IBJ Plus
IberoAmerican Journals
IBJ
IberoAmerican Journals
ISSN: 2531-0151

IBJ Plus

Volume 1, Special Issue 3, May 2019

Abstracts of 6th Symposium on Biomedical Research.

Advances and Perspectives in Molecular Endocrinology

Madrid, May 31st 2019

iBM
CSIC
Cincuenta Aniversario UAM
Facultad de Medicina

IBJ Plus
IberoAmerican Journals

ABSTRACTS BOOK
LIBRO DE ABSTRACTS

"Advances and Perspectives in Molecular Endocrinology"

"Avances y Perspectivas en Endocrinología Molecular"

Instituto de Investigaciones Biomédicas "Alberto Sols"- Facultad de Medicina
Universidad Autónoma de Madrid

Madrid, May 31, 2019
Madrid, 31 de mayo de 2019

6th Symposium on Biomedical Research
6º Simposio en Investigación Biomédica

Instituto de Investigaciones Biomédicas “Alberto Sols”- Facultad de Medicina Universidad Autónoma de Madrid.

“Advances and Perspectives in Molecular Endocrinology”
In Homage to Gabriella Morreale.

“Avances y Perspectivas en Endocrinología Molecular”
En homenaje a Gabriella Morreale.

(Certified with 1 ECTS by Universidad Autónoma de Madrid)

Madrid, May 31, 2019

Madrid, 31 de Mayo de 2019

Venue/Sede: Facultad de Medicina. Universidad Autónoma de Madrid

IBJ Plus
IberoAmