicidad de las vías de supervivencia del NMDAR y TrkB." Financiado por: Ministerio de Economía y Competitividad. Año 2017-2019

Thyroid hormones and Central Nervous System

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Keywords: Thyroid hormones, brain, transport of thyroid hormones, Allan-Herndon-Dudley syndrome, MCT8, deyodase 2, hypothyroidism, blood-brain barrier, thyromimetics.
Palabras clave: Hormonas tiroideas, encéfalo, transporte de hormonas tiroideas, Síndrome de Allan-Herndon-Dudley, MCT8, desyodasa 2, hipotiroidismo, barrera hematoencefálica, tiromiméticos.

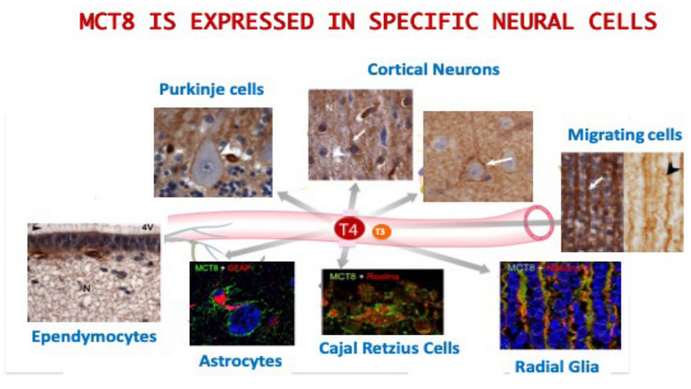
Lineas de Investigación

Our research focuses on:

Understanding the role of thyroid hormones (TH, T4 or thyroxine and T3 or triiodothyronine) in the CNS during development and adulthood. Characterization of the pathophysiology associated with defects in the availability and/or signaling of TH in the CNS, with a special interest in the study of rare diseases due to these abnormalities.

- Specifically, we study the physiopathology of Allan-Herndon-Dudley syndrome associated to mutations in the transmembrane transporter of thyroid hormones known as the Monocarboxylate transporter 8 MCT8 (SLC16A2 gene) and
- The physiopathology of congenital hypothyroidism due to dysfunction of the thyroid gland

Finally, we seek the development of possible therapies to alleviate the structural and/or functional alterations in the CNS associated with these rare diseases.



To achieve our goals:

We analyze the phenotype of several animal models, some of which have been developed in our own laboratory. These models are animals with congenital hypothyroidism, animals deficient in MCT8, the main transporter of thyroid hormones in brain barriers and neural cells, and in proteins involved in the metabolism and action of TH.
We use different experimental approaches, mainly in vivo studies. In addition, we perform preclinical studies with animal models of Allan-Herndon-Dudley syndrome to test the effectiveness of different thyroid hormone analogues that can access target neural cells under MCT8-deficient conditions.
We analyze the histopathology of human autopsy brain tissue from patients with genetic diagnosis of Allan-Herndon-Dudley syndrome.
With these studies we want to increase our knowledge of the physiopathology and disease mechanisms in the CNS associated with rare diseases due to defects in TH signaling. Our studies aim to characterize possible therapeutic targets and new approaches that favor the development of therapeutic strategies in these diseases. Our research will also contribute to a better understanding of the role of TH in brain activity and plasticity.

Research lines:

Allan-Herndon-Dudley Syndrome: Physiopathology of the Allan-Herndon-Dudley Syndrome (SLC16A2 mutations) and the consequences of TH transport deficiency using transporter deficient mice. Development of new therapeutic approaches based on TH analogues with alternative transport. Histopathological studies from MCT8-deficient human brains.

Congenital hypothyroidism and maternal hypothyroxinemia: Physiopathology of neural alterations due to TH deprivation during the fetal and neonatal periods. Influence of maternal TH and consequences of maternal hypothyroxinemia on gene expression in the fetal brain.

Mechanisms of TH availability and action in the brain: Physiopathology of animal models deficient in important proteins for the neural availability of TH. Understanding the regulation of the expression pattern of these proteins at the regional and cellular level during development and at adult stages in the human brain.

Publicaciones

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Bárez, S. , Montero-Pedrazuela, A , Bosch, D. , Venero, C. , Guadaño-Ferraz, A (2017). *Increased anxiety and fear memory in adult mice lacking type 2 deiodinase.* Psychoneuroendocrinology. 84: 51-60.

Bárez, S. , Guadaño-Ferraz, A (2017). *Thyroid Hormone Availability and Action during Brain Development in Rodents.* Front Cell Neurosci. 11: 240.

Bárez, S. , Obregón, MJ. , Bernal, J. , Guadaño-Ferraz, A (2017). *Thyroid Hormone Economy in the Perinatal Mouse Brain: Implications for Cerebral Cortex Development.* Cereb. Cortex. 1-11.

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Tesis Doctoral y otros trabajos

Soledad Bárez López

"Thyroid hormone homeostasis in the perinatal mouse brain: implications for MCT8 transport defect". Universidad Autónoma de Madrid. Medicina. 2017. Director/es: Ana Guadaño , Juan Bernal . Calificación: Sobresaliente cum laude. Premio Extraordinario.

Financiación

"Therapeutics for the Allan-Herndon-Dudley: Assessing new treatment delivery pathways." Financiado por: Sherman Foundation . Año 2018-2020

"Acciones CIBER. Área temática: Enfermedades raras, IP de la U-708." Financiado por: ISCIII. Año 2018-2100

"Mecanismos patogénicos en la deficiencia de MCT8: un enfoque multidisciplinar hacia tratamientos basados en el conocimiento." Financiado por: Ministerio de Economía, Industria y Competitividad (MINECO). Año 2018-2020

"Mecanismos de enfermedad en el síndrome de Allan-Herndon-Dudley." Financiado por: Ministerio de Economía y Competitividad (MINECO). Año 2015-2017

"Therapeutics for the Allan-Herndon-Dudley: Assessing new treatment delivery pathways." Financiado por: Sherman Foundation . Año 2016-2018

Novel Targets in Neurodegeneration and Neuroprotection

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Keywords: Alzheimer, Stroke, Excitotoxicity, Oxidative Stress, Neurodegeneration, Neuroprotection, Kidins220, Protein Kinase D1 (PKD1).
Palabras clave: Alzheimer, accidente cerebrovascular, excitotoxicidad, estrés oxidativo, neurodegeneración, neuroprotección, Kidins220, proteína quinasa D1 (PKD1)

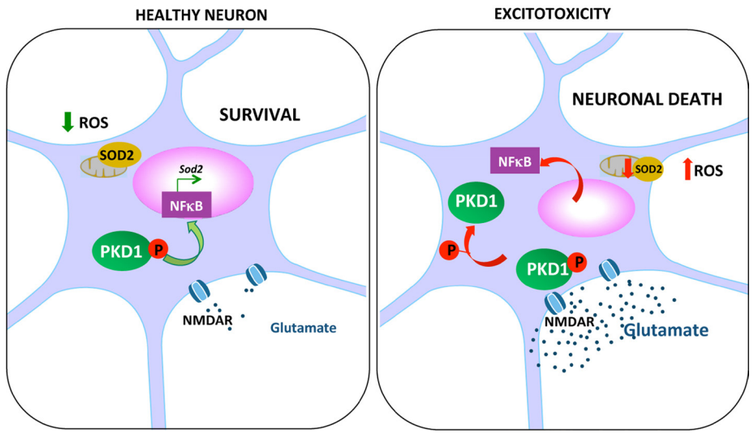
Lineas de Investigación

We have been studying mechanisms involved in neuronal death occurring in neuropathologies that produce acute neurodegeneration (such as stroke, traumatic brain injury or epilepsy) and in chronic neurodegenerative diseases (such as Alzheimer´s, Huntington´s, Parkinson´s disease and amyotrophic lateral sclerosis,).

We aim to identify molecules and pathways that participate in neuronal survival, searching how to potentiate their activity and confer neuroprotection.

- During this period, using pharmacological inhibitors and lentiviral silencing in cultured primary cortical neurons, as well as genetic elimination in mice, we have shown that PKD1 (Protein Kinase D1) is crucial for neuronal survival. PKD1 activity in healthy neurons potentiates a free-radical mitochondrial detoxification pathway (Nat Commun, 2017). This cascade may decay with aging, leaving neurons less protected and exposed to higher oxidative stress damage. Thus, one of our present aims is to study the role of PKD1 in brain aging using neuronal conditional knock-out mice.

- Excitotoxicity is a type of neuronal death that takes place in numerous neuropathologies as a consequence of an excess of the excitatory amino acid glutamate. Knowing the molecular mechanisms involved in excitotoxicity will facilitate to design neuroprotective therapies for a wide range of acute or chronic neurodegenerative conditions. In this context, we have demonstrated that excitotoxicity inactivates PKD1 in vitro and in vivo, in a mouse model of cerebral ischemia, confirming these data in human ischemic stroke necropsies. This inactivation increases reactive oxygen species (ROS) and neurodegeneration by molecular mechanisms that involve activation of phosphatases, NF-kB nuclear exit and decreases in manganese superoxide dismutase, the enzyme responsible for mitochondrial ROS elimination.



PKD1 is active in healthy neurons promoting an oxidative stress detoxification pathway that is turned off by excitotoxicity.

- Importantly, we have designed a strategy using lentivirus for the neurospecific expression of a constitutively active mutant of PKD1 that confers strong neuroprotection against excitotoxicity in primary neuronal cultures and animal models (Nat Commun, 2017). The use of this mutant by viral administration approaches in different models of neurodegenerative diseases in our future preclinical studies could have important therapeutic implications.

- Analysing samples from human Alzheimer´s disease patients we found a positive correlation of Kidins220 (Kinase D interacting substrate of 220 kDa), with tau, one of the two main neuropathological markers of this disease, indicating the possible use of Kidins220 as biomarker (J Alzheimers Dis, 2017).

- Finally, we have generated conditional PKD1 and Kidins220 deficient mice in different cell lineages and are examining their phenotype. Our initial studies show changes in brain homeostasis, neuroinflammation, and metabolic, synaptic and neurogenic dysfunctions, accompanied by behavioural and memory deficiencies. At present, we are elucidating the molecular mechanism involved in the appearance of the observed phenotypes highly related to neurodegeneration.

Publicaciones

Pose, J. , García, L. , del Puerto, AM. , Martín, A. , Jurado-Arjona, J. , de León, NS. , Gamir, A. , Sebastián, Á. , García-Gallo, M , Kremer, L. , Fielitz, J. , Ireson, C. , Pérez-Álvarez, MJ. , Ferrer, I. , Hernández, F. , Ávila, J. , Lasa,M. , Campanero, M. , Iglesias, T. (2018). *Author Correction: Excitotoxic inactivation of constitutive oxidative stress detoxification pathway in neurons can be rescued by PKD1.* Nat Commun. 9(1): 473.

Jiménez, R. , Martín, C. , Kourani, O. , Chiodo, Y. , Cordoba, R. , Domínguez-Franjo, MP. , Redondo, JMM. , Iglesias, T. , Campanero, M. (2018). *CDCA7 is a critical mediator of lymphomagenesis that selectively regulates anchorage-independent growth.* Haematologica. .

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Fernandez, AM. , Hernandez-Garzón, E., Perez-Domper, P. , Perez-Alvarez, A. , Mederos, S. , Matsui, T. , Santi, A. , Trueba-Saiz, A. , García, L. , Pose, J. , Fielitz, J. , Olson, EN. , Fernandez de la Rosa, R. , Garcia Garcia, L. , Pozo, MA. , Iglesias, T. , Araque, A. , Soya, H. , Perea, G. , Martin, ED. , Torres Aleman, I. (2017). *Insulin Regulates Astrocytic Glucose Handling Through Cooperation With IGF-I.* Diabetes. 66(1): 64-74.

Financiación

"Mecanismos moleculares implicados en daño cerebral y neurodegeneración causados por deficiencias en Kidins220 o por eliminación selectiva de PKD1 en neuronas y astrocitos"." Financiado por: MICIU. Año 2018-2020

"Bases Metabólicas de la Neurodegeneración." Financiado por: COMUNIDAD DE MADRID. Año 2018-2021

Premios

"Premio Joven Investigador CIBERNED a Julia Pose Utrilla por el mejor artículo publicado en 2017." Año 2018

Molecular mechanisms of DUSP1 phosphatase in prostate cancer

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Keywords: Prostate cancer, cell signaling, DUSP1, MAPK.
Palabras clave: Cáncer de próstata, señalización celular, DUSP1, MAPK.

Lineas de Investigación

Prostate cancer is considered the fifth most common type of cancer worldwide. The formation and progression of these tumors is due to the combination of several events, which culminate in the acquisition of an androgen-resistant phenotype, which makes their treatment difficult. Thus, advanced tumors must be treated with chemotherapeutic agents, although, in many cases, they develop resistance to these treatments and become tumors with a poor prognosis. At the molecular level, these tumors are known to have changes in signaling pathways that lead to activation of androgen receptors in the absence of ligand. Alternatively, the progression of these types of tumors is also explained through the regulation of alternative pathways that activate target genes independently of androgens.

The double specificity phosphatase DUSP1 is an inducible MAPK phosphatase that plays an important role in the formation and progression of different tumors, and can act as an anti- or pro-tumor molecule, depending on the etiology of the tumor. On the other hand, another one of the determinants in tumor development is the transcription factor NF-kB, since its hyper-activation regulates the transcription of genes associated with proliferation, suppression of apoptosis, migration and metastasis. Several studies have shown that DUSP1 performs some of its functions interacting with different signaling cascades, among which are those of NF-kB and MAPK. Thus, our group has previously shown that DUSP1 inhibits the NF-kB and p38MAPK signaling pathways and induces apoptosis in a pituitary tumor cell model. Furthermore, this same interconnection has been demonstrated in collaboration with the group of Dr. Iglesias (IIBM) in a neurotoxicity models

Taking into account all these antecedents, the general objective of our group is focused on the study of the mechanisms of action of phosphatase DUSP1 in prostate cancer..

- We have shown that DUSP1 inhibits the signaling pathways of NF-kB and p38MAPK and induces apoptosis in prostate cancer cells.
- In collaboration with Dr. Angulo (Head of the Urology Service of the University Hospital of Getafe) and with the research groups of Dr. Toledo, Dr. Ropero and Dr. Chiloeches (University of Alcalá), we have demonstrated that DUSP1 expression levels decrease as the degree of malignancy increases in human samples of prostate tumors, which shows a negative correlation of DUSP1 expression levels with p65 / NF-kB levels , as well as with the activation of p38MAPK.
- Furthermore, given that a high percentage of advanced prostate tumors develop resistance to treatment, we are also interested in studying the implication of DUSP1 in the development of more effective combinatorial therapies than traditional chemotherapy. In this regard, we have recently shown that DUSP1 mediates the antitumor effects of resveratrol, when administered alone or in combination with cisplatin

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(2017). *Excitotoxic inactivation of constitutive oxidative stress detoxification pathway in neurons can be rescued by PKD1.* Nat Commun. 8: 2275-2292.

New therapeutic strategies in neurodegenerative diseases: Parkinson's disease, tauopathies and amyotrophic lateral sclerosis

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Lineas de Investigación

The aging of the population poses a growing burden in society. This is associated with an increase in disability and diseases that have a high impact on health care, on patients and their families. Also, aging is associated with the emergence of different neurodegenerative diseases among which include Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS). Therefore, the development of advanced biological markers, new drugs and appropriate technology is the key to establishing a treatment for these diseases, which is currently an important social challenge.

In our laboratory we study the molecular basis of neurodegeneration. The research projects we develop have a multidisciplinary approach that combines basic and translational research, using cell culture techniques, murine models and postmortem samples from patients with AD, PD and ALS.

Currently, our research is focused on addressing three key aspects of neurodegeneration:

1) Proteinopathy: the accumulation of beta-amyloid plaques and neurofibrillary tangles of TAU protein, involved in neurodegeneration processes, appear in AD. In the case of PD, the alpha-synuclein protein plays a key role in the degeneration of dopaminergic neurons, forming part of the Lewy bodies. And in ALS there is alteration of RNA metabolism and homeostasis. Recent work that connects TDP-43 and FUS to stress granules has suggested how this cellular pathway, which involves the aggregation of proteins as part of their normal function, is altered in ALS. We are interested in determining the role of these proteins in the neurodegeration process.

2) Inflammation: it is a process that appears in the first stages of the disease and aggravates neurodegeneration. Alzheimer's and Parkinson's diseases are characterized by what is called chronic low-grade inflammation, so we want to determine what causes this inflammation and how it can be prevented or stopped.

3) Oxidative stress: it is imbalance between the production of reactive oxygen species and the ability of a biological system to quickly decode the intermediate reagents or repair the resulting damage. It has been observed that this imbalance is present in these neurodegenerative diseases, so we want to study what it is that causes it and how to reverse it.

Financiación

"Papel de NRF2 en la función y el destino del cerebro con Alzheimer.." Financiado por: Ministerio de Ciencia e Innovacion . Año 2017-2020

"Diseño y desarrollo de fármacos innovadores para el tratamiento de la esclerosis lateral amiotrófica." Financiado por: Conserjería de educación e investigación de la Comunidad de Madrid . Año 2018-2021

"Análisis del transporte de gránulos de RNA y traducción de proteínas in situ en ELA: ¿implicación de SATUFEN y TDP-43?" Financiado por: Fundación FundELA. Año 2019-2020

Premios

"Award I Congress of International community of ALS to the best poster." Año 2018

Analysis of human adipose tissue mitochondrial proteome in obesity and type 2 diabetes

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Keywords: Obesity, type 2 diabetes, proteomics, human adipose tissue, mitochondria, oxidative stress, redox signaling.
Palabras clave: obesidad, diabetes tipo 2, proteomica, tejido adiposo humano, mitocondria, estrés oxidativo, señalización redox.

Lineas de Investigación

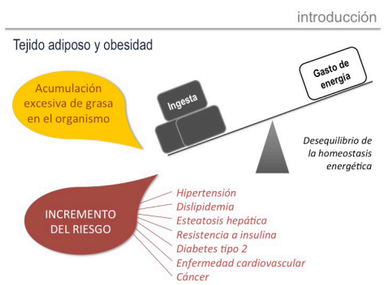
Objetivo Principal:

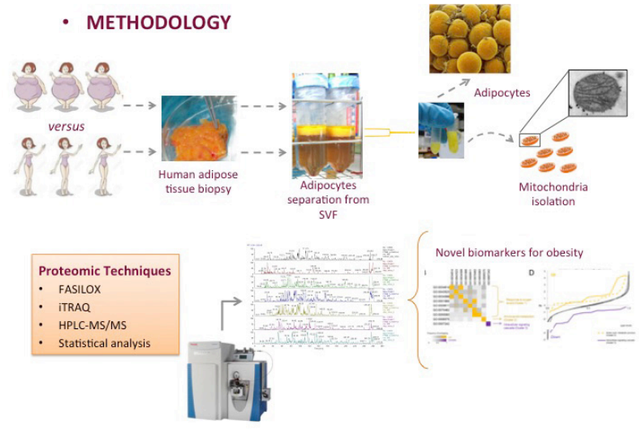
Identificar dianas para el desarrollo de modelos que integren la regulación del proteoma del tejido adiposo y las vías de señalización redox, para mejorar los tratamientos basados en la biología redox en pacientes obesos

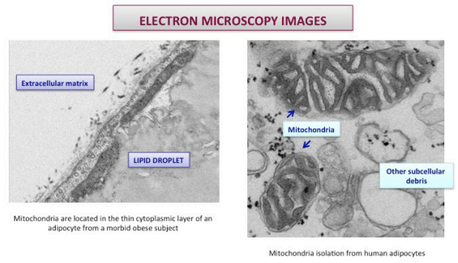
Objetivos Específicos:

Investigar el papel de las mitocondrias en las células del tejido adiposo en la obesidad y sus comorbilidades

Evaluar el papel del estrés oxidativo en la obesidad sin comorbilidades





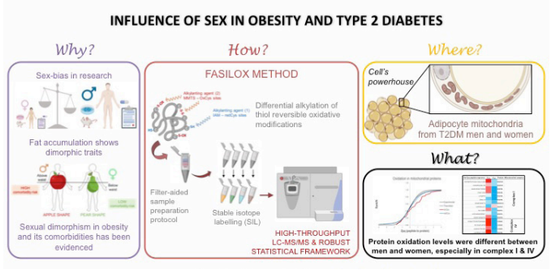


asociadas, y en la obesidad grave, cuando ya está asociada a patología metabólica y cardiovascular

Investigar los efectos del género y del envejecimiento en el proteoma mitocondrial de sujetos obesos

Evaluar los cambios redox en las mitocondrias de adipocitos en relación al envejecimiento y al sexo en sujetos obesos

Investigar si el sistema de fosforilación oxidativa (OXPHOS) podría verse afectado en la obesidad mórbida



Publicaciones

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Tesis Doctoral y otros trabajos

María Gómez Serrano

"Aplicación de técnicas proteómicas de alta resolución al estudio de la obesidad y la diabetes tipo 2: análisis de la disfunción mitocondrial en el tejido adiposo humano".

Universidad Autónoma de Madrid. Facultad de Medicina. 2017. Director/es: María Belén Peral. Calificación: Sobresaliente Cum Laude

Financiación

"Premio al mejor artículo publicado durante el año 2017 en la categoría Obesidad y Síndrome Metabólico de la Fundación Sociedad Española de Endocrinología y Nutrición." Año 2018

Role of aurora kinase B in epigenetic regulation induced by the hepatitis C virus

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Keywords: Aurora kinase B, microbiota, inmunotherapy, transcription, next generation sequence, hepatitis virus.
Palabras clave: Aurora kinase B, microbiota, inmunoterapia, trancripción,secuenciación masiva, virus de la hepatitis.

Lineas de Investigación

PAPEL DE LA AURORA QUINASA B EN LA REGULACIÓN EPIGENÉTICA INDUCIDA POR EL VIRUS DE LA HEPATITIS C

El carcinoma hepatocelular (HCC) es la mayor causa de trasplante de hígado y uno de los cánceres más comunes a nivel global, siendo en gran proporción producido por la infección crónica por el virus de la hepatitis C (HCV). Uno de los aspectos menos conocidos es la relación entre la infección por VHC y la inducción de cambios epigenéticos en las histonas, cambios de naturaleza heredable y que afectan a procesos celulares básicos como la regulación de la expresión génica, que pueden conducir al desarrollo de fibrosis y procesos neoplásicos. Uno de los objetivos de nuestro laboratorio ha sido el de analizar la capacidad del VHC de inducir cambios epigenéticos y analizar las actividades implicadas en dicho proceso, así como su potencial efecto sobre la evolución de la enfermedad hepática. Los resultados confirman que el VHC inhibe la fosforilación del residuo de Serina10 de la histona H3 (H3Ser10ph) mediante la actividad de la Aurora quinasa B (AURKB) a través de una interacción directa con la proteína del core viral. La inhibición de AURKB afecta además a la regulación de la expresión de genes de la ruta inflamatoria: NF-κB y COX-2, que intervienen en el desarrollo de fibrosis y en el control de la apoptosis y la proliferación celular. Los resultados sugieren además que la inhibición de AURKB aumenta la infectividad específica del VHC (Madejón A, Sheldon J, et al J Hepatol. 2015). Nuestros datos en su conjunto sugieren que la inhibición de AURKB podría ser un nuevo mecanismo utilizado por el VHC para asegurar la persistencia de la infección viral y señalan a la AURKB como un posible marcador de evolución de fibrosis y/o cirrosis hepática.

Por ello estamos estudiando el papel de la AURKB en el desarrollo de la fibrosis, mediante a un estudio in vivo sobre una cohorte de 348 pacientes con hepatitis C crónica que demuestra cómo la presencia de dos SNPs de AURKB se asocia significativamente con la gravedad de la fibrosis hepática. Uno de estos SNPs afecta a un residuo de treonina que contribuye a la actividad kinasa de AURKB que es esencial en la fosforilación de P53 y de la proteína CHMP4C.

Por tanto, la presencia de este SNPs podría contribuir al desarrollo de lesiones precancerosas en el hígado mediante defectos en la progresión del ciclo celular y a defectos en los procesos de segregación cromosómica y citocinesis.

Por otro lado, el tratamiento del HCV ha experimentado un gran avance con los antivirales de acción directa (DAAs) consiguiendo tasas de curación superiores al 95%. Sin embargo, se ha descrito una recurrencia de HCC asociado a HCV en aproximadamente un 25% de pacientes que han conseguido una cura virológica tras el tratamiento con DAAs. Por esta razón, en colaboración con el Dr. Esteban Domingo (CBM) y la Dra. Celia Perales (FJD) estamos estudiando los efectos epigenéticos producidos por virus de distinto fitness así como si el tratamiento con DAAs revierte estos efectos.

ALTERACIONES EN LA MICROBIOTA INTESTINAL EN PACIENTES ONCOLOGICOS EN TRATAMIENTO CON TERAPIA BIOLOGICA.

El cáncer constituye una de las principales causas de morbi-mortalidad en el mundo. La terapia biológica es una nueva terapia utilizada en el tratamiento oncológico que está basada en el bloqueo específico y dirigido frente a dianas concretas de las células tumorales, entre las que destácan los bloqueadores de puntos de control inmune como los anticuerpos anti-PD-1/PD-L1 y anti-CTL4. Estos tratamientos, aunque han incrementado la supervivencia de los pacientes, muestran una alta incidencia (entorno al 85%) de efectos secundarios gastrointestinales, colitis primaria o perforaciones intestinales que comprometen la continuidad de la terapia. Además, uno de los procesos más graves y frecuentemente asociados al cáncer es la desnutrición. En este sentido recientes investigaciones parecen indicar que una importante proporción de pacientes sometidos a este tipo de terapias sufre una modificación en la composición de la microbiota intestinal, presumiblemente en respuesta a terapia biológica.

La microbiota es indispensable para el correcto crecimiento corporal, con funciones esenciales como el metabolismo, la regulación de la inmunidad, además de mediar en la inflamación sistémica. Recientes trabajos han demostrado que modificaciones en la microbiota intestinal podrían conducir a procesos de inflamación crónica por lo que podrían considerarse un factor predictivo del desarrollo de efectos secundarios a nivel de función digestiva.

El objetivo de nuestro laboratorio es analizar la composición/evolución de la microbiota intestinal durante el tratamiento en pacientes con cáncer para prever tanto la aparición de trastornos nutricionales que comprometan la adherencia al tratamiento, como para identificar la aparición de factores de riesgo de desarrollo de enfermedad inflamatoria intestinal.

Publicaciones

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(2017). *Differential Genotype-Dependent Induction Of Cellular Epigenetic Changes By HBV X Protein Expression In Hepatoma Cell Lines.* Hepatology. 66: 807 A-807A.

Tesis Doctoral y otros trabajos

Irene Francisco Recuero

"PAPEL DE LA AURORA QUINASA B EN LA REGULACIÓN EPIGENÉTICA INDUCIDA POR EL VIRUS DE LA HEPATITIS C". Autonoma de Madrid. Medicina. 2018. Director/es: Aurora Sánchez , Javier Samaniego . Calificación: Sobresaliente Cum laude

Ana López López

"Desarrollo de kits de detección de miRNAs del epitelio de la mucosa intestinal relacionados con alteraciones en el balance de la microbiota intestinal en pacientes oncológicos en tratamiento". Autonoma de Madrid. Medicina. 2018. Director/es: Aurora Sánchez . Calificación: en curso

Financiación

"Desarrollo de kits de detección de miRNAs del epitelio de la mucosa intestinal relacionados con alteraciones en el balance de la microbiota intestinal en pacientes oncológicos en tratamiento" ." Financiado por: Comunidad de Madrid. Año 2019-2022

Genes and Signaling Pathways in Thyroid Development and Cancer

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Acuña Ruiz, Adrián. Contrato Predoctoral Ministerio

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Cobos Figueroa, Laura. UAM (hasta julio 2018)

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Wert Carvajal, Carlos. Universidad Carlos III (hasta septiembre 2017)

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Jankovic -, Jelena. Universidada de Belgrado (Servia) (hasta agosto 2018)

Keywords: Signaling, Transcription, Proliferation, Differentiation, miRNAs, iPSC, mESC, Development, Cancer, Thyroid.
Palabras Clave: Señalización, Transcripción, Proliferación, Diferenciación, miRNAs, iPSs, mESC, Desarrollo, Cáncer, Tiroides.

Lineas de Investigación

It is well accepted that normal developmental processes and cancer share multiple pathways that are related to cell proliferation and differentiation. Our model system is the thyroid gland in where we have deciphered basic molecular and cellular mechanism and studied the most prevalent thyroid pathologies related to congenital defects and cancer.

Identification of Genes and signals involved in thyroid development.

Using mESCs, iPSC and endoderm explants, we have identified new players in thyroid development, such as Sox9, which coordinately with Nkx2.1, Foxe1, and Pax8 regulates thyroid differentiation. Using a 3D model, we have shown

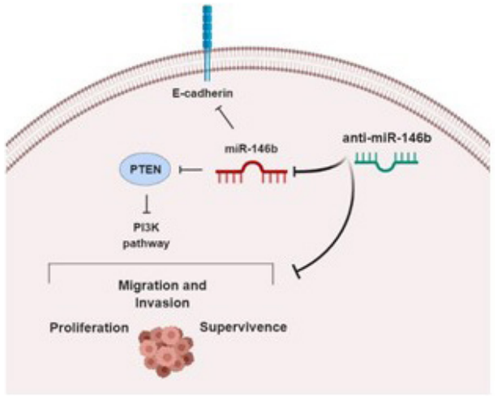

Fig. 1A

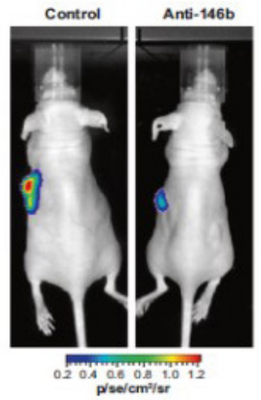

Fig. 1B

that Pax8 controls thyroid cell polarity thought cadherin-16 and consequently follicle formation, a necessary process for the synthesis of thyroid hormones. These are iodinated hormones and we have studied the role of iodine in thyroid development, demonstrating that an epigenetic mechanism is involved in the repression played by an excess of iodine during endoderm and thyroid differentiation. Congenital hypothyroidism is characterized by impairment thyroid development and we have described that the co-transcriptional factor TAZ/WWTR1 mediates the effects of NKX2.1 mutation in congenital Brain-Lung-Thyroid syndrome.

The genomic landscape of thyroid cancer

Thyroid cancer is an endocrine pathology whose incidence is increasing, although in general terms it has a good outcome. Nevertheless, some patients develop aggressive forms of thyroid cancer that are untreatable and the molecular basis of these forms is poorly understood. Our work has provided new information on cancer development and behavior, as well as new insights into genetic alterations and molecular pathways.

a) By high throughput technology we defined FOXE1 as a susceptibility gene in thyroid cancer and by genome-wide expression screening we identified several EMT-genes downstream of FOXE1.

b) By RNA-Seq we have identified the miRnome and transcriptome of papillary thyroid tumors demonstrating that miRNA expression patterns define clinically-relevant subclasses and may contribute to loss of differentiation and tumor progression. Among them, the miR-146b represses PAX8 and NIS defining a regulatory negative feedback loop. Also represses PTEN (Fig 1A), increasing PI3K signaling and therefore increases proliferation, migration and invasion. Interestingly and anti-miR-146b injected in xenotranplated thyroid tumors decreases tumor growth (Fig.1B).

c) We have studied the role of the driver mutations RAS and BRAF and the signaling pathways MAPK and PI3K in the initiation and progression of thyroid cancer. Our work demonstrated that BRAFV600E confers a biological behavior different to thyroid carcinomas. It is associated with extrathyroidal extension, with a high risk of recurrence, particularly with those who have lost the ability to accumulate iodine. We have found that the mechanism by which BRAF decreases iodide uptake is mediated by a TGFβ autocrine loop, which decreases the expression of the iodide symporter NIS, impairing its trafficking to the cell membrane, and accordingly causing refractory metastatic disease.

Publicaciones

Ziros, PG. , Habeos, I. , Chartoumpekis, DV., Ntalampyra, E. , Somm, E. , Renaud, CO. , Bongiovanni, M. , Trougakos, IP. , Yamamoto, M. , Kensler, TW. , Santisteban, P. , Carrasco, N. , Ris-Stalpers, C. , Amendola,E. , Liao, X. , Rossich, L. , Thomasz, L. , Juvenal, GJ.,Refetoff, S. , Sykiotis, GP. (2018). *The NFE2-related transcription factor 2 (Nrf2) coordinates antioxidant defense with thyroglobulin production and iodination in the thyroid gland.* Thyroid. 28: 780-798.

Huang, Y. , Qu, S. , Zhu, G. , Wang, F. , Liu, R. , Shen, X. , Viola, D. , Elisei, R. , Puxeddu, E. , Fugazzola, L. , Colombo, C. , Jarzab, B. , Czarniecka, A. , Lam, AK. , Mian, C. , Vianello, F. , Yip, L. , Riesco, G. , Santisteban, P. , O'Neill, CJ. , Sywak, MS. , Clifton-Bligh, R. , Bendlova, B. , Sýkorová, V. , Xing, M. (2018). *BRAF V600E Mutation-Assisted Risk Stratification of Solitary Intrathyroidal Papillary Thyroid Cancer for Precision Treatment.* J. Natl. Cancer Inst. 110(4): 362-370.

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Peyret, V. , Nazar, M. , Martín, M. , Quintar, AA. , Fernandez, EA. , Geysels, RC. , Fuziwara, CS. , Montesinos, MM. , Maldonado, CA. , Santisteban, P. , Kimura, ET. , Pellizas, CG. , Nicola, JP. , Masini-Repiso, AM. (2018). *Functional Toll-like Receptor 4 Overexpression in Papillary Thyroid Cancer by MAPK/ERK-Induced ETS1 Transcriptional Activity.* Mol. Cancer Res. 16(5): 833-845.

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Choe, J. , Lin, S. , Zhang, W. , Liu, Q. , Wang, L. , Ramírez, JA. , Du, P. , Kim, W. , Tang, S. , Sliz, P. , Santisteban, P. , George, RE. , Richards, WG. , Wong, K. , Locker, N. , Slack, FJ. , Gregory, RI. (2018). *mRNA circularization by METTL3-eIF3h enhances translation and promotes oncogenesis.* Nature. 561: 556-560.

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Zaballos, MA. , Santisteban, P. (2017). *Key signaling pathways in thyroid cancer.* J. Endocrinol. 235(2): R43-R61.

Tesis Doctoral y otros trabajos

Aristides López Márquez

"Expresión y función de los factores de transcripción Foxe1 y Sox9 en la célula folicular tiroidea". **Autonoma de Madrid. Ciencias Biologicas. 2017. Director/es: Pilar Santisteban . Calificación: Sobresaliente Cum Laude**

Financiación

"Nuevas dianas moleculares en la ruta RAS-ERK: Potencial terapéutico en el cáncer de tiroides." Financiado por: Asociación Española Contra el Cancer (AECC). Año 2014-2020

"Re-engineering Radioiodine Treatment." Financiado por: Medical Research Council UK. Año 2016-2020

"Genes y vías de señalización emergentes en el desarrollo y el cáncer de tiroides." Financiado por: MINECO. Año 2017-2019

"Fisiopatología tiroidea: Mecanismos implicados en cáncer, autoinmunidad y mecanismo de acción de hormonas tiroideas (TIRONET2)." Financiado por: Comunidad Autónoma de Madrid. Año 2018-2021

Transcriptional control of metabolic homeostasis

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Keywords: Metabolic homeostasis, Diabetes, Pancreatic islets, Arcuate nucleus, Neurodegeneration
Palabras clave: Homeostasis metabólica, Diabetes, Islotes pancreáticos, Núcleo arcuado, Neurodegeneración

Lineas de Investigación

Our group is interested in the study of the mechanisms that regulate the maintenance of metabolic homeostasis, both peripherally and centrally.

In the first case, we focused our attention on the study of the transcription factor ALX3. We had previously shown that in embryos ALX3 plays an important role in the development of craniofacial structures and the neural tube. However, our studies in adult mice showed its importance in the regulation of glycemic homeostasis. We discovered that ALX3 is expressed in the pancreatic islets of Langerhans, where it participates in the transcriptional regulation of the insulin gene in beta cells. In subsequent studies we documented that ALX3 deficiency compromises cell survival in pancreatic islets, leading to hyperglycemia and glucose intolerance that aggravates with age. We also documented an important regulatory role of ALX3 in alpha cells that express glucagon. In this case ALX3 acts as a sensor of glucose levels in a bimodal mode. When blood glucose levels decrease, ALX3 promotes glucagon gene expression acting on its promoter. On the contrary, when glucose levels raise, ALX3 interacts with the transcription factor PAX6 and inhibits the expression of glucagon. These findings identify mechanisms with a possible etiopathogenic significance in the development of diabetes mellitus.

In relation with these studies, and due to our interest in the central nervous system, we have investigated the mechanisms by which diabetes affects the function of particularly vulnerable neurons in the brain, increasing the risk of neurodegeneration as indicated by several epidemiological studies. In this sense, our most recent studies indicate that diabetes produces alterations that alter the processes of neurotransmission of certain dopaminergic neurons at the molecular level.

We are also interested in the study of the mechanisms by which different hypothalamic nuclei regulate the metabolic homeostasis of the organism via the coordinated control of processes such as food intake, energy expenditure, fat distribution and body composition. These studies were initiated after discovering that Alx3 is expressed in the arcuate nucleus of the hypothalamus, which plays a fundamental role in the control of food intake. Our studies indicate that ALX3 is important for the expression of proopiomelanocortin-related genes in arcuate nucleus neurons that regulate feeding.

In addition, ALX3 is important for the maintenance of energy balance, since ALX3-defcient mice exhibit reduced energy expenditure and a higher proportion of fat relative to muscle mass.

Finally, we are also involved in the study of how energy homeostasis is regulated cyclically under circadian hypothalamic control. In these studies, we are investigating the importance of photic entrainment of the suprachiasmatic nucleus via the establishment of retinohypothalamic connections for the regulation of cyclic metabolic and hormonal outputs by other hypothalamic nuclei including the ventromedial hypothalamus and the paraventricular nucleus.

Publicaciones

Ramon-Krauel, M. , Pentinat, T. , Bloks, VW. , Cebrià, J. , Ribo, S. , Pérez-Wienese, R. , Vilà, M. , Palacios-Marin, I. , Fernández, A. , Vallejo, M. , Téllez, N. , Rodríguez, MÀ. , Yanes, O. , Lerin, C. , Díaz, R. , Plosch, T. , Tietge, UJF., Jimenez-Chillaron, JC. (2018). *Epigenetic programming at the Mogat1 locus may link neonatal overnutrition with long-term hepatic steatosis and insulin resistance.* FASEB J. fj201700717RR.

García, P. , Mirasierra, M. , Moratalla, R., Vallejo, M. (2017). *Embryonic defence mechanisms against glucose-dependent oxidative stress require enhanced expression of Alx3 to prevent malformations during diabetic pregnancy.* Sci Rep. 7(1): 389.

Molinero, A. , Fernández, A. , Mogas, A. , Giralt, M. , Comes, G. , Fernandez-Gayol, O. , Vallejo, M. , Hidalgo, J. (2017). *Role of muscle IL-6 in gender-specific metabolism in mice.* PLoS ONE. 12(3): e0173675.

Tesis Doctoral y otros trabajos

Laura Ruiz Cañas

"Regulación de la homeostasis glucémica y del metabolismo lipídico por el factor de transcripción Alx3".

Universidad Autónoma de Madrid. Facultad de Medicina. 2017. Director/es: Mario Vallejo . Calificación: Sobresaliente cum laude

Financiación

"Mecanismos de control de la homeostasis metabólica y consecuencias de su desajuste."
Financiado por: Ministerio de Economía, Industria y Competitividad. Año 2018-2020

Neurobiology of Hearing

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Vallecillo Hernandez, Nestor

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García Alcántara, Fernando
Giraldez Orgaz, Fernando

Keywords: Rare diseases, deafness, hearing, IGF-1, oxidative stress, senescence and apoptosis.
Palabras clave: Enfermedades raras, sordera, audición, IGF-1, estrés oxidativo, senescencia y apoptosis.

Lineas de Investigación

1. Bases genéticas y moleculares de la pérdida de audición de diferente etiología.

1.1 Deficiencia de IGF-1: una sordera humana sindrómica rara. Fisiopatología del déficit y de la haploinsuficiencia en IGF-1. Modelos animales y celulares. Redes de respuesta al IGF-1. Firma neuroinflamatoria y balance redox.

1.2 Predisposición genética al daño auditivo. Interacción ambiente-genoma en modelos animales de hipoacusia hereditaria sometidos a estrés ambiental: ototóxicos, ruido y déficit nutricional. Daño mitocondrial. La senescencia celular durante el desarrollo del oído interno y en la progresión de la patología auditiva.

1.3 Tumores de cabeza y cuello: schwannoma vestibular.

1.4 Sordocegueras. Degeneracion retiniana asociados a déficit en el sistema IGF y alteraciones en sus dianas intracelulares.

2. Identificación de nuevas dianas terapéuticas y biomarcadores de progresión de la hipoacusia.

2.1 Reguladores de quinasas pro-inflamatorias p38 MAPK/JNK y sus fosfatasas.

2.2 Reguladores de la función de genes de las vías catabólicas de la autofagia.

2.3 Micronutrientes y metabolismo de la homocisteína (hiperhomocisteinemias).

3. Ensayo pre-clínico de nuevas terapias con pequeñas moléculas en modelos animales y celulares de sordera neurosensorial. Co-terapias para el implante coclear.

3.1 Inhibidores de apoptosis.

3.2 Facilitadores de la supervivencia celular. Antioxidantes.

3.3 Desarrollo de vías de administración, imagen biomédica y testaje de vehículos biocompatibles.

3.4 Aplicación y desarrollo de las líneas de investigación antes descritas para mejorar el diagnóstico y utilización de implantes cocleares.

Publicaciones

Varela-Nieto, I, Chowen, JA., García-Segura, LM. (2018). *Editorial: Hormones and Neural Aging: Lessons From Experimental Models.* Front Aging Neurosci. 10: 374.

Schosserer, M., Banks, G., Dogan, S., Dungel, P., Fernandes, A., Presen, DM., Matheu, A., Osuchowski, M., Potter, P., Sanfeliu, C., Tuna, BG., Varela-Nieto, I, Bellantuono, I. (2018). *Modelling physical resilience in ageing mice.* Mech. Ageing Dev. .

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Wesdorp, M., Murillo, S., Peters, T., Celaya, A., Oonk, A., Schraders, M., Oostrik, J., Gomez-Rosas, E., Beynon, AJ., Hartel, BP., Okkersen, K., Koenen, HJPM., Weeda, J., Lelieveld, S., Voermans, NC., Joosten, I., Hoyng, CB., Lichtner, P., Kunst, HPM., Feenstra, I., de Bruijn, SE., Admiraal, RJC., Yntema, HG., van Wijk, E., Del Castillo, I., Serra, P., Varela-Nieto, I, Pennings, RJE., Kremer, H. (2018). *MPZL2, Encoding the Epithelial Junctional Protein Myelin Protein Zero-like 2, Is Essential for Hearing in Man and Mouse.* Am. J. Hum. Genet. 103(1): 74-88.

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Lassaletta, L., Polak, M., Huesers, J., Díaz-Gómez, M., Calvino, M., Varela-Nieto, I, Gavilán, J. (2017). *Usefulness of Electrical Auditory Brainstem Responses to Assess the Functionality of the Cochlear Nerve Using an Intracochlear Test Electrode.* Otol. Neurotol. 38(10): e413-e420.

Magariños, M., Pulido, S., Rodríguez, M., de Iriarte Rodríguez, R., Varela-Nieto, I (2017). *Autophagy in the Vertebrate Inner Ear.* Front Cell Dev Biol. 5: 56.

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Tesis Doctoral y otros trabajos

Adelaida Celaya Puértolas

"Bases genéticas y moleculares de la sordera progresiva." UAM. Medicina. 2018. Director/es: Isabel Varela , Julio Contreras . Calificación: Sobresaliente "cum laude"

Nestor Vallecillo Hernandez

"Nuevas estrategias nutricionales y farmacológicas para la prevención de la pérdida auditiva neurosensorial en el ratón". UAM. Medicina. 2017. Director/es: Calificación: Sobresaliente cum laude

Financiación

"AGEAR-Mecanismos de protección y neuropatogénesis en la pérdida auditiva. Factores de protección y reparación ." Financiado por: FEDER/MINECO. Año 2015-2018

"MouseAGE-Development of a European network for preclinical testing of interventions in mouse models of age and age-related diseases." Financiado por: COST. Año 2015-2018

"TARGEAR-Targeting challenges of active ageing: innovative integrated strategies for the healing of age-related hearing loss." Financiado por: Comisión Europea Marie Curie . Año 2014-2017

"MULTITARGET&VIEW-CM." Financiado por: Comunidad de Madrid. Año 2018-2021

"HEARCODE-Desarrollo de nuevas terapias para la prevención y tratamiento de la pérdida auditiva basadas en la identificación de parámetros genéticos, bioquímicos y moleculares ." Financiado por: FEDER/MINECO. Año 2018-2020

Premios

"Accesit XXVIII Premio Dr. Font ." Año 2018

3 Departamento de Metabolismo y señalización celular

2017
2018

3 Departamento de Metabolismo y señalización celular

Metabolism and Cell Signaling

The Metabolism and Cell Signaling Program integrates studies on how organs and cells adapt and respond to biological and environmental stressors and the diseases arising from the dysregulation of these responses. Cell stressors include pathogenic insults, inflammation, ischemia, nutrient deficiency, genotoxic agents and autoantigens. Our Department focuses on both basic and translational research aiming to: a) understand how cells translate the environmental into biochemical events that trigger specific signaling and metabolic pathways, control gene activity, and modify cell behavior; b) identify potential biomarkers and molecular targets for diagnosis, prevention and therapeutic intervention of human diseases; c) identify and assess at preclinical level new therapies against different diseases, and d) develop new yeast mutants with industrial interest based on metabolic adaptations.

The Metabolism and Cell Signaling Department brings together investigators with complementary expertise in biochemistry, biotechnology, cellular and molecular biology, immunology, physiology, nanobiology and comparative medicine. Our multidisciplinary research involves the study of diseases ranging from diabetes mellitus, metabolic syndrome, heart failure and Parkinson's disease to autoimmunity, inflammation-driven diseases and cancer. Our goal is to provide new insights and therapeutic avenues for combating these major human diseases.

The department of Metabolism and Cell Signaling has a strong translational vocation which is reflected in patent applications and multiple collaborations with biotechnology and biomedical companies.

The department is structured in three major research areas embracing different laboratories with complementary goals, aiming to promote collaborations and to maximize resources. These areas are:

Physiopathology of the immune system: Susana Alemany, Lisardo Bosca, Victor Calvo, Antonio Castrillo, Alicia González Martín, Manuel Izquierdo and Juan Manuel Zapata

Complex diseases: Juan Jose Aragon, Carmen Delgado, Jose Gonzalez Castaño, Paloma Martin Sanz, Oscar Martinez Costa, Angela Martinez Valverde and Maria Monsalve.

Metabolism of yeasts: Carlos Gancedo

A brief description of the research performed by the members of the Department in 2017 and 2018 is provided in the following pages.

Role of map3k8 and thyroid hormones in survival and immune response to malaria

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Lineas de Investigación

Map3k8 regula la producción de mediadores inflamatorios como citoquinas y quimioquinas y es requerida por generar una respuesta eficaz frente a distintos tipos de patógenos, incluyendo parásitos. Map3k8 interviene en la fosforilación de Erk1/2 tras la activación de distintos TLRS y modula el estado de activación de Akt y JNK, y también participa en la señalización intracelular de otros tipos de receptores inmunes estructuralmente distintos. También hemos demostrado que las hormonas tiroideas alteran la sensibilidad a sepsis y el desarrollo de fibrosis por su capacidad de controlar el estado de activación de elementos cruciales involucrados en diferentes rutas intracelulares de señalización en células inmunes, como Erk1/2 y Stat3 tras la activación por IL6 o la activación de factores de transcripción Smad por TGFbeta. Además, pacientes infectados con Plasmodium presentan una disminución de la función tiroidea, aunque se desconoce si dicha disminución representa un mecanismo de defensa o es perjudicial para los pacientes.

En este proyecto proponemos investigar el efecto de la Map3k8 y las hormonas tiroideas sobre la infección por Plasmodium en un modelo de malaria experimental en ratón, incluyendo la malaria cerebral, la forma más letal de esta patología.

Para ello, analizaremos la supervivencia de ratones Wt, Map3k8-/- y con distintos niveles de hormonas tiroideas, tras la infección con P.berghei, que es la especie que reproduce más fielmente los síntomas neurológicos observados en humanos con malaria cerebral. En estos grupos de ratones también examinaremos el daño cerebral y la infiltración de células inmunes.

También analizaremos el papel de Map3k8 y las hormonas tiroideas en la severidad de la anemia, una seña de identidad de la enfermedad, así como en la eritropoiesis in vivo e in vitro, tras la infección con P.yoelli que causa que causa una forma no letal de malaria en ratón.

Ya que la anemia causada por la malaria está acompañada de una expansión de células mieloides y tanto éstas como las células del sistema linfoide tienen un papel esencial en la respuesta a la malaria, proponemos estudiar las poblaciones de las diferentes células inmunes incluyendo monocitos, células dendríticas, macrófagos, linfocitos T y B, y NK en los animales infectados.

También se examinará la correlación de las poblaciones celulares afectadas con la expresión de citoquinas y quimioquinas, que tienen un papel fundamental en la respuesta inmune a malaria.

Por último, proponemos llevar a cabo una serie de experimentos in vitro en macrofagos de los distintos ratones en presencia y ausencia de T3, con el propósito de analizar los mecanismos celulares y moleculares por los cuales Map3k8 y las hormonas tiroideas modulan el desarrollo y severidad de la infección por malaria, con la expectativa de generar nuevos conocimentos que puedan ayudar al desarrollo de nuevas estrategias terapeúticas en la lucha contra esta enfermedad.

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Financiación

"Papel de la Map3k8 y las hormonas tiroideas en la supervivencia y respuesta inmune a la malaria." Financiado por: MINECO. Año 2017-2020

Pathophysiology of inflammatory processes in the cardiovascular system

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Lineas de Investigación

Crossroad between bioactive lipids and purinergic signalling in macrophages

Cardiovascular diseases (CVD) originated from atheromatous lesions and subsequent plaque rupture is one of the major causes of morbidity and mortality around the World. Macrophages are key components and players in atherogenesis initiation and progression and, even today, at least half of the 'Major Adverse CV Events (MACE)' cannot be ascribed to specific causes (non-culprit MACE). Our aim it to understand the metabolic phenotype of these macrophages to develop new therapeutic strategies to avoid atherothrombotic events. In this line, we envision to integrate the metabolic role of the mammalian target of rapamycin (mTOR), that plays a crucial role in the metabolism of macrophages, with the sensing of 'danger signals' associated to the necrotic environment of the atheroma, in particular the role of the P2Y2/4/6 and P2X7 purinergic receptors, and the fate of the active lipids that accumulate in the course of inflammation. By studying this crosstalk we can establish how macrophage metabolism is controlled by these regulatory nodes, and provide a better understanding on how its manipulation can stabilize the plaque. The ultimate aim is to metabolically re-program macrophages to choose the right phenotype that preserves plaque integrity and stability, attenuating the extension of the lesion and, if possible, favoring regression.

Immunometabolic regulation of macrophage fate: Interaction with graphene layers

The development of new materials such as graphene, with unique properties in its conductivity, allow designing new biomaterials whose expectations for biotechnology, therapeutic and diagnostic use are poorly defined and in full expansion. Our aim is to design graphene:macrophage structures of different natures. The capacity of these biomaterials to integrate efficient remodeling of the extracellular matrix through regulating the functional macrophage polarization based on the control of its electrophysiological properties are a goal that few laboratories have the appropriate tools and experience for its characterization. We are characterizing the mechanical, physical, chemical and biological properties of graphene: macrophage dual systems.

We also propose to determine its functional response, ability to phagocytose, to remodel the extracellular matrix and to produce bioactive molecules in the cardiovascular field, such as the stabilization of atherogenic lesions, the prevention of cardiac fibrosis and the promotion of heart endo-regeneration. These studies will be performed both in murine and human macrophages, in which we have achieved conditions that maintain a high viability of these cells. These new composite biomaterials will allow a functionalization of the macrophage contributing to the resolution of the inflammation characteristic of the processes in which these cells participate, accelerating the production of the molecules responsible for tissue homeostasis.

The development of new materials such as graphene, with unique properties in its conductivity, allow designing new biomaterials whose expectations for biotechnology, therapeutic and diagnostic use are poorly defined and in full expansion. Our aim is to design graphene:macrophage structures of different natures. The capacity of these biomaterials to integrate efficient remodeling of the extracellular matrix through regulating the functional macrophage polarization based on the control of its electrophysiological properties are a goal that few laboratories have the appropriate tools and experience for its characterization. We are characterizing the mechanical, physical, chemical and biological properties of graphene: macrophage dual systems. We also propose to determine its functional response, ability to phagocytose, to remodel the extracellular matrix and to produce bioactive molecules in the cardiovascular field, such as the stabilization of atherogenic lesions, the prevention of cardiac fibrosis and the promotion of heart endo-regeneration. These studies will be performed both in murine and human macrophages, in which we have achieved conditions that maintain a high viability of these cells. These new composite biomaterials will allow a functionalization of the macrophage contributing to the resolution of the inflammation characteristic of the processes in which these cells participate, accelerating the production of the molecules responsible for tissue homeostasis.

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Tesis Doctoral y otros trabajos

Ana Ramón Vázquez

"Estudio del perfil transcripcional de los receptores nucleares LXR en un modelo celular de macrófago murino inmortalizado". Complutense de Madrid. Ciencias Químicas. 2017. Director/es: Lisardo Boscá , Antonio Castrillo . Calificación: Sobresaliente cum laude

César Eduardo Rosales Mendoza

"Papel de la pro-proteína convertasa subtilisina kexina de tipo 9 (PCSK9) en el macrófago. Implicaciones en el desarrollo de aterosclerosis". Autónoma de Madrid. Medicina. 2017. Director/es: Lisardo Boscá . Calificación: Sobresaliente cum laude

Premios

"Premio de la Real Academia de Medicina."
Año 2018

Molecular bases and intracellular signals involved in the polarized secretion of bioactive exosomes in the immune synapse and their involvement in apoptosis processes

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Lineas de Investigación

Estudio de las bases moleculares y de las señales intracelulares implicadas en la secreción polarizada de exosomas bioactivos en la sinapsis inmune y su implicación en los procesos de apoptosis.

Vesículas intraluminales dentro de los endosomas, para formar los cuerpos multivesiculares (MVBs). La estimulación de las células induce la fusión los MVBs con la membrana plasmática y la secreción de las vesículas intraluminales como exosomas. Los exosomas son una nueva modalidad de intercambio y comunicación intercelulares, especialmente en el sistema inmune. En este sistema, la activación antigénica de los linfocitos T a través del receptor para el antígeno (TCR) induce la adquisición de funciones efectoras e inmunorreguladoras fundamentales en las que participan los exosomas. Estas funciones incluyen la actividad citolítica de los linfocitos T citotóxicos (CTLs) y la apoptosis inducida por activación (AICD) de los linfocitos T. En los CTLs, los MVBs se denominan gránulos líticos. Cuando se activa el TCR, los CTLs secretan el contenido de los gránulos líticos en la sinapsis inmune, lo que induce la apoptosis de las células diana. Uno de los componentes de los gránulos líticos es el ligando de Fas (FasL) pro-apoptótico, el cual puede inducir la muerte por apoptosis de las células diana. Además, tanto los CTLs como los linfocitos T cooperadores secretan exosomas que contienen FasL, y esta secreción está implicada en el proceso de muerte celular inducida por activación (AICD). La AICD mediada por el sistema Fas/FasL se considera un proceso clave implicado en el control de la homeostasis de los linfocitos T en el sistema inmune.

Nuestros objetivos son:

1) Profundizar en los mecanismos que controlan en los linfocitos T el tráfico polarizado de los MVBs/gránulos líticos y estudiar la participación de los MVBs en la secreción de exosomas.
2) Estudiar la implicación de los exosomas en la apoptosis inducida por los CTLs, así como en el proceso de AICD. Estos estudios permitirán desarrollar estrategias dirigidas a modificar funciones esenciales de los linfocitos T, como es el caso de la citotoxicidad mediada por los CTLs, y el mantenimiento de la homeostasis de los linfocitos T a través de la AICD.

Financiación

"Estudio de las bases moleculares implicadas en el tráfico de los cuerpos multivesiculares y en secreción polarizada de exosomas por los linfocitos t: función en apoptosis y en migración linfocitarias." Financiado por: Ministerio de Economía y Competitividad. Año 2016-2019

Transcriptional Regulation of macrophage functions by LXR Nuclear Receptors

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Lineas de Investigación

Transcriptional regulation of macrophage functions

Macrophages are professional phagocytic cells that play crucial roles in immune processes, but they also perform other important functions in the regulation of metabolism and maintenance of tissue homeostasis. A simple definition of the term “macrophage” is currently a challenge due to the continuous advances in the field, with the classification of their multiple origins, the study of their reprogramming capacities during homeostasis and disease. Indeed, exciting research findings have emerged during the last several years, in which macrophage heterogeneity is now believed to be determined by a combination of signals governed by the cellular origin and others coming from the environment. Our group has studied the transcriptional regulatory circuits that control macrophage behaviour in response to different physiological or pathological situations. A fraction of the transcriptional control of macrophage functions is achieved by the Liver X receptors, LXRαand LXRβ, which are transcription factors that belong to the nuclear hormone receptor superfamily. LXRs are involved in the regulation of cholesterol, fatty acid and phospholipid metabolism. In addition to their role in sterol metabolism, LXRs are important for the immune response against microbial pathogens. LXRα and LXRβ are highly similar in sequence and most of their reported functions are substantially overlapping. During this period of 2017-18, we have expanded our understanding of LXR biology. With a combination of genetically engineered mice, functional assays, expression profiling and ChIP-sequencing data, we paved the path to understand LXR´s cell-specific targets and the specific actions of LXRα and LXRβ in macrophage immune responses. Collectively, our work aims to understand the role of LXR transcription factors in immune processes and their impact in macrophage biological processes.

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"Estudio del perfil transcripcional de los receptores nucleares LXR en un modelo celular de macrófago murino inmortalizado".
Universidad Complutense de madrid . CC Quimicas. 2017. Director/es: Antonio Castrillo .
Calificación: sobresaliente

Molecular and cellular regulation of cardiac hypertrophy and heart failure

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Keywords: cardiac hypertrophy, heart failure, ionic channels, patch-clamp technique, vitamin D, calcitriol, paricalcitol, Aril hydrocarbon receptor (AhR), kynurenines.
Palabras clave: hipertrofia cardíaca, insuficiencia cardíaca, canales iónicos, técnica de fijación con parche, vitamina D, calcitriol, paricalcitol, receptor de hidrocarburos Aril (AhR), kinurenинas.

Molecular and cellular regulation of cardiac hypertrophy and heart failure.

Myocardial hypertrophy in response to pathological stimuli has traditionally been seen as an adaptive response of cardiac muscle to the altered conditions of haemodynamic load, during which the increase in wall thickness fulfils the function of regaining normal wall stress. However, in the long term, myocardial hypertrophy predisposes individuals to heart failure, arrhythmia and sudden death. This clinical evidence suggests that the hypertrophic process cannot be entirely beneficial. We are actively engaged in attempting to understand the cellular and molecular events that underlie the hypertrophic response in the adult heart in response to pathological stimuli such as pressure overload (hypertension), ischemic injury, obesity or inflammatory mediators.
Last stage of cardiac pathologies, heart failure (HF) is a major cause of morbility and mortality. Despite therapeutic improve HF patients 's prognostic is very poor and more than 50% of those patients with severe HF are likely to die within one year. Sudden arrhythmogenic cardiac death is the major cause of mortality of these patients. We are working on elucidate the pathological mechanisms involved in contractile dysfunction and arrthythmogenesis, in order to find new therapeutic targets and develop efficient pharmacology.
Our Research Group has dilated experience and expertise on cellular cardiac electrophysiological techniques (patch-clamp) to study the cardiac channel remodeling that play an important role in the higher risk for cardiac arrhythmias associated with hypertrophied and failing hearts.

RESEARCH LINES IN PROGRESS

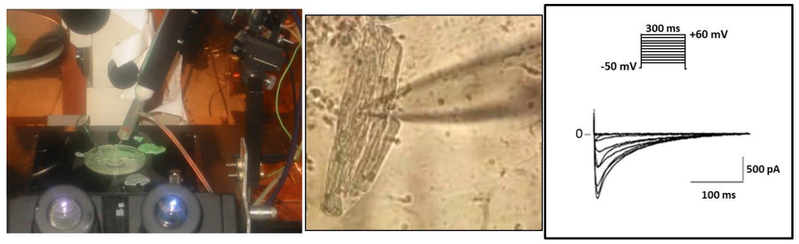
Cellular and molecular mechanisms underlying the cardioprotective effects of vitamin D.

Calcitriol, the bioactive metabolite of vitamin D, exerts its effects through interaction with the nuclear

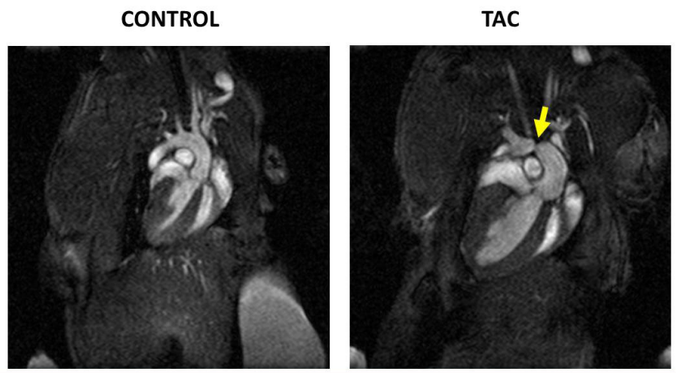
vitamin D receptor (VDR) to induce genomic responses. Calcitriol may also induce rapid responses via plasma membrane-associated VDR, involving the activation of second messengers and modulation of voltage dependent channels. We have investigate the effects of calcitriol on L-type Ca2+ channels, K+channels and intracelular calcium handling (Cai2+) in ventricular myocytes. Furthermore, we have used a model of HF induced by pressure overload to test the hypothesis that the treatment with paricalcitol (vitamin D analogue), prevents the progression of the disease and has cardioprotective effects.

Aryl hdrocarbon receptor (AhR) in myocardial infarction.

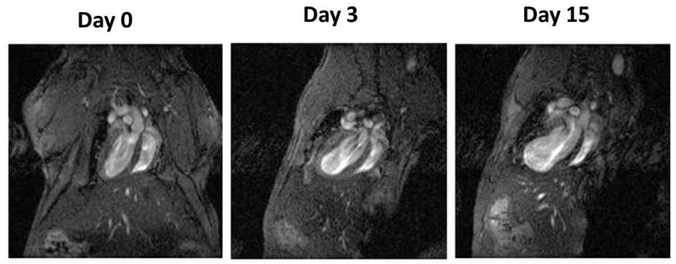
Aril hydrocarbon receptor (AhR) is a ligand activated transcription factor that mediates the toxicity of environmental pollutants. In addition, there is growing evidence suggesting that AhR has normal physiological functions and that it likely has endogenous ligands. In recent years, the AhR endogenous ligand L-kynurenine has been recognized as a biomarker that could influence cardiovascular diseases. In the present project we propose to integrate both the biology of kynurenines and AhR to gain insight on new mechanisms that can be involved on adverse ventricular remodeling after experimental myocardial infarction with the kynurenine pathway emerging as a new target for drug development.



Patch-clamp technique used to record L-type Ca^{2+} current in Ventricular cardiomyocytes isolated from a mouse heart



Cardiac magnetic resonance images obtained in one control mouse and in one mouse with transverse aortic constriction (TAC)



Cardiac magnetic resonance images obtained in the same mouse 0, 3 and 15 days after ligation of left anterior descending coronary artery (LAD). The progression of cardiac dilation is evident

Publicaciones

Tamayo, M. , Martin-Nunes, L. , Val-Blasco, A. , Piedras, MJ. , Larriba, MJ. , Gómez-Hurtado, N. , Fernández, M. , Delgado, C. (2018). *Calcitriol, the Bioactive Metabolite of Vitamin D, Increases Ventricular K+ Currents in Isolated Mouse Cardiomyocytes.* Front Physiol. 9: 1186.

Val-Blasco, A. , Navarro-García, JA. , Tamayo, M. , Piedras, MJ. , Prieto, P. , Delgado, C. , Ruiz-Hurtado, G. , Rozas-Romero, L. , Gil-Fernández, M. , Zaragoza, C. , Boscá, L. , Fernández, M. (2018). *Deficiency of NOD1 Improves the β-Adrenergic Modulation of Ca2+ Handling in a Mouse Model of Heart Failure.* Front Physiol. 9: 702.

Navarro-García, JA. , Fernández, M. , Delgado, C. , Delgado, JF. , Kuro-O, M. , Ruilope, LM. , Ruiz-Hurtado, G. (2018). *PTH, vitamin D, and the FGF-23-klotho axis and heart: Going beyond the confines of nephrology.* Eur. J. Clin. Invest. 48(4).

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Tamayo, M. , Manzanares, E. , Bas, M. , Martín-Nunes, L. , Val-Blasco, A. , Jesús Larriba, M. , Fernández, M. , Delgado, C. (2017). *Calcitriol (1,25-dihydroxyvitamin D3) increases L-type calcium current via protein kinase A signaling and modulates calcium cycling and contractility in isolated mouse ventricular myocytes.* Heart Rhythm. 14(3): 432-439.

Val-Blasco, A. , Prieto, P. , Gonzalez-Ramos, S. , Benito, G. , Vallejo-Cremades, MT. , Pacheco, I. , González-Peramato, P. , Agra, N., Terrón, V. , Delgado, C. , Martín, P. , Boscá, L. , Fernández, M. (2017). *NOD1 activation in cardiac fibroblasts induces myocardial fibrosis in a murine model of type 2 diabetes.* Biochem. J. 474(3): 399-410.

Tesis Doctoral y otros trabajos

"Mecanismos celulares y moleculares implicados en el efecto cardioprotector de la vitamina D." Financiado por: MINECO. Año 2015-2018

"Papel del receptor de hidrocarburos de arilos (AhR) en el infarto agudo de miocardio." Financiado por: MINECO. Año 2018-2020

"Efectos del paricalcitol, un activador del receptor de vitamina D sobre el acoplamiento excitación-contracción cardiaco y el remodelado eléctrico arritmogénico en un modelo experimental de insuficiencia cardiaca en el ratón." Financiado por: Sociedad Española de Cardiología (SEC). Año 2018-2022

Patentes

"Modulating compounds of KCHIP2 and its use for the treatment of cardiovascular pathologies." Año 2018

N-acetylglucosamine kinase from Yarrowia lipolytica as a moonlighting protein

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Keywords: Moonlighting/N-acetylglucosamine/Yarrowia/Yeast/Interaction/ transcription/ Glucosamine.
Palabras clave: Luz de luna / N-acetilglucosamina / yarrowia / levadura / interacción / transcripción / glucosamina.

Lineas de Investigación

Moonlighting proteins are a subset of the multifunctional proteins group. Curently there are about 400 proteins identifies in that subset. Results from our group have identified the N-acetylglucosamine (NAGA) kinase from Yarrowia lipolytica as a potential moonlighting protein. We are working to verify this idea and, if positive, identify interactions of the protein with other components of the cell.

- A first objective is to establish if the catalytic activity of the NAGA kinase is necessary for the regulatory function of this enzyme. To approach this we cloned genes encoding NAGA kinases from Homo sapiens, Candida albicans, Magnaporthe grisea and Arabidopsis thaliana and inserted them in adequate plasmids. Mutants of Y. lipolytica lacking NAGA kinase (nag5) were transformed with these plasmids and both the complementation of the growth phenotype and the transcription of the genes of the NAGA catabolic pathway were examined in the transformants.

- We are trying to localize sites that may affect the putative non-canonical activity of the protein. This is not straightforward the amino acid sequence of YlNag5 has no strong similarity with that of other NAGA kinases. However, we have identified a conserved site in a region of conserved structure whose mutation in the mammalian protein abolishes its kinase activity but does not affect its regulatory role in dendritic arborization. We are performing the mutation of this site to study its effect on the yeast protein.

- We have generated an antibody against the NAGA kinase from Y. lipolytica to study its intracellular localization and its possible interactions with other proteins.

- In the catabolism of NAGA glucosamine-6-phosphate in Y. lipolytica appears as an intermediary metabolite. In the model yeast Saccharomyces cerevisiae this metabolite is generated in the presence of glucosamine, However, S.cerevisiae does not metabolize the sugar-phosphate so that glucosamine is toxic for S. cerevisiae. We have constructed a strain of S. cerevisiae that expresses the YlNAG1 gene from Y. lipolytica encoding the glucosamine-6-phosphate deaminase.

This new strain utilizes glucosamine as carbon and nitrogen source. Metabolism of glucosamine in this new strain requires a functional respiratory chain.

Publicaciones

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Financiación

"Interacciones entre la proteína N-acetilglucosamina kinasa y diferentes circuitos de regulación génica en Yarrowia lipolytica." Financiado por: Fundación Ramón Areces. Año 2017-2020

Patentes

"Sistema de expresión en levadura de una enzima ADN polimerasa libre de ADN de origen bacteriano." Año 2017

Proteostais and neurodegerenation

Investigador Principal
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Predoctorales
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Lineas de Investigación

Mechanism of degradation of SMN and SMN delta7 implicated in Spinal Muscular Atrophy

Summary of the published paper

Spinal muscular atrophy (SMA) by loss of lower motor neurons and atrophy of muscle is the leading genetic cause of infant mortality. Spinal muscular atrophy is due to mutations affecting the SMN1 gene coding for the full-length protein (survival motor neuron; SMN) and the SMN2 gene that preferentially generates an exon 7-deleted protein (SMNΔ7) by alternative splicing. We have studied SMN and SMNΔ7 degradation in the cell,using tagged versions at the N- (Flag) or C-terminus (V5) of both proteins. Transfection of those constructs into HeLa cells and treatment with cycloheximide showed that those protein constructs were degraded. Proteasomal degradation usually requires prior lysine ubiquitylation. Surprisingly, lysine-less variants of both proteins tagged either at N- (Flag) or C-terminus (V5) were also degraded. The degradation of the endogenous SMN protein, and the protein constructs mentioned above, was mediated by the proteasome, as it was blocked by lactacystin, a specific and irreversible proteasomal inhibitor. We have also tried by cotransfection of wild-type or K0 SMN constructs with HA-ubiquitin to detect both canonical and non-canonical ubiquitylation sites like Ser/Thr/Tyr or Cys, but no ubiquitylation was detected even in the presence of proteasome inhibitors. These results indicated that degradation of SMN and SMNΔ7 does not absolutely require usual internal Lys or N-terminal ubiquitylation for degradation. Another critical point, overlooked previously, is that tagging at the N-terminus of a protein also blocks its N-terminal acetylation. In fact, the N-terminal of SMN (and likely of SMNΔ7) has been shown to be acetylated at two positions in acetylome studies (30). The N-terminal sequence of SMN is MAMSS (acetylated residues indicated with bold characters). The acetylation observed in SMN proteins by MS studies is either at the N-terminal Ala2 residue, exposed after removal of the N-terminal Met by methionine aminopeptidase or at Ser4. Ser4 acetylation is likely due to a translational initiation of SMN protein at Met3, leaving Ser4 at the N-terminus after Met3 removal by the aminopeptidase. Accordingly, SMN (and likely SMNΔ7) could be a substrate of the N-terminal acetylated N-rule pathway of degradation mediated by Doa10/March6 in a physiological context and tagging at the N-terminus prevents N-terminal acetylation. The use of the tagged of wild type and mutant proteins for the study of the physiological relevant mechanisms of the degradation of SMN and SMNΔ7 is inadequate, as those tagged constructs are unlikely to match all post-translational modifications and interactions of the natural cell endogenous SMN proteins. To untangle the problem of SMN turnover, deep proteomic techniques have to be developed for the study of the turn-over of the components of SMN (orphan and bound) complex , in order to get the basic physiological mechanisms of degradation of steady state SMN protein and its regulation. Eventually, these studies will allow the development of strategies aimed to increase SMN expression levels by regulation of its degradation as a possible therapeutic intervention for SMA patients.

Role of lysosomal and chaperone mediated autophagy in the degradation of DJ-1/PARK7, a protein implicated in Parkinson's disease

Summary of the published research

We have shown previously, using a lymphoblastoid cell line from a Danon patient, that the steady-state mRNA and protein levels of alpha-synuclein, IKBα, Rcan1, and glyceraldehyde-3-phosphate dehydrogenase, four proteins reported to be selective substrates of the chaperone mediated autophagy (CMA) pathway, were similar in control and Lamp-2-deficient cells. Furthermore, inhibition of protein synthesis showed that the half-life of alpha-synuclein, IKBα, and Rcan1 was similar in control and Lamp-2-deficient cells and its degradation prevented by proteasome inhibitors. We have now extended those results with the study of the role of lysosomes and the CMA pathway in the degradation of DJ-1/PARK7, whose mutations are associated with familial autosomal recessive Parkinson disease, moved by a recent publication reporting that those pathways participate in tits degradation. Using several cell lines with disrupted LAMP2 gene expression and their respective control cells, we show that Interruption of LAMP-2 expression did not result in an increase of the steady-state protein levels of DJ-1 /PARK7, as it would have been expected. Furthermore, no change in DJ-1 /PARK7 protein levels were observed upon inhibition of lysosomal function with NH4Cl or NH4Cl plus leupeptin, or after activation of CMA by serum starvation for 24h. Accordingly, we have found no evidence that DJ-1 /PARK7, or alpha-synuclein, (both proteins are implicated in Parkinson's disease) protein levels are regulated via lysosomal degradation or the CMA pathway.

Publicaciones

Sánchez, R. , González, J. (2018). *Inhibitors of lysosomal function or serum starvation in control or LAMP2 deficient cells do not modify the cellular levels of Parkinson disease-associated DJ-1/PARK 7 protein.* PLoS ONE. 13(7): e0201152.

Sánchez, R. , González, J. (2017). *Lysine-Less Variants of Spinal Muscular Atrophy SMN and SMNΔ7 Proteins Are Degraded by the Proteasome Pathway.* Int J Mol Sci. 18(12).

Morales, JÁ. , Gine, E. , Hernandez-Encinas, E. , Aguilar, D. , Sierra, A. , Sanz, M. , Alonso, S. , Sanchez-Lanzas, R. , González, J. , Santos, A. , Pérez-Castillo, A.M (2017). *CCAAT/Enhancer binding protein β silencing mitigates glial activation and neurodegeneration in a rat model of Parkinson's disease.* Sci Rep. 7(1): 13526.

Financiación

"CCAAT/Enhancer binding protein beta (C/EBPbeta) as a modulator of neuroinflammation. A new therapeutic target in Parkinson's disease." Financiado por: MINECO. Año 2018-2020

"Mwtabolic Basis of Neurodegeneration." Financiado por: Comunidad de Madrid. Año 2018-2021

MicroRNA control of immune tolerance, autoimmunity and cancer

Investigadora Principal
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Lineas de Investigación

Our laboratory is interested in understanding the cellular and molecular mechanisms of immune tolerance, autoimmunity and cancer. Specifically, we focus on studying how microRNAs (miRNAs) and their target genes regulate immune tolerance, autoimmune diseases and antitumor immunity. In addition, we are actively developing innovative genome engineering strategies for therapeutic purposes.

MicroRNAs have recently emerged as important factors in the post-transcriptional control of protein concentrations in metazoan organisms. For the past few years, we studied the functions of miRNAs in the mammalian immune system. We identified the first miRNA that regulates B cell tolerance and established its causative role in the development of lethal autoimmunity (Gonzalez-Martin et al, Nature Immunology, 2016 Apr;17:433-40). We also discovered critical roles for other microRNAs in different immune tolerance mechanisms and autoimmune diseases (Gonzalez-Martin and Lai et al, Nature Communications, 2016 Aug 2;7:12207, Ichiyama et al, Immunity, 2016 Jun 21;44:1284-98 and Liu et al, Journal of Experimental Medicine, Aug 22;213:1901-19). In addition, we developed the first B cell receptor reprogramming strategy using the latest genome editing technologies (Elife, 2019 Jan 17;8). Previously, work on tumor immunology established an important role for the chemokine receptor CCR5 in T cell antitumor responses (Gonzalez-Martin et al, Cancer Research, 2011 Aug 15;71:5455-66). Overall, our studies have established miRNAs as critical regulators of immune tolerance and autoimmunity, and revealed new mechanisms controlling antitumor immunity.

Current research in the lab continues to identify and study the roles of miRNAs and their target genes in immune tolerance, autoimmunity and tumor immunology by combining genetic, genomic, biochemical, and functional screen approaches to understand the functions and molecular mechanisms of miRNA control at molecular, cellular, and system levels. The mechanisms identified might provide valuable biomarkers or therapeutic targets for the treatment of autoimmune diseases and for cancer immunotherapy.

Publicaciones

Jin, HY. , Oda, H. , Chen, P. , Yang, C. , Zhou, X. , Kang, SG. , Valentine, E. , Kefauver, JM. , Liao, L. , Zhang, Y. , González, A. , Shepherd, J. , Morgan, GJ. , Mondala, TS. , Head, SR. , Kim, P. , Xiao, N. , Fu, G. , Liu, W. , Han, J. , Williamson, JR. , Xiao, C. (2017). *Differential Sensitivity of Target Genes to Translational Repression by miR-17~92.* PLoS Genet. 13(2): e1006623.

Financiación

"Functions of miRNAs in immune tolerance, autoimmunity and cancer." Financiado por: Ministry of Science, Universities and Innovation. Año 2018-2023

Premios

"L´Oréal-UNESCO For Women in Science."
Año 2018

Nanoinmunology of the linfocytes T activation and apoptosis

Investigador Principal
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Lineas de Investigación

Los exosomas son nanovesículas (50-100 nm) de doble membrana lipídica que se acumulan como vesículas intraluminales dentro de los endosomas, para formar los cuerpos multivesiculares (MVBs). La estimulación de las células induce la fusión los MVBs con la membrana plasmática y la secreción de las vesículas intraluminales como exosomas. Los exosomas son una nueva modalidad de intercambio y comunicación intercelulares, especialmente en el sistema inmune. En este sistema, la activación antigénica de los linfocitos T a través del receptor para el antígeno (TCR) induce la adquisición de funciones efectoras e inmunorreguladoras fundamentales en las que participan los exosomas. Estas funciones incluyen la actividad citolítica de los linfocitos T citotóxicos (CTLs) y la apoptosis inducida por activación (AICD) de los linfocitos T. En los CTLs, los MVBs se denominan gránulos líticos. Cuando se activa el TCR, los CTLs secretan el contenido de los gránulos líticos en la sinapsis inmune, lo que induce la apoptosis de las células diana. Uno de los componentes de los gránulos líticos es el ligando de Fas (FasL) pro-apoptótico, el cual puede inducir la muerte por apoptosis de las células diana. Además, tanto los CTLs como los linfocitos T cooperadores secretan exosomas que contienen FasL, y esta secreción está implicada en el proceso de muerte celular inducida por activación (AICD). La AICD mediada por el sistema Fas/FasL se considera un proceso clave implicado en el control de la homeostasis de los linfocitos T en el sistema inmune.

Nuestros objetivos son:

1) Profundizar en los mecanismos que controlan en los linfocitos T el tráfico polarizado de los MVBs/gránulos líticos y estudiar la participación de los MVBs en la secreción de exosomas.

2) Estudiar la implicación de los exosomas en la apoptosis inducida por los CTLs, así como en el proceso de AICD.
Estos estudios permitirán desarrollar estrategias dirigidas a modificar funciones esenciales de los linfocitos T, como es el caso de la citotoxicidad mediada por los CTLs, y el mantenimiento de la homeostasis de los linfocitos T a través de la AICD.

Publicaciones

(2018). *Imaging Polarized Secretory Traffic at the Immune Synapse in Living T Lymphocytes.* Frontiers in Immunology. 9:684: 1-13.

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(2017). *Exosomes from eosinophils autoregulate and promote eosinophil functions.* Journal of Leukocyte Biology. 101:5: 1191-1199.

Financiación

"Estudio de las bases moleculares implicadas en el tráfico de los cuerpos multivesiculares y en secreción polarizada de exosomas por los linfocitos t: función en apoptosis y en migración linfocitarias." Financiado por: Ministerio de Economía y Competitividad. Año 2016-2019

COX-2 and liver physiopathology

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Keywords: COX-2, prostaglandins, liver, NAFLD, fibrosis, ischemia/reperfusion, miRNAs.
Palabras clave: COX-2, prostaglandinas, hígado, NAFLD, fibrosis, isquemia / reperfusión, miRNAs.

Lineas de Investigación

We study the relationship between COX-2 expression and liver pathology in experimental models and human biopsies and understanding the molecular mechanisms implicated in these processes. Cyclooxygenase (COX) is the enzyme that catalyzes the rate limiting step in the synthesis of prostanoids. Prostaglandins play an important role in many biological processes such as platelet aggregation, maintenance of the gastric mucosa, reproduction, etc. and also in pathological processes such as inflammation and cancer. Work of our research group have shown that the COX-2 expression promotes the development of preneoplastic foci without affecting malignant transformation and this data can be related to the anti-apoptotic effect and the inflammatory phenomenon that occurs in the early stages of the chronic liver disease. We have also shown that the expression of COX-2 in hepatocytes protects against liver damage induced by hyperglycemia, the insulin resistance and obesity as well as against the steatohepatitis and fibrosis, suggesting improved mitochondrial function and oxidative phosphorylation. Actually, we are studying the role of COX-2 in liver ischemia/reperfusion injury and the effect on liver transplantation. COX-2, prostaglandins, liver, NAFLD, fibrosis, ischemia/reperfusion, miRNAs.

Objectives

- Dual Role of COX-2 in hepatic pathophysiology: Given the protective role of COX-2 in many of the studied diseases but also taking into account its role as inflammatory agent; it is clear that COX-2 exerts various effects depending on the time and cell type that expresses. For this we have transgenic animals and cell models for COX-2.

- Contribution of COX-2-dependent prostaglandins to the onset and progression of non-alcoholic fatty liver disease (NAFLD): Our results have shown that COX-2 attenuates non-alcoholic steatohepatitis and liver fibrosis in mice. COX-2-dependent prostaglandins induce apoptosis of hepatic stellate cells and attenuate liver fibrosis by downregulating miRNAs. Our goal is to advance the study evaluating the role of COX-2 and associated miRNAs in the progression of the lesion, analyzing involved signaling pathways and molecular mechanisms, as well as the expression of COX-2 in human samples of NAFLD and its relationship with the disease.

- COX-2 and mitochondrial function. Role in ischemia reperfusion (I/R) in the liver: Our data support the view of a novel protective effect of COX-2 induction in hepatic ischemia/reperfusion injury through a significant attenuation of the IRI-induced increase in oxidative stress and hepatic apoptosis, an increase in autophagic flux and a decrease in endoplasmic reticulum stress. Furthermore, measurement of PGE2 levels in plasma from patients who underwent liver

transplantation revealed a significantly positive correlation of PGE2 levels and graft function, and an inverse correlation with the time of ischemia. These data suggest that the presence of prostaglandins in the graft may be a marker of prognosis in recovery of liver function in the transplanted organ.

Publicaciones

Brea, R. , Motiño, O. , Francés, D. , García-Monzón, C. , Vargas, J. , Fernández, M. , Boscá, L. , Casado, M. , Martín, P. , Agra, N. (2018). *PGE2 induces apoptosis of hepatic stellate cells and attenuates liver fibrosis in mice by downregulating miR-23a-5p and miR-28a-5p.* Biochim. Biophys. Acta. 1864(2): 325-337.

Lambertucci, F. , Arboatti, A. , Sedlmeier, MG., Motiño, O. , Alvarez, MDL. , Ceballos, MP. , Villar, SR. , Roggero, E. , Monti, JA. , Pisani, G. , Quiroga, AD. , Martín, P. , Carnovale, CE., Francés, DE. , Ronco, MT. (2018). *Disruption of tumor necrosis factor alpha receptor 1 signaling accelerates NAFLD progression in mice upon a high-fat diet.* J. Nutr. Biochem. 58: 17-27.

Mojena, M. , Pimentel, M. , Povo, A. , Fernández, BV. , González, S. , Rada, P. , Tejedor, A. , Rico, D. , Martín, P. , Valverde, A.M. , Boscá, L. (2018). *Protection against gamma-radiation injury by protein tyrosine phosphatase 1B. Redox Biol.* 17: 213-223.

Mojena, M. , Povo, A. , González, S. , Fernández, BV. , Regadera, J. , Zazpe, A., Artaiz, I. , Martín, P. , Ledo, F. , Boscá, L. (2018). *Benzylamine and Thenylamine Derived Drugs Induce Apoptosis and Reduce Proliferation, Migration and Metastasis Formation in Melanoma Cells.* Front Oncol. 8: 328.

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Lambertucci, F. , Motiño, O. , Villar, S. , Rigalli, JP. , de Luján Alvarez, M. , Catania, VA. , Martín, P. , Carnovale, CE. , Quiroga, AD. , Francés, DE. , Ronco, MT. (2017). *Benznidazole, the trypanocidal drug used for Chagas disease, induces hepatic NRF2 activation and attenuates the inflammatory response in a murine model of sepsis.* Toxicol. Appl. Pharmacol. 315: 12-22.

Val-Blasco, A. , Prieto, P. , Gonzalez-Ramos, S. , Benito, G. , Vallejo-Cremades, MT. , Pacheco, I. , González-Peramato, P. , Agra, N., Terrón, V. , Delgado, C. , Martín, P. , Boscá, L. , Fernández, M. (2017). *NOD1 activation in cardiac fibroblasts induces myocardial fibrosis in a murine model of type 2 diabetes.* Biochem. J. 474(3): 399-410.

Martín, P. , Casado, M. , Boscá, L. (2017). *Cyclooxygenase 2 in liver dysfunction and carcinogenesis: Facts and perspectives.* World J. Gastroenterol. 23(20): 3572-3580.

Tesis Doctoral y otros trabajos

Rocío Brea Contreras

"Papel de la prostaglandina E2 (PGE2) dependiente de COX-2 en el desarrollo de la esteatohepatitis no alcohólica (EHNA) y fibrosis hepática. Implicación de miR-23a-5p y miR-28a-5p". Autónoma de Madrid. Medicina. 2018. Director/es: Paloma Martín . Calificación: Sobresaliente cum laude

Financiación

"Red de Medicina de Sistemas e Integración de Tecnologías Ômicas:Transcriptómica, proteómica, metabolómica y fluxómica." Financiado por: MINECO. Año 2016-2017

"Papel de la ciclooxigenasa-2 en el daño por isquemia/reperfusión en el hígado. Estudio de la función mitocondrial." Financiado por: MINECO. Año 2017-2019

"Papel de la ciclooxigenasa-2 en el daño por isquemia/reperfusión en el hígado." Financiado por: CSIC. Año 2017-2018

"Consorcio para el estudio del fracaso renal agudo: Fisiopatología, nuevas terapias, biomarcadores y modelos experimentales. CIFRA2-CM. ." Financiado por: CAM. Año 2018-2021

"CIBER de Enfermedades Hepáticas y Digestivas. CIBERehd." Financiado por: Instituto de Salud Carlos III. Año 2008-2022

Molecular mechanisms underpinning diabetes mellitus type 2 development and its complications

Investigadora Principal
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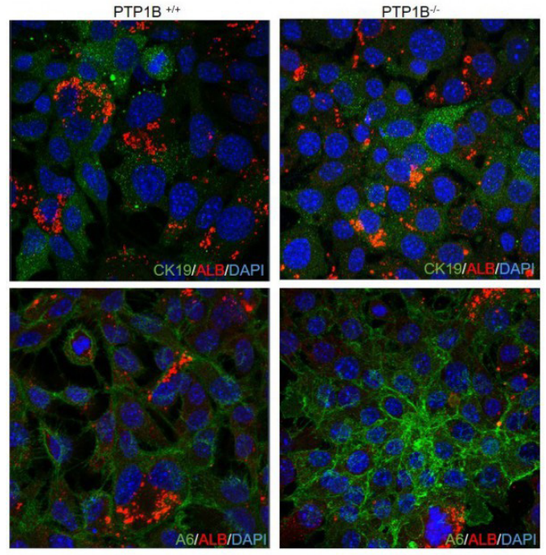
Lineas de Investigación

Molecular mechanisms associated to the progression of non-alcoholic fatty liver disease.

Keywords: Non-alcoholic fatty liver disease, inflammation, insulin resistance, obesity.
Palabras clave: enfermedad del hígado graso no alcohólico, inflamación, resistencia a la insulina, obesidad.

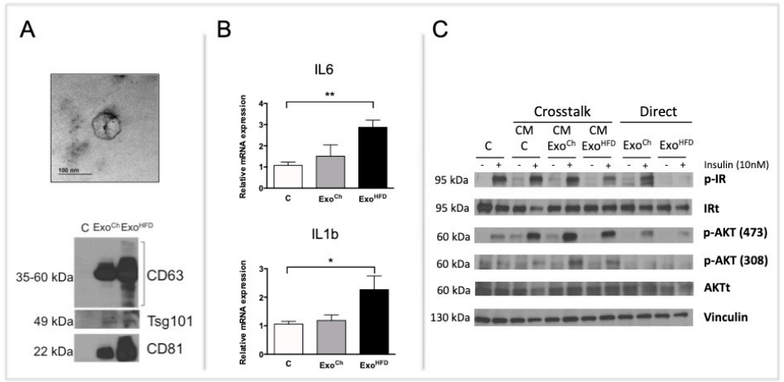
We found that protein tyrosine phosphatase 1B modulates the progression of non-alcoholic faNAFLD to non-alcoholic steatohepatitis (NASH). PTP1B-deficient mice showed an accelerated progression of NASH manifested by higher infiltration of immune cells in the liver parenchyma. On the other hand, PTP1B deficiency led to an improvement in the reversion of the disease partly due to the increased sensitivity of PTP1B-deficient oval liver cells to HGF/Met signaling.



Representative fluorescence microscopy images after staining of PTP1B $^{+/+}$ and PTP1B $^{-/-}$ Oval Cells with Albumin (ALB), Cytokeratin 19 (CK19) and A6.

EXOSOMES: NEW MESENGERS OF THE ENDOCRINE INTREACTOME IN METABOLIC SYNDROME WITH DIAGNOSTIC POTENTIAL

Keywords: Exosomes, Obesity, Liver, Inflammation, Non-alcoholic Fatty Liver Disease (NAFLD).
Palabras clave: exosomas, obesidad, hígado, inflamación, enfermedad del hígado graso no alcohólico (NAFLD)

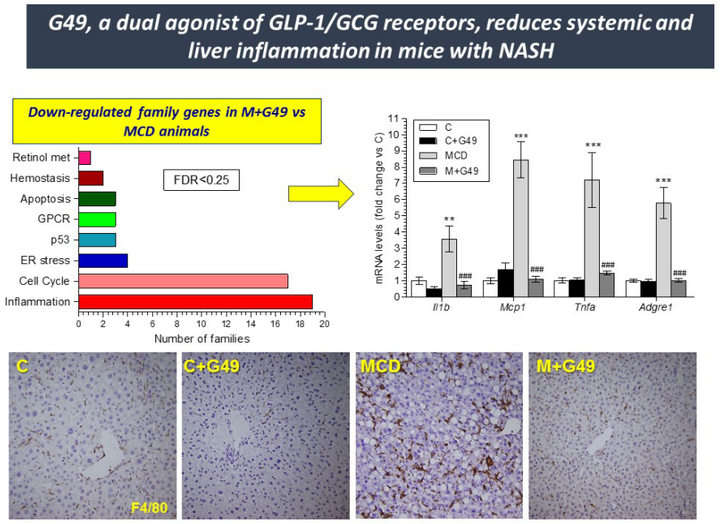


A) Characterization of exosome fraction from plasma of obese (Exo^{HFD}) and non-obese mice (Exo^{Ch}) by TEM and Western blot. **B)** Effect of exosomes on peritoneal macrophages inflammation by the expression of proinflammatory cytokines by qPCR. **C)** Study of hepatic insulin resistance by Western blot. "Crosstalk": primary hepatocytes were stimulated for 24h with conditioned medium (CM) from peritoneal macrophages treated with exosomes. "Direct": primary hepatocytes were stimulated with exosomes for 24h.

We are currently investigating the role of exosomes as new players in the interactome that modulates insulin sensitivity in liver cells. For this goal, exosomes are isolated from primary hepatocytes of different models of NAFLD and used to further stimulate different hepatic cell types (i.e. Kupper Cells, Hepatic Stellate Cells, Hepatocytes) and direct (hepatocyte-hepatocyte) or indirect (mediated by other cell types of the liver) effects on insulin sensitivity are analyzed.

Therapies based on dual agonism for GLP-1 and glucagon receptors agonists to combat NASH

Keywords: Non-alcoholic Steatohepatitis, Inflammation; GLP-1 receptor, Glucagon receptor, liver regeneration.
Palabras clave: esteatohepatitis no alcohólica, inflamación; Receptor de GLP-1, receptor de glucagón, regeneración hepática

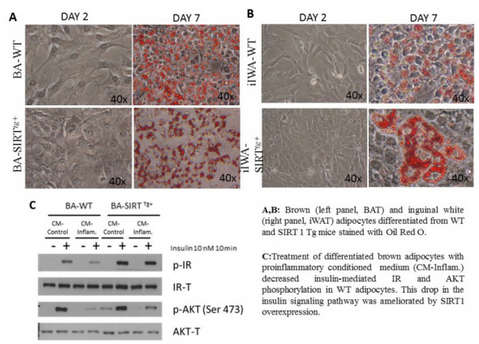


In relation to new therapeutic strategies against NASH, we investigated the efficacy of G49, a dual agonist peptide of GLP-1 and glucagon receptors, in the reversion of NASH in mice. This treatment also improved the regenerative capacity of the liver after partial hepatectomy. At a molecular level, the mechanism of action of G49 included modulation of hepatic inflammation, mitochondrial biogenesis, as well as lipid and glucose metabolism in the liver.

Inflammation linked to obesity in Brown Adipose Tissue: molecular mechanisms and therapeutic approaches

Keywords: Brown adipocytes, Inflammation, Thermogenesis, Insulin signaling, Sirtuin 1, Metformin.
Palabras clave: adipocitos marrones, inflamación, termogénesis, señalización de insulina, sirtuina 1, metformina

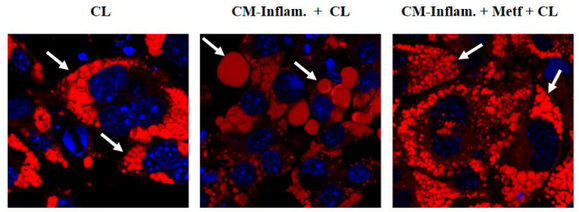
Obesity-induced chronic inflammation has a crucial role in the pathogenesis of insulin resistance and type 2 diabetes mellitus. We are investigating the impact of the inflammatory environment in insulin sensitivity and thermogenic gene expression in differentiated brown and beige adipocytes and in mice with inflammation. Our ongoing data has revealed a deleterous effect



A,B: Brown (left panel, BAT) and inguinal white (right panel, iWAT) adipocytes differentiated from WT and SIRT 1 Tg mice stained with Oil Red O.

C: Treatment of differentiated brown adipocytes with proinflammatory conditioned medium (CM-Inflam.) decreased insulin-mediated IR and AKT phosphorylation in WT adipocytes. This drop in the insulin signaling pathway was ameliorated by SIRT1 overexpression.

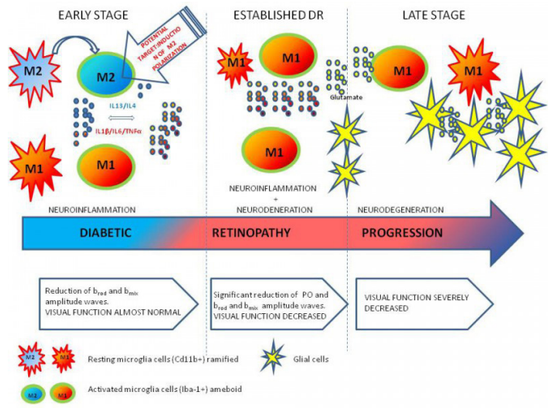
of the conditioned medium from LPS-treated macrophages in insulin-mediated signaling and noradrenaline-induced UCP-1 in brown adipocytes. This effect was ameliorated by the tratment of macrophages with LPS with metformin. We are currently investigating the molecular mechanism involved, in particular the role of HIF1α and Sirtuin 1 as well as therapeutic approaches with insulin and Sirt1 activators.



Incubation of brown adipocytes with inflammatory conditioned medium (CM-Inflam) abolished the effect of the beta 3 agonist CL 316243 in the induction of lipolysis as shown in the middle panel by the big size of lipid droplets. Inflammatory conditiones medium supplemented with metformin (CM-Inflam. + Metf.) restored the capacity of CL316243 in inducing lipolysis in brown adipocytes. Smaller lipid droplets can be observed in the right panel. BODIPY 493/503 staining after fixation is shown.

Inflammation as an early stage of diabetic retinopathy: terapeutical approaches.

Keywords: Diabetic retinopathy, inflammation, microglia.
Palabras clave: retinopatía diabética, inflamación, microglia.

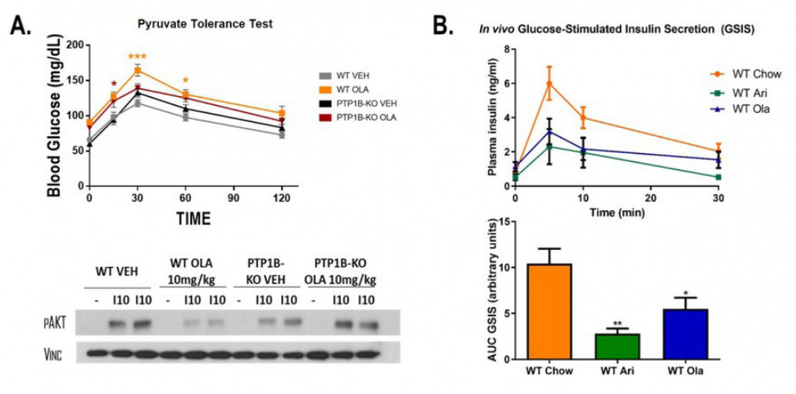


Gliosis is a hallmark of diabetic retinopathy (DR). We have reported the beneficial effects of DSO2-ONJ, a sp2-iminosugar glycolipid, in targeting microglia and reducing gliosis in retinal explants from diabetic db/db mice. The anti-inflammatory effect of DSO2-ONJ was mediated by inhibition of NFκB signaling together with a direct p38α MAPK activation in microglial cells. By computational docking experiments we demonstrated that DSO2-ONJ binds to p38α MAPK at the kinase C′-lobe. Moreover, treatment of microglial cells with DSO2-ONJ increased both HO-1 and IL10 expression. In retinal explants from db/db mice, DSO2-ONJ also induced HO-1 and reduced gliosis. Since IL-10-mediated induction of HO-1 expression is mediated by p38α MAPK activation, our results suggest that this molecular mechanism is involved in the anti-inflammatory effects of DSO2-ONJ in microglia.

Metabolic side effects of long treatment with antipsichotics: TREATMENT

Keywords: Second Generation Antipsychotics, Insulin resistance, Insulin secretion, Type 2 Diabetes Mellitus.
Palabras clave: Antipsicóticos de segunda generación, resistencia a la insulina, secreción de insulina, diabetes mellitus tipo 2.

We are evaluating the metabolic side effects of second generation antipsychotics (olanzapine and aripiprazole) in whole body insulin sensitivity and glucose homeostasis in mice treated with this drugs.

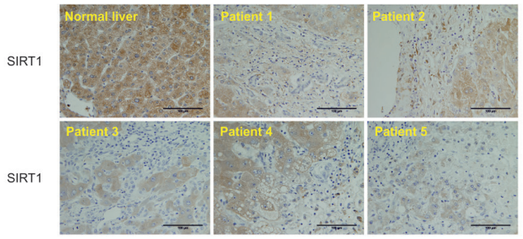


A. (Upper panel) Pyruvate tolerance test (PTT) in $PTP1B^{+/+}$ and $PTP1B^{-/-}$ mice treated for 8 weeks with olanzapine (OLA:10mg/kg/day, intraperitoneally) or vehicle (VEH) *p< 0.05; ***p< 0.001 comparisons between OLA-treated groups and VEH-treated groups of the same genotype (n=6-10 mice/group). (Lower panel) Primary hepatocytes isolated from VEH or OLA-treated mice were stimulated with insulin (10 nM) for 15 min. AKT phosphorylation was analyzed by Western blot. **B.** WT females were fed a chow diet supplemented with OLA or Aripiprazole (ARI) for after 6 months (5 mg/kg/day). Glucose-stimulated insulin secretion (GSIS) was performed at the end of the treatment. Both aripiprazole (**p<0.001) and olanzapine (*p<0.01) reduced GSIS compared to chow diet (n=6-13/group).

We are focusing in peripheral tissues (fat, liver and skeletal muscle) as well as in pancreatic beta cells. Ongoing research has evidenced differential effects of both drugs in triggering different signaling cascades that interfere with metabolic responses.

Sirtuin 1 protects against hepatotoxicity induced by paracetamol by modulating inflammatory pathways.

Keywords: Sirtuin 1, Inflammation, Hepatotoxicity.
Palabras clave: Sirtuina 1, Inflamación, Hepatotoxicidad.



SIRT1 levels are decreased in the liver of humans upon APAP intoxication. Representative anti-SIRT1 immunostaining in human liver sections from 5 individuals with severe APAP intoxication that required liver transplantation and from a healthy individual as control. Scale bars = 100 μm.

We investigated the role of Sirtuin 1 in acetaminophen (APAP)-mediated hepatotoxicity and found that SIRT1 protein levels decreased in human livers following APAP overdose. In vitro experiments in hepatocytes/macrophages and in vivo analysis in wild-type and mice overexpressing SIRT1 (SIRT1-Tg) demonstrated that SIRT1 protein levels are downregulated by IL1β/NFκB signaling in APAP hepatotoxicity, resulting in inflammation and oxidative stress. Genetic or pharmacological NFκB inhibitor preserved SIRT1 levels and protected from APAP-mediated hepatotoxicity. Thus, maintenance of SIRT1 during APAP overdose by inhibiting NFκB might be clinically relevant.

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Tesis Doctoral y otros trabajos

Andrea Villar Lorenzo

"Papel del sustrato del receptor de la insulina 2 en la susceptibilidad al daño colestático en el hígado". Universidad Autónoma de Madrid. Facultad de Mecicina. 2018. Director/es: Ángela María Martínez . Calificación:

Carmen Rubio Caballero

"Changes in gut microbiota associated to inflammation during ageing ans non-alcoholic steatohepatitis". Universidad Autónoma de Madrid. Facultad de Ciencias. 2018. Director/es: Ángela María Martínez . Calificación:

Financiación

"SPONSORED RESEARCH AGREEMENT BETWEEN MEDIMMUNE, LLC, AND." Financiado por: MEDIMMUNE SA (ASTRAZENECA). Año 2012-2017

"DESARROLLO DE MECANISMO DE ACCIÓN DEL GLICINATO DE." Financiado por: LABORATORIOS SILANES SA de CV. Año 2015-2017

"RED DE INVESTIGACION EN NRF2 COMO NODO DEL "PATOGENOSOMA." Financiado por: Ministerio de Economia y Competitividad. Año 2015-2017

"Inflammation associated with chronic metabolic damage in Type 2 diabetes and its complications." Financiado por: Ministerio de Economía y Competitivida. Año 2016-2018

"Identification of novel modulators of chronic inflammation in prevalent diseases: unveiling divergent mechanisms of disease. INFLAMES." Financiado por: Instituto de Salud Carlos III. Año 2015-2018

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"MECANISMOS MOLECULARES Y COMUNICACIÓN INTERTISULAR EN LA RESISTENCIA A LA." Financiado por: Comunidad de Madrid. Año 2018-2021

Premios

"Premio Margarita Lorenzo (Fundación Lilly) otorgado por la SEBBM." Año 2018

Mitochondrial dysfunction in metabolic diseases

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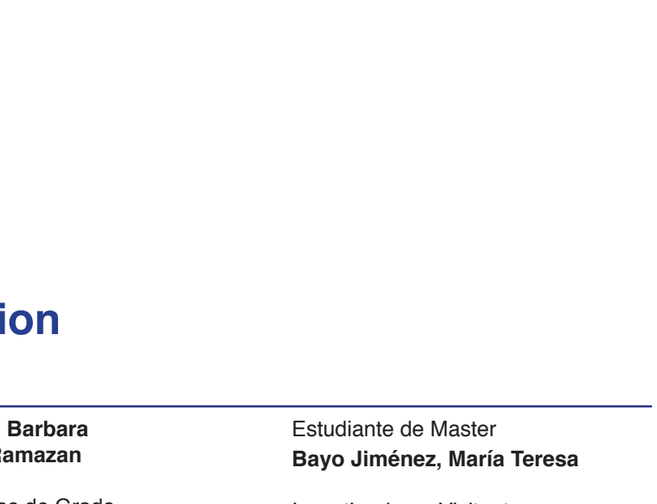
Metabolismo oxidativo y desarrollo tumoral

(Quintela, C. , Prieto, IB. , Martínez, JC. , Guerrero, D. , García, R. , Córdova, I. , Bayo, MT. , Monsalve, M)

Obesity is considered the worldwide pandemia of the XXI century. It's association with cardiovascular diseases and type 2 diabetes has been clearly established, more recently it has also being recognized a s relevant risk factor for tumor development. One study, using NCI Surveillance, Epidemiology, and End Results (SEER) data, estimated that in 2007 in the United States, about 34,000 new cases of cancer in men (4 percent) and 50,500 in women (7 percent) were due to obesity. The percentage of cases attributed to obesity varied widely for different cancer types but was as high as 40 percent for some cancers. Obesity not only increases cancer incidence, it also worsens prognosis, increasing the risk of metastasis and reducing the effectiveness of therapy.



However, the mechanisms that link tumor development to metabolic control are still very poorly understood and the use of metabolic biomarkers or metabolism based therapeutical approaches is very limited in common medical practice.

The molecular basis of the association between metabolism and cancer could be dependent on the regulation of tumor suppressor genes by factors that control metabolic pathways. Both tumors and obese subjects are characterized by a suppression of oxidative metabolism and mitochondrial production of ATP, relying heavily on glycolysis as the major source of ATP and reducing equivalents. Suppression of mitochondrial activity is also associated with elevated production of mitochondrial reactive oxygen species (ROS) and subsequent activation of NOX activity. These elevated levels of ROS are functionally relevant in tumor progression since they facilitate cellular proliferation and migration having been associated with growth factor independent cell proliferation, epitelium-mesenquimal transition, tumor angiogenesis and metastasis.

Control of oxidative metabolism, mitochondrial activity and cellular antioxidant capacity are under the regulation of the transcriptional coactivator PGC-1α. PGC-1α activity is induced by caloric restriction and reduced in obesity, and would be expected to be reduced in tumor cells. Importantly, PGC-1α regulates the activity of the tumor suppressors p53 and TLS. PGC-1α activity is particularly high in metabolically active tissues.

However, PGC-1α activity has been proposed to be associated with poor prognosis, because it induces the expression of genes that promote resistance to radiation and chemo-therapeutic agents, including antioxidant enzymes, xenobiotic catabolism enzymes, and solute carriers, that promote cellular extrusion of bioactive drugs and to induce pro-angiogenic factors that could promote tumor angiogenesis and facilitate tumor growth.

Therefore, our aim was to evaluate how the control of oxidative metabolism mediated by PGC-1α impacts on tumor development, and identify metabolic biomarkers of tumor development that could be applied to provide a personalized medicine approach to cancer treatment. To that end we used a translational perspective, starting from in vitro data to provide an much needed understanding of the mechanism of action (MOA), the implications will be validated in a mouse model of disease and finally its applicability to clinical practice will be tested through the validation of non invasive metabolic biomarkers in humans.

Efectos metabólicos colaterales debido a los tratamientos farmacológicos

(Yildiz, R. , Patel, GA. , Kramar, B. , Monsalve, M.)

Long term administration of pharmacologycal drugs may result in relevant metabolic side effects.

The molecular basis of these alterations is poorly characterized but likely related to the liver catabolism of the pharmaceutical drugs and hence to liver toxicity.

Drug detoxification mechanisms vary widely with the chamistry of the drug and among individuals, and hence there is currenly a lack of diagnostic procedures that allow to detect the subjects at risk and adjust the chemistry to the patient.

We aim to characterize the early signals of stress induced by drug administration that could allow us to predict adverse cardiovascular outcomes of long term drug administration.

Impacto en la salud debido al consumo de agua alcalina

(García, R. , Monsalve, M. , Prieto, IB.)

The tap water that most of the Spanish population drinks, despite having an excellent sanitary conditions, suffers from an ionic imbalance, which could have a negative long-term effects on human health.

This has led to the development of filtering systems for domestic use, such as the one that is owned intellectual of the Spanish company ALKANATUR. The poor implementation of these Systems in Spain it gives on the one hand a window of opportunity for the economic development of this area, and for other health improvement and its socio-economic impact especially in terms of diseases associated with aging.

In this context, ALKANATUR, a Spanish company, is in a position of socio-economic advantage. For the development of thispotentiality it is necessary to make direct assessments on the impact of the filtering of ALKANATUR water in health, and specifically in pathologies with high socio-economic cost, such as cancer and diabetes.

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Tesis Doctoral y otros trabajos

Ignacio Borja Prieto Arroyo

"Role of PGC-1α in myocardium viability and ventricular remodeling following acute myocardial infarction." Universidad de Valencia. Facultad de Medicina. 2017. Director/es: María Monsalve . Calificación: Sobresaliente Cum Laude

"Estudio del Papel de PGC-1α en Senescencia Celular y Transformación Tumoral". Universidad Autónoma de Madrid. Facultad de Medicina. 2018. Director/es: María Monsalve . Calificación: Sobresaliente Cum Laude

Financiación

"Nuevos Biomarcadores del Desarrollo Tumoral: Metabolismo y Resistencia al Estrés." Financiado por: Ministerio de Economía y Competitividad . Año 2016-2018

"Consolidación Red Multidisciplinar en Biología Redox." Financiado por: Ministerio de Economía y Competitividad . Año 2016-2018

"Training European Network: Metabolic Dysfunctions associated with PharmacologicalTreatment of Schizophrenia." Financiado por: European Commission. Año 2017-2020

"Valoración dle filtrado de agua corriente de los filtros Alkanatur sobre el dessarrollo de procesos tumorales en ratones." Financiado por: Alkanatur. Año 2018-2018

"Relación entre los daños en el ADN mitocondrial y el desarrollo de complicaciones crónicas en pacientes diabéticos tipo 2." Financiado por: Universidad Europea de Madrid. Año 2018-2018

Preclinical models and new therapies

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Carr Baena, Pablo Miguel

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Ortiz de Zarate, Sonsoles

Estudiante de Master
De Andrés Murillo, Andrea

Colaboraciones
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Estudiantes de Licenciatura
Peña Gutiérrez, Irene

Investigadores Visitantes
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Jiménez Gómez, Blanca
Balbi Santana, Oriana. University of Cincinnati, EEUU

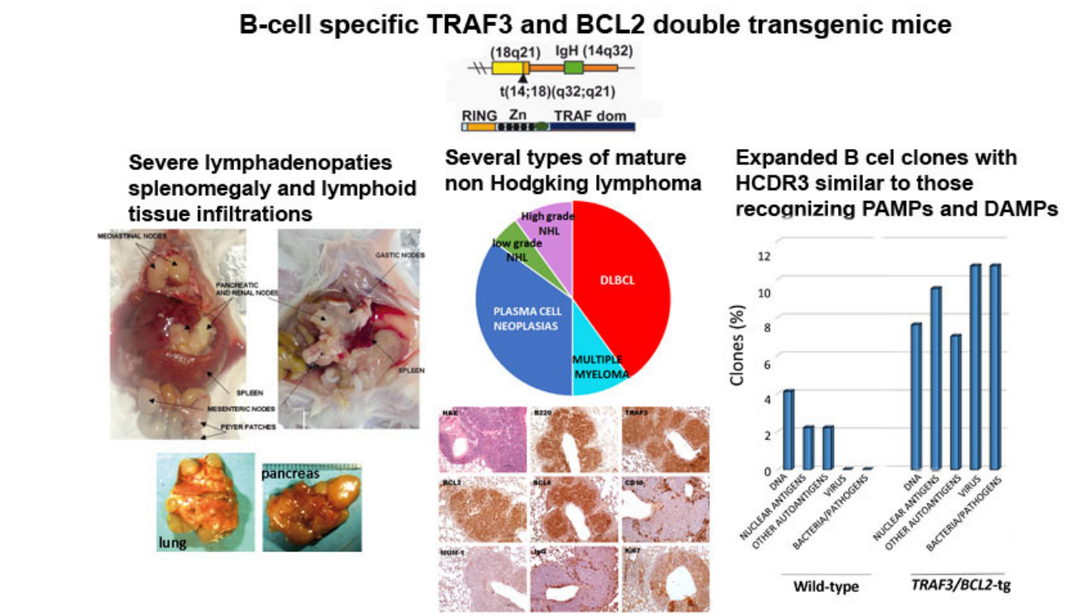
Lineas de Investigación

Preclinical models: Role of TRAF3 in B cell lymphomagenesis.

TRAF3 is a master regulator of B cell homeostasis and function that has been shown to bind and regulate various proteins involved in the control of innate and adaptive immune responses.

Our results show that transgenic mice overexpressing TRAF3 and BCL2 in B cells develop with high incidence severe lymphadenopathy, splenomegaly and lymphoid infiltrations into tissues and organs, as a result of the growth of clonal B cell neoplasms, as demonstrated by analysis of VHDJH gene rearrangement.

TRAF3/BCL2 mice developed a variety of mature B cell neoplasms, mostly mature B cell neoplasms consistent with diffuse large B cell lymphoma and plasma cell neoplasms. The Ig isotypes expressed by the expanded B-cell clones included IgA, IgG and IgM, with most having undergone somatic hypermutation. In contrast, mouse littermates representing all the other genotypes (TRAF3-/BCL2-; TRAF3+/BCL2- and TRAF3-/BCL2+) did not develop any lymphadenopathy within the observation period of 20 months. Remarkably, a large representation of the HCDR3 sequences expressed in the TRAF3-tg and TRAF3/BCL2-double-tg B cells are highly similar to those recognizing pathogen-associated molecular patterns and damage-associated molecular patterns, strongly suggesting a role for TRAF3 in promoting B cell differentiation in response to these antigens and supporting previous results from the laboratory showing that TRAF3 overexpression renders B cells hyper-reactive to antigens and Toll-like receptor (TLR) agonists. Finally, TRAF3/BCL2 tumor B cells were successfully allotransplantated into SCID/NOD immunodeficient mice. Altogether, these results indicate that TRAF3,

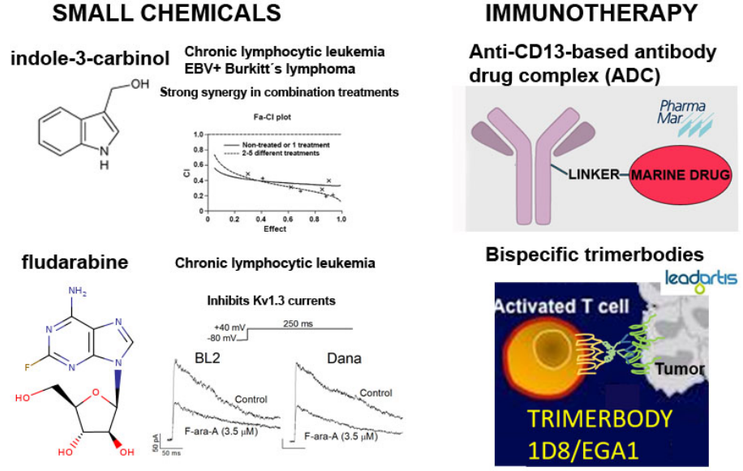


perhaps by promoting exacerbated B cell responses to certain antigens, and BCL2, presumably by supporting survival of these clones, cooperate to induce mature B cell neoplasms in transgenic mice.

New Therapies: small chemicals and immunotherapeutic tools

Small Chemicals

We have identified indole-3-carbinol (I3C), a nutraceutical found in Cruciferae plants, as a new drug suitable for treating chronic lymphocytic leukemia (CLL) and Epstein-Barr virus Burkitt´s lymphoma. Our data indicate that bioavailable concentrations of I3C strongly synergize with fludarabine and other chemotherapeutic drugs ex vivo in cells from CLL patients that have developed multiresistances to treatment.
In collaboration with T. Rodriguez (IIBm) we have identified a new activity for the anti-tumor drug fludarabine as an inhibitor of Kv1.3 channel, a voltage-dependent potassium channel family member.



New tools for immunotherapy

In collaboration with LeadArtis, we have described the anti-tumoral activity of an Fc-free tumor-targeted 4-1BB-agonistic trimerbody, 1D8n/cEGa1, consisting of three anti-4-1BB single-chain variable fragments and three anti-EGFR single domain nanobodies. This dual trimerbody has strong affinity for both 4-1BB and EGFR and rapidly accumulates in EGFR-positive tumors, exhibiting potent anti-tumor activity without the hepatotoxicity associated with IgG-based 4-1BB agonists.

In collaboration with Pharma Mar, UAM and UB we have developed a new antibody drug complex (ADC) based on an anti-CD13 mAb and the marine compound PM050489, which shows an excellent anti-tumor activity in a CD13-positive fibrosarcoma murine xenograft model. In addition, we also have participated in the characterization of new linkers for ADC production.

In collaboration with A. Rodriguez we have developed new NF-κB-driven IL12-based lentiviral vectors for intratumoral delivery that maintain their anti-tumoral activity with reduced systemic toxicity.

Publicaciones

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Financiación

"Papel de TRAF1 en la regulación de la función de los miembros de la familia de los TNFR en linfocitos T: implicaciones en la maduración del timo y en patologías de linfocitos T." Financiado por: Instituto de Salud Carlos III. Año 2017-2019

"Inmunoterapia del cáncer mediante anticuerpos biespecíficos coestimuladores." Financiado por: Ministerio de Economía y Competitividad. Año 2017-2019

Patentes

"Antibody drug conjugates." Año 2018

Premios

"Professor Durantez - Foundation L.A.I.R. prize for the best article in the field of immunology carried out in a Spanish laboratory." Año 2017

4 Modelos Experimentales de Enfermedades Humanas

2017
2018

4 Modelos Experimentales de Enfermedades Humanas

Experimental Models of Human Disease

The development of experimental models of the different human diseases is one of the bases of the present progress in medical sciences. These models allow the study of the molecular bases of the diseases and are of paramount importance for the search and testing of new drugs and treatments. The development of these models is the common goals of the research that takes place in our Department. The models systems used and the diseases studies are diverse. Among the diseases are mitochondrial-related pathologies, neurodegenerative, cardiovascular, muscular, bone diseases and syndromes, telomere-related diseases and cancer. Some of diseases studied are of very low prevalence and are considered rare diseases. Besides these basic studies, an important part of our work is translational and focused on the attention to the patients. For example, genetic studies on patient samples aimed to the molecular diagnosis of several diseases are carried out. These clinically oriented studies are made in collaboration with several Hospitals of the Spanish sanitary system.

Human clinical samples and cell lines are used for these studies together with experimental models such as mice, Drosophila melanogaster, Saccharomyces cerevisiae or Dictyostelium dicoideum. These studies have allowed the identification of new therapeutic targets, molecules with possible pharmaceutical application and biomarkers.

The Department is presently formed by 16 tenured scientists. Among the research topics are the following:

- Cardiac electrophysiology (Carmen Valenzuela, Teresa Gonzalez)
- Neurodegenerative diseases (Ana Perez-Castillo)
- Mitochondrial biogenesis and physiopathology (Miguel Fernandez Moreno, Juan José Arredondo, Rafael Garesse)
- Bone and muscular hereditary diseases and ciliopathies (Victor Ruiz and Francesc García Gonzalo)
- Telomere-related diseases (Rosario Perona, Isabel Sanchez- Perez, Leandro Sastre)
- Protein trafficking and degradation (Olivier Vincent, Ricardo Escalante)
- Tumor microenvironment and metastasis (Francisco Portillo, Pilar Eraso, María Jesús Mazón, together with Amparo Cano, of the Cancer Department)

Role of EMT-TFs and Lysyl Oxidase-like 2 and 3 (LOXL2/LOXL3) in tumour progression and metastasis

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Vázquez Naharro, Alberto

Personal de Apoyo
Santos Fernández, Vanesa
Yuste Pérez, Lourdes. UAM (hasta diciembre 2018)

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Lineas de Investigación

Role of EMT-TFs and Lysyl Oxidase-like 2 and 3 (LOXL2/LOXL3) in tumour progression and metastasis

LOXL2 and LOXL3 proteins belong to the lysyl oxidase family, constituted by lysyl oxidase (LOX) and four lysyl oxidase-like paralogs (LOXL1 to LOXL4). LOX family members are lysine-tyrosylquinone-dependent copper amine oxidases that catalyze the oxidative de-amination of the ε-amino group in certain peptidyl lysine residues promoting covalent cross-linkages. Accumulating evidence indicates the participation of lysyl oxidases in a plethora of biological extra- and intra-cellular functions ranging from extracellular matrix maturation to tumorigenesis and metastasis,. Our previous studies described that intracellular LOXL2 and LOXL3 regulate Snail1 stability and functionality being in the case of LOXL2 independent of its catalytic activity, and further studies indicated that LOXL2 plays also Snail1-independent roles in EMT and cooperates with other EMT-TFs, like E47/TCF3. LOXL2 perinuclear localization is a poor prognosis factor in human squamous cell carcinomas and it is associated to metastatic basal breast carcinomas (BBC). Regarding LOXL3, our studies identified LOXL3 overexpression in a broad cohort of human melanoma samples and an essential role for LOXL3 in melanoma cell survival. Our main research interest focus on a deep understanding of the role of LOXL2 and LOXL3 in tumorigenesis and metastasis, in particular we aim to dissect the contribution of their intra and extracellular functions to initiation and/or progression of breast carcinoma and melanoma, respectively. To this end, we have develop genetically modified mouse models (GEMs) for conditional deletion of Loxl2 and Loxl3, as well as conditional overexpression of

Loxl2 in specific mouse cancer model, as breast and melanoma, together with a broad range of mouse and human tumor-derived cell lines manipulated for Loxl2 or Loxl3 expression. We have also generated and characterized GEM with conditional deletion of E2A gene (coding for E47/E12 EMT-TF) in the context of PyMT breast cancer.

During the last two years (2017 and 2018), the main objectives addressed are summarized as:

1. Characterization of LOXL2 action in breast tumors. In vivo and in vitro studies have allowed identify the prominent action of Loxl2 in lung breast cancer metastasis. Mechanistically, Loxl2 induces invasion by regulating Snail1 stability and favors the generation of the lung pre-metastatic niche.

2. Characterization of LOXL3 action in melanoma. In vitro analyses in human melanoma cell lines identified LOXL3 pro-survival action mediated by regulation of DNA repair and mitotic exit contributing to maintain the high genetic instability of melanoma. Further studies on GEM of melanoma support a role for Loxl3 in melanoma initiation and lymph node metastatic dissemination

3. Characterization of E47/E12 action in breast cancer initiation and metastasis. The GEM of E2A KO gene in the PyMT breast cancer model has provided strong evidence for the participation of E47 EMT-TF in breast cancer initiation and lung metastasis. At least, some of the E47 actions are mediated by functional interaction with Snail1 as well as with Loxl2.

Publicaciones

Kober, KI., Cano, A., Géraud, C., Sipilä, K., Mobasseri, SA., Philippeos, C., Pisco, AO., Stannard, A., Martín, A., Salvador, F., Santos, V., Boutros, M., Rognoni, E., Watt, FM. (2018). *Loxl2 is dispensable for dermal development, homeostasis and tumour stroma formation.* PLoS ONE. 13(6): e0199679.

Pérez, EM., Eraso, P., Mazón, MJ., Santos, V., Moreno, G., Cano, A., Portillo, F. (2017). *LOXL2 drives epithelial-mesenchymal transition via activation of IRE1-XBP1 signalling pathway.* Sci Rep. 7: 44988.

González, P., Floristán, A., Fontanals-Cirera, B., Vázquez, A., Santos, V., Morales, S., Yuste, ML., Peinado, H., García-Gómez, A., Portillo, F., Hernando, E., Cano, A. (2018). *Lysyl oxidase-like 3 is required for melanoma cell survival by maintaining genomic stability.* Cell Death Differ. 25:935-950

Salvador, F., Martín, A., López, C., Moreno, G., Santos, V., Vazquez-Naharro, A., González, P., Morales, S., Dubus, P., Muinelo-Romay, L., López López, R., Tung, JC., Weaver, VM., Portillo, F., Cano, A. (2017). *Lysyl oxidase-like protein LOXL2 promotes lung metastasis of breast cancer.* Cancer Res. 77:5846-5859

Santamaria, PG., Moreno, G., Portillo, F., Cano, A. (2017). *EMT: Present and future in clinical oncology.* Mol Oncol. 11: 718-738

Financiación

"Contribution of LOXL3 to melanomagenesis." Financiado por: Worldwide Cancer Research (UK). Año 2016-2018

"Contribution of LOXL2 and LOXL3 to tumour progression and metastasis ." Financiado por: Subdirección General de Investigación. Ministerio de Economía y Competititvidad. Año 2017-2019

"Consorcio Ciber. Area temática de cáncer (CIBERONC)." Financiado por: Fondo de Investigaciones Sanitarias (FIS). Instituto de Salud Carlos III. Año 2017-202

Premios

A. Cano

"Premio Internacional de Investigación Oncológica Ramiro Carregal. VII Edición." Año 2018

A. Cano

"Premio Honorífico a la mejor trayectoria investigadora. IdiPAZ ." Año 2017

"Tercer premio. Revisiones mas citadas publicadas ultimos 5 años. IdiPAZ." Año 2018

In vivo and ex vivo applications of Magnetic Resonance Imaging and Spectroscopy in Bioedicine

Investigador Principal
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Investigadores Asociados
Lado Touriño, Isabel. Universidad Europea de Madrid (hasta diciembre 2018)

Investigadores Contratados
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García Álvarez, Isabel. Agencia Estatal CSIC (hasta diciembre 2017)
Lage Negro, Eduardo. Universidad Autónoma de Madrid (hasta diciembre 2017)
Lizarbe Serra, Blanca. Agencia Estatal Consejo Superior de Investigaciones Científicas (hasta junio 2019)
Pacheco Torres, Jesús. Agencia Estatal CSIC (hasta diciembre 2021)
Negri -, Viviana. Agencia Estatal CSIC (hasta diciembre 2017)

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Benitez Sánchez del Campo, Ania. Agencia Estatal CSIC (hasta diciembre 2017)
Gandía González, Maria Luisa. Agencia Estatal CSIC (hasta agosto 2020)

Personal de Apoyo
Guillén Gómez, María José (hasta junio 2019)

Lineas de Investigación

Artifical Intelligence Analysis from Magnetic Resonance Images of Hunger Stimulation

We have designed, implemented and validated a novel image processing strategy to obtain in vivo maps of hunger stimulation in the brain of mice, rats and humans, combining Diffusion Weighted Magnetic Resonance Imaging (DWI) datasets from fed and fasted subjects.Hunger maps were obtained from axial/coronal (rodents/humans) brain sections containing the hypothalamus and coplanar cortico-limbic structures using Fisher's Discriminant Analysis of the combined voxel ensembles from both feeding situations. These maps were validated against those provided by the classical mono-exponential diffusion model as applied over the same subjects and conditions. Mono-exponential fittings revealed significant Apparent Diffusion Coefficient (ADC)decreases through the brain regions stimulated by hunger, but rigorous parameter estimations imposed the rejection of considerable number of pixels. Theproposed approachavoided pixel rejections and provided a representation of the combined DWI dataset as a pixel map of the "Hunger Index" (HI), a parameter revealing the hunger score of every pixel. The new methodology proved to be robust both, by yielding consistent results with classical ADC maps and, by reproducing very similar HI maps when applied to newly acquired rodent datasets. ADC and HI maps demonstrated similar patterns of activation by hunger in hypothalamic and cortico-limbic structures of the brain of rodents and humans, albeit with different relative intensities, rodents showing more intense activations by hunger than humans, for similar fasting periods. The proposed methodology may be easily extended to other feeding paradigms or even to alternative imaging methods.

Correlations between Magic Angle Spinning Magnetic Resonance Spectra and Genomic Expression

We used 1H, 13C HRMAS and genomic analysis to investigate regionally the transition from oxidative to glycolytic phenotype and its relationship with altered gene expression in adjacent biopsies through the brain of rats bearing C6 gliomas. Tumor-bearing animals were anesthetized and infused with a solution of [1-13C]-glucose, and small adjacent biopsies were obtained spanning transversally from the contralateral hemisphere (regions I and II), the right and left peritumoral areas (regions III and V, respectively), and the tumor core (region IV). These biopsies were analyzed by 1H, 13C HRMAS and by quantitative gene expression techniques. Glycolytic metabolism, as reflected by the [3-13C]-lactate content, increased clearly from regions I to IV, recovering partially to physiological levels in region V. In contrast, oxidative metabolism, as reflected by the [4-13C]-glutamate labeling, decreased in regions I-IV, recovering partially in region V. This metabolic shift from normal to malignant metabolic phenotype paralleled changes in the expression of HIF1α, HIF2α, HIF3α genes, downstream transporters, and regulatory glycolytic, oxidative, and anaplerotic genes in the same regions. Together, our results indicate that genetic and metabolic alterations occurring in the brain of rats bearing C6 gliomas colocalize in situ and the profile of genetic alterations in every region can be inferred from the metabolomic profiles observed in situ by multinuclear HRMAS.

Advances Contrast Agents for Multimodal Biomedical Imaging based in Nanotechnology

Clinical imaging modalities have reached a prominent role in medical diagnosis and patient management in the last decades.
Different image methodologies as Positron Emission Tomography, Single Photon Emission Tomography, X-Rays, or Magnetic Resonance Imaging are in continuous evolution to satisfy the increasing demands of current medical diagnosis. Progress in these methodologies has been favored by the parallel development of increasingly more powerful contrast agents. These are molecules that enhance the intrinsic contrast of the images in the tissues where they accumulate, revealing noninvasively the presence of characteristic molecular targets or differential physiopathological microenvironments. The contrast agent field is currently moving to improve the performance of these molecules by incorporating the advantages that modern nanotechnology offers. These include, mainly, the possibilities to combine imaging and therapeutic capabilities over the same theranostic platform or improve the targeting efficiency in vivo by molecular engineering of the nanostructures. In this review, we provide an introduction to multimodal imaging methods in biomedicine, the sub-nanometric imaging agents previously used and the development of advanced multimodal and theranostic imaging agents based in nanotechnology. We conclude providing some illustrative examples from our own laboratories, including recent progress in theranostic formulations of magnetoliposomes containing ω-3 poly-unsaturated fatty acids to treat inflammatory diseases, or the use of stealth liposomes engineered with a pH-sensitive nanovalve to release their cargo specifically in the acidic extracellular pH microenvironment of tumors.

Biomedical MRI applications of functionalized multi-walled carbon nanotube suspensions

We investigated the magnetic properties of stable suspensions from oxidized Multiwalled Carbon Nanotubes (MWCNT) functionalized with aminopyrene (AP). MWCNT form π–π stacking adducts with AP (AP-MWCNT), originating homogenous, stable, suspensions in N,N-dimethylformamide (DMF) or melted agarose.First, we investigated the magneto-optical properties of these adducts. When applying series of pulsed magnetic fields to nanotube suspensions in DMF, the pattern of light dispersed increased during the magnetic pulse and decreased in the intervals, a behavior consistent with magnetic field induced orientation of the adducts. When adducts were suspended in a melted agarose gel under an external magnetic field, the extinction coefficient of polarized light through the gel, was larger when the polarization plane was parallel to the magnetic field direction. Based on the magneto-optical responses observed, we further investigated the magnetic properties of AP-MWCNT implementing measurements with Superconducting Quantum Interference Device, Zero Field Cooling and Field Cooling, Thermogravimetric and Differential Scanning Calorimetry.Pre-oriented AP-MWCNT suspensions depicted a clear superparamagnetic character with hysteresis loops revealing larger magnetic susceptibility values along their longitudinal axis. In summary, magneto-optical and SQUID measurements revealed that nanotube adducts in suspension, behave as nanoscale compass needles aligning their long axis parallel to externally applied magnetic fields.

Carbonic anhydrase IX is a pH-stat that sets an acidic tumour extracellular pH in vivo.

We used 1H magnetic resonance spectroscopic imaging (MRSI) of the extracellular pH probe imidazolyl succinic acid (ISUCA) to measure and spatially map extracellular pH in HCT116 tumours transfected to express CAIX and empty vector controls in SCID mice. We also measured intracellular pH in situ with 31P MRS and measured lactate in freeze-clamped tumours. CAIX-expressing tumours had 0.15 pH-unit lower median extracellular pH than control tumours (pH 6.71 tumour vs pH 6.86 control, P = 0.01). Importantly, CAIX expression imposed an upper limit for tumour extracellular pH at 6.93. Despite the increased lactate concentration in CAIX-expressing tumours, 31P MRS showed no difference in intracellular pH, suggesting that CAIX acidifies only the tumour extracellular space. CAIX acidifies the tumour microenvironment, and also provides an extracellular pH control mechanism. We propose that CAIX thus acts as an extracellular pH-stat, maintaining an acidic tumour extracellular pH that is tolerated by cancer cells and favours invasion and metastasis.

Publicaciones

(2018). *Advanced Contrast Agents for Multimodal Biomedical Imaging Based on Nanotechnology.* Methods Mol Biol. 1718: 441-457.

(2018). *Spatially Resolved Bioenergetic and Genetic Reprogramming Through the Brain of Rats Bearing Implanted C6 Gliomas As Detected by Multinuclear High-Resolution Magic Angle Spinning and Genomic Analysis.* J. Proteome Res. 17: 2953-2962.

(2018). *Magnetic Anysotropy of Functionalizad Multi-Walled Carbon Nanotubes.* En: Carbon. (Mauricio Torres eds.). Elsevier, Amsterdam. pp.229-237.

(2018). *Carbonic anhydrase IX is a pH-stat that sets an acidic tumour extracellular pH in vivo.* Br. J. Cancer. 119: 622-630.

(2018). *Premios nobel de Quimica 2017.* En: Premios Nobel 2017: Comentarios a sus actividades y descubrimientos. (Cascales, M., Mayor Zaragoza, F., Ortiz-Melon, J.M. eds.). Fundación Ramón Areces, Madrid. pp.75-95.

(2017). *Drug delivery from engineered organisms and nanocarriers as monitored by multimodal imaging technologies.* En: AIMS Bioengeneering. (Ioanis Androulakis eds.). AIMS Press, New York.

Tesis Doctoral y otros trabajos

Ania Benitez Sánchez del Campo

"Intelligent Analysis of Cerebral Magnetic Resonance Images: Extracting Relevant Information from Small Datasets". Universidad Autonoma de Madrid. Escuela Politécnica Superior. 2017. Director/es: Sebastián Cerdán. Calificación: Sobresaliente

Financiación

"Advances theranostic nanomedicines for oncology." Financiado por: Union Europea. Año 2018-2021

"Papel de los centros de recompensa cerebral en la regulación del apetito detectada mediante imagen por resonancia magnética ponderada en difusión 2018-2021." Financiado por: Ministerio de Economia y Competitividad. Año 2018-2021

"Imagen multimodal de la respuesta terapéutica a estrategias multidiana en enfermedades neurologicas." Financiado por: Comunidad de Madrid. Año 2018-2021

Molecular mechanism of autophagy in Dictyostelium and human cell lines with a focus on rare diseases

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Lineas de Investigación

Autophagy is a degradative process of cellular components that has been conserved in eukaryotic evolution. In certain circumstances, like starvation or cellular stress, parts of the cytoplasm are included in double membrane vesicles called autophagosomes that fuse later to lysosomes where they are degraded. Autophagy is also induced in other circumstances like the elimination of protein aggregations, organelles or bacteria and it is therefore of immense importance in diverse pathological processes as well as in aging.

We use an integrated approach that combines biochemistry, genetics and cell biology in the experimental model Dictyostelium discoideum and mammalian cells to study the molecular mechanism of autophagosome formation and the role of autophagy in rare disease.

The specific aims are:

· Identification of new proteins of the autophagic machinery and its regulation
· Function of Vmp1 in the origin of autophagosomes and regulation of PtdIns3P signalling
· Study of the function of VPS13 protein family. The possible role of autophagy in the associated diseases: Chorea-acanthocytosis and Cohen Syndrome
· WIPI proteins in autophagy and its role in the rare disease BPAN.

Publicaciones

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Tesis Doctoral y otros trabajos

Sandra Muñoz Braceras

"The role of VPS13 proteins in autophagy". Universidad Autónoma de Madrid. Medicina. 2017. Director/es: Ricardo Escalante . Calificación: Sobresaliente Cum Laude y Premio Extraordinario

Luis Carlos Tábara Rodríguez

"Role of VMP1 in membrane trafficking". Universidad Autónoma de Madrid. Medicina. 2018. Director/es: Ricardo Escalante . Calificación: Sobresaliente Cum Laude

Eunice Alejandra Domínguez Martín

"La respuesta al estrés de retículo endoplásmico en Dictyostelium discoideum". Universidad Autónoma de Madrid. Medicina. 2018. Director/es: Ricardo Escalante . Calificación: Sobresaliente Cum Laude

Financiación

"VPS13Aand autophagy, possible connections and preclinical studies." Financiado por: Advocacy for Neuroacanthocytosis Patients (ANP). UK.. Año 2017-2018

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Molecular Basis of Ciliopathies

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Lineas de Investigación

Identificación de señales de localización ciliar en GPCRs

Identificación y caracterización mecanística de las señales de localización ciliar (CLSs) necesarias y suficientes para que HTR6 y SSTR3, dos receptores acoplados a proteína G (GPCRs) ciliares, se acumulen en el cilio.

Identificación de señales de localización ciliar en INPP5E

Identificación y caracterización mecanística de las señales de localización ciliar (CLSs) necesarias y suficientes para que INPP5E, una fosfoinosítido 5-fosfatasa cuyas mutaciones causan las ciliopatías síndrome de Joubert y MORM, se acumule en el cilio.

Análisis funcional de las proteínas ciliopáticas B9

Mutaciones en MKS1, B9D1 y B9D2, tres proteínas de la base del cilio, dan lugar a los síndromes de Meckel y Joubert. Estudiamos cómo estas proteínas interaccionan con otras proteínas y lípidos de la base ciliar y cómo dichas interacciones regulan la formación y composición de los cilios primarios. También estudiamos cómo todo ello es perturbado por mutaciones causantes de ciliopatías.

Papel de INPP5E en el desensamblaje ciliar

Mecanismos de control de la fosforilación e interacciones de INPP5E en respuesta a factores de crecimiento que inducen el desensamblaje del cilio primario previo a la mitosis.

Regulación de ciliogénesis y la vía de Hedgehog por NRF2

El factor de transcripción NRF2 regula la transcripción de genes ciliares y de la vía de Hedgehog.

Publicaciones

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Financiación

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"Mecanismos moleculares de la función de cilios primarios." Financiado por: MINECO. Año 2015-2020

Ion channels (II)

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Lineas de Investigación

Kv1.5 channelosome

Kv1.5 channels generate the outward potassium current IKur, responsible for the atrial repolarization process and the atrial action potential duration in humans. These channels represent a pharmacological target for the development of antiarrhythmic drugs useful in the treatment of supraventricular arrhythmias, such as atrial fibrillation. Ion channels form signalling complexes or channelosomes and we are interested in the protein composition of the human cardiac Kv1.5 channelosome, as it is an essential feature for an optimal, fast and efficient transmission of signals either from the extracellular or from intracellular medium.

Ion channels pharmacology

Ion channels are ubiquitous proteins involved in many different physiological and pathophysiological processes. They are suitable drug targets for a plethora of drugs useful for the treatment of many diseases such as cardiac and neurological diseases. In addition, many drugs exert their undesirable effects by affecting ion channel function. We are interested in elucidate the mechanisms of action of new drugs acting on ion channels and in the determination of the binding sites of these drugs to the channels.

Channelopathies

One of our research lines is the electrophysiological characterization of new mutations on ion channels or in its modulatory subunits. These are new mutation found in the clinics that can induce cardiac arrhythmias as Long QT, Short QT and Brugada Syndromes.

Potassium channels and cancer

Ion channels are involved in other cellular functions apart from regulation of membrane potential and electrical signalling such as cell proliferation, apoptosis and differentiation. Therefore, there is an increasing interest in understanding the role of ion channels in the progression of cancer.

Publicaciones

Moreno, C. , Oliveras, A. , Bartolucci, C. , Muñoz, C. , Cruz, ADL. , Peraza, DA. ,Gimeno, JR. , Martín-Martínez, M. , Severi, S. , Felipe, A. , Lambiase, PD. , González, T. , Valenzuela, C. (2017). *D242N, a KV7.1 LQTS mutation uncovers a key residue for IKs voltage dependence.* J. Mol. Cell. Cardiol. 110: 61-69.

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Tesis Doctoral y otros trabajos

Alba Vera Zambrano

"Inhibition of Kv1.3 channels as a new approach for the treatment of chronic lymphocytic leukemia". UAM. Medicina. 2017. Director/es: Teresa González.

Judith Berlinches López

"Modulación del canal Kv1.5 por el receptor sigma-1 y su agonista selective PRE-084". UAM. Medicina. 2018. Director/es: Teresa González .

"Modulation of Kv1.3 channels by sigma-1 receptor and its selective agonist PRE-084". UAM. Medicina. 2018. Director/es: Teresa González .

"Inhibición del canal Kv1.3 de linfocitos B de leucemia linfática crónica por una familia de compuestos indólicos". UAM. Medicina. 2017. Director/es: Teresa González.

"Regulation of Kv4 channels by accessory beta subunits". UAM. Medicina. 2017. Director/es: Teresa González .

"Physiological and pharmacological modulation of Kv7". UAM. Medicina. 2017. Director/es: Teresa González .

Financiación

"Estudio en profundidad del canalosoma de Kv1.5." Financiado por: CSIC-UAM. Año 2017-2019

Magnetic resonance in the study of the physiopathology of the central nervous system

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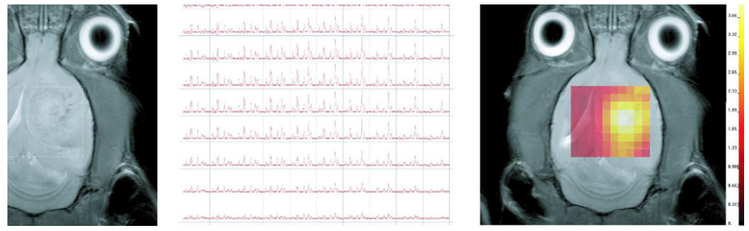
Lineas de Investigación

Multiparametric magnetic resonance characterization of the tumor microenvironment

This line is focused in the non-invasive characterization of the main features that define the tumoral physiopathology in brain tumor animal models. The obtained results can be direct and easily translate to the clinical setup to improve the diagnosis, prognosis and therapy validation of similar pathologies in human beings. The studies will develop a multiparametric evaluation supported in magnetic resonance imaging (MRI) and spectroscopy (MRS) methodologies to characterize the tumoral microenvironment, validating the results with histologic and genomic evaluation. The last aim is to identify the radiomic-histologic-genomic interaction of high- and low-grade brain tumors orthotopically growing in rats and mice.

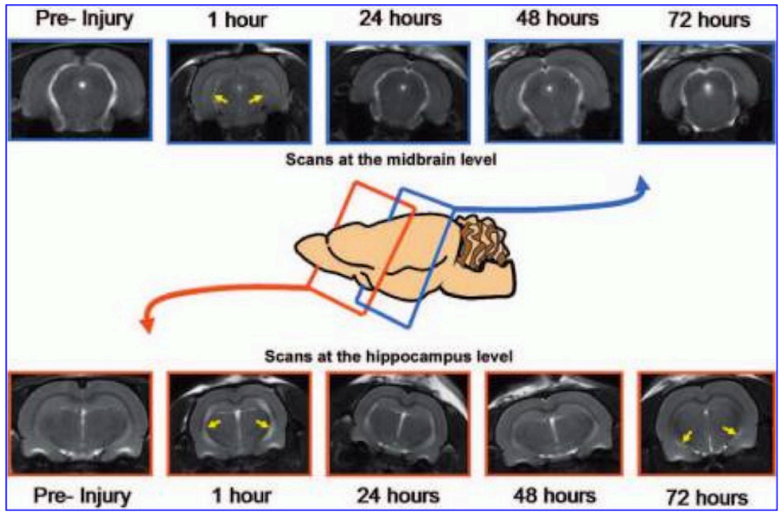


1H-Magnetic resonance spectroscopic imaging of cerebral lactate distribution in the C6 glioma model.

Our group also will assess some functional parameters in tumors like capillary permeability, extracellular pH (pHe), oxygen tension (pO2) and metabolomic profile. The obtained results will be correlated with the expression of genes related to vascularization (VGEF, VGEFR…), hypoxia (HIF1), monocarboxylate and glucose metabolisms (SLC12, SLC16…) and tumoral transformation (TP53, PTEN…) in brain tumors. Finally, a linear discriminant analysis (LDA) will evaluate all the variables to hierarchically select those variables that better discriminate between different tumors types and grades, significantly improving the clinical management of these pathologies.

Identification of biomarkers of brain inflammation

Iammation is the intricate process within the body in charge of overcoming damaging conditions caused by virtually any organism or injury from any traumatic event. Acute inflammation is the body's healthy reaction to traumatized tissues discharging histamine, which in turn causes capillaries to expand and even rupture, maximizing the flow of blood within the affected area and adjoining damaged tissues. However, the mechanisms of inflammatory responses



Early anatomical ventricles evolution in a traumatic brain injury animal model

in the induction of a wide range of inflammatory diseases or cancer that are manifested in tissues as site-specific conditions are not well understood.

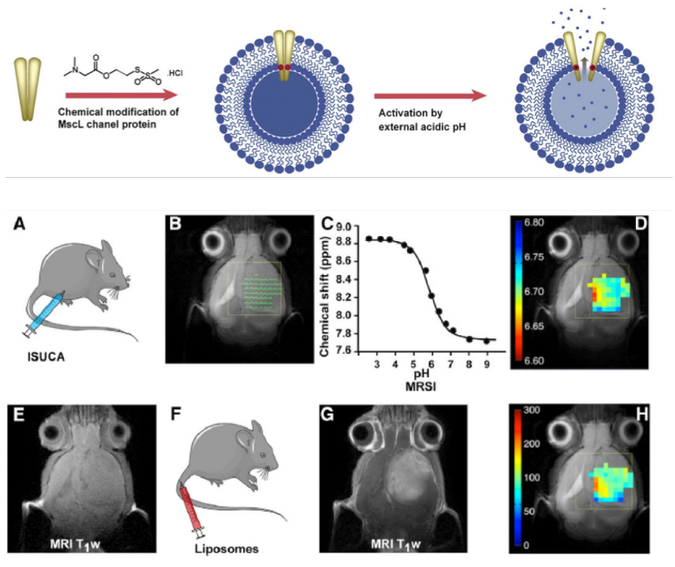
Magnetic resonance imaging (MRI) and spectroscopy (MRS) acquisitions are nowdays routinely used for clinical diagnosis and assessment of different diseases like cancer (breast, brain, liver, …), brain injury, rheumatoid arthritis, crown disease, inflammatory muscle diseases, multiple sclerosis, and so on. But the contribution of inflammatory processes to those MR data is not clear. Inflammation can induce a range of different processes all of which are potentially identifiable using magnetic resonance, including alterations in tissue perfusion, changes in tissue water diffusion related to energetic compromise, edema formation and demyelination prodecces, water distribution between different pools, modifications of relaxation parameters, and more recently, the development of molecular imaging techniques that can accurately identify markers of early inflammation by using new contrast agents.

On these grounds, in our groups are working with all these in vivo and ex vivo MR tools to signal the main inflammation biomarkers and contribute to a better understanding of the inflammatory response in the body. So, to identify the role played by inflammation either in the development or the outcome of the pathology, we are performing in vivo MRI/MRS and ex vivo MRS studies of different animal models of brain diseases like: cancer (glioblastoma), depression (chronic mild stress), traumatic brain injury (TBI) or acute brain inflammation induced with lipopolysaccharide (LPS) intracranially injected.

Liposomes as multitarget theragnostic compounds for glioma treatment

Gliomas represent the most common brain tumor with the glioblastoma multiforme (GBM) as the most aggressive manifestation. Currently, there is not any curative treatment but palliative strategies that mainly involve the maximal surgical resection, radiotherapy and co-adjuvant chemotherapy, with an overall survival expectation of 12-14 months. The treatments employed usually failed because of the unavoidable adverse drug effects, including tumor resistance and recurrence. In this line we aim to improve both circumstances by using multitarget strategies with lower drug doses, effectively targeted to the tumor and non-invasively visualized with magnetic resonance imaging (MRI). For that, we are developing liposomes containing the therapeutic of interest (temozolamide, irinotecan, bevacizumab, genitibib…), an MRI detectable contrast agent and a structure that enables the theranostic liposome to target and bound the cancer cells.

On these grounds, we want to develop and validate theragnostic multitarget liposomes to be used in the GBM treatment. We work with orthotopic animal models (rats and mice) of high-grade glioma, employing different tumoral cell lines, that are characterize and monitor with in vivo and ex vivo MR methodologies identifying biomarker of the pathology to be used in the therapy validation. As antitumoral multitarget formulation we propose to use liposomes a generic platform including several drugs like alkylating agents, topoisomerase inhibitors or tyrosine kinases.



Design of liposomes as theranostic platforms in glioma management

On the other side, the genomic profile of gliomas has been described recently. Between the most relevant findings, the IDH1 mutations linked to a higher survival are specially highlighted, but the relationship of this mutation with the tumoral response to antineoplastic compounds remains without clarify yet. The new metabolomic tools accessible by 1H HRMAS (proton high resolution magic angle spinning) can contribute to a better understanding of this evidence. In order to assess the role of the IDH1 mutation in the response to antineoplastic multitarget treatments, we are working with human biopsies from patients diagnosed with high grade glioma (provided by the Neurosurgery Department, Hospital Universitario La Paz). Our objective is to generate neutrospheres from biopsies IDH1+ and IDH1- to be injected in the caudate nucleus of NOD-SCID mice, and perform the same characterization and biomarkers identification previously carried out in animals with glioma murine cells. Also, the multitarget liposomes will be tested in these avatars of human glioma.

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Financiación

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"Terapias multidiana guiadas por imagen contra el glioblastoma." Financiado por: Comunidad de Madrid. Año 2018-2021

"Regulación cerebral del metabolismo global de la energía en la salud y en la enfermedad detectada mediante MRI ponderada en difusión ." Financiado por: Ministerio de Economía y Competitividad. Año 2015-2017

Identification of new therapeutic targets for the treatment of neurodegenerative diseases. Adult neurogenesis regulation

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Keywords: Alzheimer, APP, Ayahuasca, C / EBPβ, LRRK2, neurogenesis, neuroinflammation, neuroprotection, Parkinson's.
Palabras clave: Alzheimer, APP, Ayahuasca, C/EBPβ, LRRK2, neurogénesis, neuroinflamación, neuroprotección, Parkinson.

Lineas de Investigación

Our research is focused on identification of new therapeutic targets for the treatment of neurodegenerative diseases. To that purpose our work is based on the use of several preclinical models that mimics some of the aspects that characterize Alzheimer's and Parkinson's diseases. Using these models we identify and analyze potential cellular targets in order to develop new drugs for the treatment of these diseases. We have studied the processes that characterize these pathologies describing the involvement of several genes in different brain disorders such as C/EBPβ, whose inhibition has been shown to have a potent neuroprotector in a Parkinson's model. Some other gen of interest we have analyzed is PDE7, which codes for an enzyme involved in the degradation of cAMP. Our results suggest that this gene is expressed early in degenerative processes that affect the dopaminergic neurons of the substantia nigra, as well as promotes the appearance of pro-inflammatory phenomena.

Also, a main focus of the lab concerns research on neurogenesis and aging. In this regard we are expanding our previous observations that describe the neurogenic effect of certain components of the brew known as Ayahuasca. In this sense, we are currently working in the role of different new cellular targets which can expand our knowledge of the processes that lead to improved neurogenesis and that can be of use for a better understanding and new treatments of aging-related disorders.

Publicaciones

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Morales, JÁ. , Gine, E. , Hernandez-Encinas, E. , Aguilar, D. , Sierra, A. , Sanz, M. , Alonso, S. , Sanchez-Lanzas, R. , González, J. , Santos, A. , Pérez-Castillo, A.M (2017). *CCAAT/Enhancer binding protein β silencing mitigates glial activation and neurodegeneration in a rat model of Parkinson's disease.* Sci Rep. 7(1): 13526.

Morales, JÁ. , Salado, IG. , Sanz, M. , Gil, C., Pérez-Castillo, A.M , Martínez, A. , Pérez, DI. (2017). *Biological and Pharmacological Characterization of Benzothiazole-Based CK-1δ Inhibitors in Models of Parkinson's Disease.* ACS Omega. 2(8): 5215-5220.

Morales, JÁ. , de la Fuente Revenga, M. , Alonso, S. , Rodríguez-Franco, MI. , Feilding, A. , Pérez-Castillo, A.M , Riba, J. (2017). *The alkaloids of Banisteriopsis caapi, the plant source of the Amazonian hallucinogen Ayahuasca, stimulate adult neurogenesis in vitro.* Sci Rep. 7(1): 5309.

García, AM. , Salado, IG. , Perez, DI. , Brea, J. , Morales, JÁ. , González-García, A. , Cadavid, MI. , Loza, MI. , Luque, FJ. , Pérez-Castillo, A.M , Martinez, A. , Gil, C. (2017). *Pharmacological tools based on imidazole scaffold proved the utility of PDE10A inhibitors for Parkinson's disease.* Future Med Chem. 9: 731-748

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Financiación

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"Blood Biomarker-based Diagnostic Tools for Early Stage Alzheimer's Disease." Financiado por: Unión Europea. Año 2017-2021

"Bases metabólicas de la neurodegeneración." Financiado por: Comunidad de Madrid. Año 2017-2021

Patentes

"Combination product for the treatment of enurological and/or psychiatric disorders." Año 2017

Study of diseases related to telomeric shortening. Diagnosis and new therapies

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Lineas de Investigación

Diagnostico y nuevas terapias en disqueratosis congénita y fibrosis pulmonar idiopática

The group has been focussed in the last years in the study of telomeres and telomere-related diseases. Telomeres are nucleo-protein complexes at the terminal end of the chromosomes and protect them from degradation. The human telomere sequence consists in tandem repetitions of the AATGGG sequence that is recognized by a protein complex named shelterin to form a stable heterochromatin structure. Placed at the end of a lineal DNA molecule, telomeres cannot be completely replicated by DNA polymerases and that results in shortening in every replication cycle. This process is prevented by the activity of the telomerase complex that elongates telomeres in embryonic, germinal and tissue stem cells. In most cells of somatic tissues telomerase activity is not expressed and their telomeres are shortened with the aging of the individual. Excessively short telomeres produce cell-cycle arrest, senescence or apoptosis that is one of the causes of aging.

There are a number of rare diseases that are being studied by our group, including dyskeratosis congenita, aplastic anemia and pulmonary fibrosis that harbour mutations in genes coding for components of the telomerase, shelterin complexes and auxiliary proteins. Shortening of telomeres is also observed in related diseases such as Ataxia telangiectasia.

Our research is focussed in the following topics:

1. GSE4 as possible therapeutic molecule. Our group has described that a dyskerin-derived peptide (GSE4) has a potentially therapeutic effect on telomere-related diseases. Expression of this peptide increases telomerase activity and cell proliferation in cells isolated from patients of dyskeratosis congenita and Ataxia telangiectasia. In addition, oxidative stress and DNA damage is prevented by the expression of the peptide that has been designed as orphan drug for treatment of dyskeratosis congenita. The mechanism of action of GSE4 and the possible therapeutic effects in these and other telomere-related diseases are presently being studied.
2. Diagnosis of telomere-related diseases. We are collaborating with several hospitals in the diagnosis of telomere-related diseases that are very difficult to diagnose based exclusively on clinical criteria. Telomere length is first determined since patients affected by these diseases have very short telomeres, below the 10% and frequently below the 1% of the control population. Once diagnosed, the molecular cause of the disease is studied by determining possible pathological variants in the genes coding for proteins involved in telomere homeostasis. Massive sequencing of a panel of related genes and exome sequencing are used in these

studies. Finally, we perform in vitro studies to determine the functional relevance of the possibly pathogenic variants.

Publicaciones

Pajuelo, N. , Bargiela, J. , Domínguez, G., Quiroga, AG. , Perona, R. , Sánchez, MI. (2018). *XPA, XPC, and XPD Modulate Sensitivity in Gastric Cisplatin Resistance Cancer Cells.* Front Pharmacol. 9: 1197.

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Carrillo, J. , Calvete, O. , Pintado Berninches, L. , Manguán, C. , Sevilla Navarro, J. , García, E. , Sastre, L. , Guenechea, G. , López Granados, E. , de Villartay, J. , Revy, P. , Benitez, J. , Perona, R. (2017). *Mutations in xlf/nhej1/cernunnos Gene Results In Downregulation of Telomerase Genes Expression and Telomere Shortening.* Hum. Mol. Genet. 15: 1900-1914.

Tesis Doctoral y otros trabajos

Laura Pintado Berninches

"Uso de péptidos GSE24.2 y GSE4 como posible tratamiento de células de pacientes de ataxia telangiectasia".
Universidad Autonoma de Madrid. Medicina.
2017. Director/es: Rosario Perona .
Calificación: Apto Cum laude

Financiación

"Estudio Molecular integrado en CNMP. Búsqueda de marcadores moleculares pronósticos, heterogeneidad de células circulantes tumorales y sensibilidad extrema a tratamiento. Proyecto coordinado." Financiado por: ISCIII. Año 2015-2017

"Acortamiento telomérico y su regulación." Financiado por: CIBER. Año 2016-2017

"TELOMEREPAIR." Financiado por: CIBER. Año 2017-2018

"Neumonitis y Fibrosis pulmonar inducidas por radioterapia. Posibles tratamientos curativos con péptidos encapsulados en nanopartículas, papel de JNK/MKP1 y del acortamiento telomérico." Financiado por: ISCIII. Año 2018-2020

Human Genetics and Molecular Pathology

Investigador Principal
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Palencia Campos, Adrián

Personal de Apoyo
Fernández Núñez, Elisa

Estudiantes de Grado
Carretero Pérez, Alba
Chico Sordo, Lucía
Martín Quintín, Cristina

Estudiante de Master
Martín Bravo, Carolina

Investigadora Visitante
Rodríguez Laguna, Lara

Keywords: Ellis-van Creveld syndrome, EVC, EVC2, primary cilia, hedgehog signaling, GLI1, osteogenesis imperfecta, bone disorders.
Palabras clave: Síndrome de Ellis-van Creveld, EVC, EVC2, cilios primarios, señalización de hedgehog, GLI1, osteogénesis imperfecta, trastornos óseos.

Lineas de Investigación

ELLIS VAN-CREVELD SYNDROME AND PHENOTYPICALLY OVERLAPPING CILIOPATHIES

Ellis-van Creveld syndrome (EvC) is an autosomal recessive condro-ectodermic dysplasia primarily caused by mutations in EVC or EVC2. The proteins encoded by these genes form a protein complex localized at the base of the primary cilium and act as a positive mediators of hedgehog signaling (Hh). In vertebrates, the transduction of the Hh signal is completely dependent on the primary cilium, a structure that has received enormous attention in recent years due to the large number of human disorders associated with mutations in proteins that localize to this organelle, currently known as ciliopathies. Our goal is to continue progressing in the understanding of the molecular physiopathology of EvC and the function of Evc and Evc2 within the Hh pathway.

OSTEOGENESIS IMPERFECTA AND BONE FRAGILITY

Osteogenesis imperfecta (OI) is a bone-related disorder characterized by an increased risk of fractures. The large majority of OI cases have a dominant mode of inheritance and are caused by mutations in COL1A1 or COL1A2, the genes encoding the procolagen type I peptidic chains. However, there is a small fraction of cases with mutations in other

genes which have resulted to be highly genetically heterogeneous. Our goal in this line of research is to ivestigate the molecular pathomechanisms leading to this condition and other forms of bone fragility.

Publicaciones

Rodriguez-Laguna, L. , Ibañez, K. , Gordo, G., Garcia-Minaur, S. , Santos-Simarro, F. , Agra, N. , Vallespín, E. , Fernández-Montaño, VE. , Martín-Arenas, R. , Del Pozo, Á. , González-Pecellín, H. , Mena, R. , Rueda-Arenas, I. , Gomez, MV. , Villaverde, C. , Bustamante, A. , Ayuso, C. , Ruiz-Perez, V.L , Nevado, J. , Lapunzina, P. , Lopez-Gutierrez, JC. , Martinez-Glez, V. (2018). *CLAPO syndrome: identification of somatic activating PIK3CA mutations and delineation of the natural history and phenotype.* Genet. Med. 20(8): 882-889.

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Gordo, G. , Tenorio, J. , Arias, P. , Santos-Simarro, F. , García-Miñaur, S. , Moreno, JC. , Nevado, J. , Vallespin, E. , Rodriguez-Laguna, L. , de Mena, R. , Dapia, I. , Palomares, M. , Del Pozo, Á. , Ibañez, K. , Silla, JC. , Barroso, E. , Ruiz-Perez, V.L , Martinez-Glez, V. , Lapunzina, P. (2017). *mTOR mutations in Smith-Kingsmore syndrome: four additional patients and a review.* Clin. Genet. .

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Palencia, A. , Ullah, A. , Nevado, J. , Yildirim, R. , Unal, E. , Ciorraga, M. , Barruz, P. , Chico, L. , Piceci-Sparascio, F. , Guida, V. , De Luca, A. , Kayserili, H. , Ullah, I. , Burmeister, M., Lapunzina, P. , Ahmad, W. , Morales, A. , Ruiz-Perez, V.L (2017). *GLI1 Inactivation is associated with Developmental Phenotypes Overlapping with Ellis-Van Creveld Syndrome.* Hum. Mol. Genet.

Tenorio, J. , Álvarez, I. , Riancho-Zarrabeitia, L. , Martos-Moreno, GÁ. , Mandrile, G. , de la Flor Crespo, M. , Sukchev, M. , Sherif, M., Kramer, I. , Darnaude-Ortiz, MT. , Arias, P. , Gordo, G. , Dapía, I. , Martinez-Villanueva, J. , Gómez, R. , Iturzaeta, JM. , Otaify, G. , García-Unzueta, M. , Rubinacci, A. , Riancho, JA. , Aglan, M. , Temtamy, S. , Hamid, MA. , Argente, J. , Ruiz-Perez, V.L , Heath, KE. , Lapunzina, P. (2017). *Molecular and clinical analysis of ALPL in a cohort of patients with suspicion of hypophosphatasia.* Am. J. Med. Genet. A. .

Caparros-Martin, JA. , Aglan, MS. , Temtamy, S. , Otaify, GA. , Valencia, M. , Nevado, J. , Vallespin, E. , Del Pozo, A. , Prior de Castro, C. , Calatrava-Ferreras, L. , Gutierrez, P., Bueno, AM. , Sagastizabal, B. , Guillen-Navarro, E. , Ballesta-Martinez, M. , Gonzalez, V. , Basaran, SY. , Buyukoglan, R. , Sarikepe, B. , Espinoza-Valdez, C. , Cammarata-Scalisi, F. , Martinez-Glez, V. , Heath, KE. , Lapunzina, P. , Ruiz-Perez, V.L (2017). *Molecular spectrum and differential diagnosis in patients referred with sporadic or autosomal recessive osteogenesis imperfecta.* Mol Genet Genomic Med. 5(1): 28-39.

Financiación

"Caracterización de procesos moleculares del desarrollo óseo implicados en enfermedades esqueléticas de base genética." Financiado por: MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD. Año 2016-2019

"Nuevas perspectivas en las bases moleculares y los mecanismos fisiopatológicos del sindrome de Ellis-van Creveld y osteogénesis imperfecta." Financiado por: MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD. Año 2014-2017

"Osteogénesis aproximación clínica, molecular y terapéutica (Proyecto colaborativo en el que participan 4 Unidades CIBERER)." Financiado por: CIBERER (Acciones Cooperativas y Complementarias Intramurales (convocatoria 2017)). Año 2018-2019

Premios

"Premio de Excelencia de IdiPaz. Artículos más citados publicados hace 5 años. (Martinez-Glez et al., Identification of a mutation causing deficient BMP1/mTLD proteolytic activity in autosomal recessive osteogenesis imperfecta. Hum Mut 2012)." Año 2017

Chromosome Instability & Cancer

Investigadora Principal
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Predoctorales
Pajuelo Lozano, Natalia
Bargiela Iparraguirre, Jone
Navas López, Francisco

Estudiantes de Grado
de Villa Sánchez, Elena
Menéndez Ribes, Marta

Lineas de Investigación

Chromosome instability and therapy response

Overview

Our group centres its research on understanding how deregulation of mitotic checkpoint drives tumorigenesis and threrapy response in gastric cáncer (GC). GC is still the fourth main cause of cancer related death all over the world. In GC, adenocarcinomas gastrectomy, and adjuvant radio/chemotherapy are the election treatment. Our focus of interest is to gain insight into the molecular pathways that condition the response to specific therapies in GC. Furthermore, GC is asolid tumor characterized by high rates of chromosomal instability (CIN) and aneuploidy. One of the causes of CIN and aneuploidy is a failure in mitosis due to weakness or overactivation of the mitosis control point known as spindle assembly checkpoint (SAC). Throughout the years, our laboratory has analyzed the expression levels of the different components of SAC, correlating the key mitotic proteins Mad2 and BubR1 with CIN. In addition, the interference of the corresponding genes modifies the migration and invasion of cells derived from GC, so our studies are directed to the molecular mechanism that intervenes in this effect. Cancer stem cells are responsable for recidives, heterogenity and treatment resistance of tumor. Mitosis plays important roles balancing stem cells between self-renewal and differentiation to progenitor cells by regulating symmetric and asymmetric division. Mitotic checkpoint proteins as Mad2 plays an important role maintaining the CSC population. Our studies have enhanced our understanding of the impact of Mad2 on GCSC and have provided novel promising cisplatin drugs with antitumoural potential against these cells.

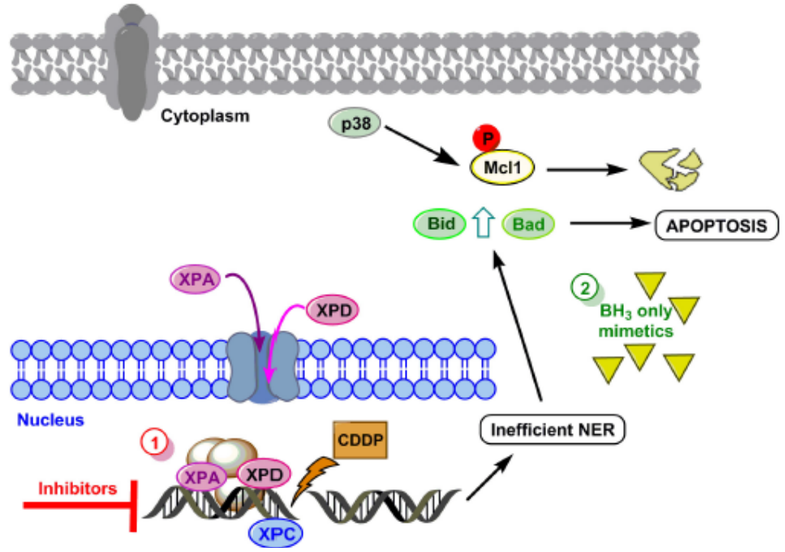
Research Highlights

1.- Coupling NER with apoptosis induction.

Cisplatin is a drug widely used in clinic for the treatment of advanced gastric cancer. However, the heterogeneity of the GC and its resistance to the drugs, make the prognosis unpredictable. We have studied the molecular processes involved in cisplatin-induced apoptosis in gastric cancer cell lines with different sensitivity to the treatment. We demostrated that NER pathway is impair in sensitive cells due to low levels of XPC and the absence of translocation of XPA and XPD to the nucleus after stimuli. In this situation, the intrinsic apoptotic pathway it is activated through degradation of Mcl-1 together with an increase of Bid and Bad levels, which results in sensitivity to CDDP. Altogether, these results suggest that NER and Bcl-2 family proteins are potential targets to improve the response to cisplatin treatment. We are currently investigating the role of NER factors in the context of resistance to cisplatin.

2.- New platinum compounds

We have sintetized three platinum complexes with cis and trans configuration: cis-[Pt(TCEP)2Cl2], cis-[Pt(tmTCEP)2Cl2] and trans-[Pt(TCEP)2Cl2. The stability in solution of the three compounds and their interaction with biological models such as DNA (pBR322 and calf thymus DNA) and proteins (lysozyme and RNase) have also been studied. Furthermore these compountds are able to reduce viability in a panel of cancer cells. Now we are focused on the deep study to understand the molecular mechanims of apoptosis induction of these new drugs in comparation with the well known cisplatin.



Hypothetical model to sensitize GC

Publicaciones

Pajuelo, N. , Bargiela, J. , Domínguez, G., Quiroga, AG. , Perona, R. , Sánchez, MI. (2018). *XPA, XPC, and XPD Modulate Sensitivity in Gastric Cisplatin Resistance Cancer Cells.* Front Pharmacol. 9: 1197.

Niell, N. , Larriba, MJ. , Ferrer-Mayorga, G , Sánchez, MI. , Cantero, R. , Real, FX. , Peso, LD. , Muñoz, A. , González, JM. (2018). *The human PKP2/plakophilin-2 gene is induced by Wnt/β-catenin in normal and colon cancer-associated fibroblasts.* Int. J. Cancer. 142(4): 792-804.

Long, Y. , Stahl, Y. , Weidtkamp-Peters, S. , Postma, M. , Zhou, W. , Goedhart, J., Sánchez, MI. , Gadella, TWJ. , Simon, R. , Scheres, B. , Blilou, I. (2017). *In vivo FRET-FLIM reveals cell-type-specific protein interactions in Arabidopsis roots.* Nature. 548:97-102.

Tesis Doctoral y otros trabajos

Jone Bargiela Iparraguirre

"Estudio de biomarcadores de pronóstico y respuesta a terapia en cáncer gástrico". UAM. Medicina. 2017. Director/es: María Isabel Sánchez . Calificación: sobresaliente cum laude

Telomeres and telomere-related diseases

Investigador Principal
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Co-Investigadora Principal
Perona Abellón, Rosario

Investigadoras Asociadas
Iarriccio Silva, Laura
García Arias-Salgado, Elena

Predoctorales
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Bolelli -, Aronne

Estudiantes de Grado
Izquierdo Simarro, Inmaculada (hasta junio 2017)
Portuondo Muñoz, Yon (hasta junio 2018)
Olalla Chantal, Carmen (hasta junio 2018)

Colaboración
Manguán García, Cristina

Lineas de Investigación

Telomeres and telomere-related diseases

The group has been centred during these years in the study of telomeres and telomere-related diseases. These nucleo-protein complexes constitute the terminal end of the chromosomes and protect them from degradation. Human telomere sequence is formed by tandem repetitions of the AATGGG sequence that is recognized by a protein complex named shelterin to form a stable heterochromatin structure. Placed at the end of a lineal DNA molecule, telomeres cannot be completely replicated by DNA polymerases and would get shorter every replication cycle. This process is prevented by the activity of the telomerase complex that elongates telomeres in embryonic, germinal and tissue stem cells. Most cells in the somatic tissues do not express telomerase activity and their telomeres are shortened with the age of the individual. Excessively short telomeres produce cell-cycle arrest, senescence or apoptosis that is one of the causes of aging. Mutations in genes coding for components of the telomerase and shelterin complexes and auxiliary proteins cause a number of rare diseases that are being studied by our group, including dyskeratosis congenita, aplastic anemia and pulmonary fibrosis and also related diseases such as Ataxia telangiectasia. In particular, our projects are focussed in the following topics:

1. Diagnosis of telomere-related diseases. We are collaborating with several hospitals in the diagnosis of telomere-related diseases that are very difficult to diagnose based exclusively on clinical criteria. Telomere length is first determined since patients affected by these diseases have very short telomeres, below the 10% and frequently below the 1% of the control population. Once diagnosed, the molecular cause of the disease is studied by determining possible pathological variants in the genes coding for proteins involved in telomere

homeostasis. Massive sequencing of a panel of related genes and exome sequencing are used in these studies. Finally, we perform in vitro studies to determine the functional relevance of the possibly pathogenic variants.

2. Telomere structure and extension in Dictyostelium discoideum. Our group has experience in the use of this organism and we are using it as model system for the study of telomere-related diseases. As a firs step, we have determined the structure of D. discoideum telomeres and studied the elongation mechanism. Later on, we have generated dyskerin mutants that genocopy mutations found in dyskeratosis congenita patient to study the pathophysiology of these gene variants.

Publicaciones

Perona, R. , Manguán, C. , García, E. , Sastre, L. (2018). *Enfermedades con acortamiento telomérico: disqueratosis congénita y fibrosis pulmonar.* En: Revista de ciencias y humanidades. Fundación Ramón Areces, Madrid. pp.112-121.

Carrillo, J. , Calvete, O. , Pintado Berninches, L. , Manguán, C. , Sevilla Navarro, J. , García, E. , Sastre, L. , Guenechea, G. , López Granados, E. , de Villartay, J. , Revy, P. , Benitez, J. , Perona, R. (2017). *Mutations in xlf/nhej1/cernunnos Gene Results In Downregulation of Telomerase Genes Expression and Telomere Shortening.* Hum. Mol. Genet. 15-1900-1914

Perona, R. , García, E. , Sastre, L. (2017). *Personalized Medicine. Medical opportunities and challenges in the massive sequencing era.* Intern. Med. Rev. 3 (7): 1-34.

Tesis Doctoral y otros trabajos

Javier Rodríguez Centeno

"Estudio de los telomeros en Dictyostelium discoideum. Desarrollo de un modelo celular de disqueratosis congénita". Universidad Autónoma de Madrid. Medicina. 2017. Director/es: Leandro Sastre . Calificación: Sobresaliente cum laude

Financiación

Rosario Perona Abellón
Sastre, L. , Manguán, C.

"Estudio Molecular integrado en CNMP. Búsqueda de marcadores moleculares pronósticos, heterogeneidad de células circulantes tumorales y sensibilidad extrema a tratamiento." Financiado por: Instituto de Salud Carlos III, Fonde de Investigaciones Sanitarias. Año 2015-2017

Rosario Perona Abellón
Sastre, L. , García, E. , Manguán, C.

"Cohorte FPI: Acortamiento telomérico y su regulación." Financiado por: CIBER de enfermedades raras (CIBERER). Año 2016-2017

Leandro Sastre Garzón
Rosario Perona Abellón

"Neumonitis y Fibrosis pulmonar inducidas por radioterapia. Posibles tratamientos curativos con péptidos encapsulados en nanopartículas, papel de JNK/MKP1 y del acortamiento telomérico." Financiado por: Instituto de Salud Carlos III. Fondo de Investigaciones Sanitarias. Año 2018-2020

Ion channels (I)

Investigadora Principal
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Prieto Folgado, Ángela

Predoctorales
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de Benito Bueno, Ángela

Personal de Apoyo
Arias Sánchez, Sara

Estudiantes de Licenciatura
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González Merinero, Yaiza
Peña Hidalgo, Javier
Sánchez Ruz, Andrea

Investigador Visitante
Khemili -, Dalila

Lineas de Investigación

Ion channels

Our research team studies the physiological and pharmacological modulation of ion channels present in the plasma membrane of human cardiac myocytes. In order to assess this issue, we use electrophysiological techniques (patch-clamp). Ionic channels are membrane proteins able to generate and maintain the action potentials and also to maintain the resting membrane potential. Therefore, these molecules are responsible, among other functions, of muscle contraction, cardiac rhythm and synaptic transmission. We focus our resarch interest in the potassium channels present into the human myocardium. Because these channels are responsible of the cardic repolarization, they represent pharmacological targets of antiarrhythmic drugs useful in the treatment of cardiac arrhythmias.

Publicaciones

Moreno, C. , Oliveras, A. , Bartolucci, C., Muñoz, C. , Cruz, ADL. , Peraza, DA. , Gimeno, JR. , Martín-Martínez, M. , Severi, S. , Felipe, A. , Lambiase, PD. , González, T. , Valenzuela, C. (2017). *D242N, a KV7.1 LQTS mutation uncovers a key residue for IKs voltage dependence.* J. Mol. Cell. Cardiol. 110: 61-69.

Cruz, ADL. , Vera, A. , Peraza, DA. , Valenzuela, C. , Zapata, JM. , Pérez, G. , González, T. (2017). *Fludarabine Inhibits KV1.3 Currents in Human B Lymphocytes.* Front Pharmacol. 8: 177.

Tesis Doctoral y otros trabajos

Alicia de la Cruz Fernández

"Physiological and pharmacological modulation of Kv7 channels". Universidad Autónoma de Madrid. Facultad de Medicina. 2017. Director/es: Carmen Valenzuela . Calificación: Sobresaliente cum laude por unanimidad

Ángela Prieto Folgado

"Regulación de canales Kv4 por subunidades beta accesorias". Universidad Autónoma de Madrid. Facultad de Medicina. 2017. Director/es: Carmen Valenzuela. Calificación: Sobresaliente cum laude por unanimidad

Financiación

"CIBER de Enfermedades Cardiovasculares." Financiado por: FIS. Año 2017-2018

"Estudio en profundidad del canalosoma cardiaco de Kv1.5." Financiado por: MINECO. Año 2016-2019

"Canalosoma de Kv1.5: papel de Lgi1-4 y Sig-1R. Consecuencias farmacológicas." Financiado por: MICINN. Año 2014-2017

"SAFETOLL - Desarrollo de nuevas aplicaciones terapéuticas de ApTOLL en enfermedades vasculares y autoinmunes." Financiado por: MINECO. Año 2018-2020

Patentes

"Compuestos moduladores del sensor neuronal de calcio DREAM y sus usos terapéuticos." Año 2017

"Moduladores de KChIP2 para el tratamiento de patologías cardiovasculares." Año 2018

Traffic and protein degradation

Investigador Principal
Olivier Vincent

Predoctoral
Bueno Arribas, Miranda (desde octubre 2017)

Estudiantes de Grado
Cerveró García, M. Pilar (dic 2017 hasta junio 2018)
Pons Sánchez, Adrián (hasta julio 2017)

Estudiantes de Master
Zapata del Baño, Antonia (hasta junio 2019)

González Álvarez, José Carlos (hasta jun 2018)
Pons Sánchez, Adrián (hasta junio 2018)
Bueno Arribas, Miranda (hasta junio 2017)

Investigadores Visitantes
Navas Hernández, Mª Angeles

Keywords: Autophagy, VMP1, VPS13, WIPI, BPAN, Chorea-acanthocytosis, Saccharomyces cerevisiae.
Palabras clave: Autofagia, VMP1, VPS13, WIPI, BPAN, corea-acantocitosis, Saccharomyces cerevisiae.

Lineas de Investigación

Our main goal is to characterize molecular mechanisms that control protein trafficking and degradation, and are potentially involved in human diseases.

In the past years, we have studied the regulatory mechanisms of arrestin-related proteins that function as endocytic adaptors for receptors and transporters at the plasma membrane.

More recently, we started a project to characterize the function of VMP1, VPS13 and WIPI proteins in the process of autophagy.

Autophagy is an intracellular degradation mechanism involved in several pathologies such as neurodegenerative diseases ChAc (Corea-acanthocytosis) and BPAN (Beta-propeller Protein-Associated Neurodegeneration). Mutations in the VPS13A and WIPI4/WDR45 genes are responsible for these diseases.

We aim to determine the function of these proteins in autophagy. VPS13 and WIPI proteins are evolutionarily conserved and we use the model organism S. cerevisiae to analyze their function and to identify their interactome by using the two-hybrid system.

The specific goals are:

- Identification of new VMP1 and VPS13 interactors and analysis of their possible role in lipid trafficking
- Characterization of the molecular mechanisms involved in WIPI-mediated recruitment of the autophagic machinery to the autophagosomal membrane
- Functional analysis of a new Atg2 interactor potentially involved in autophagy
- Generation by CRISPR/Cas9 genome editing and characterization of WIPI KOs in HeLa cells

Publicaciones

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Financiación

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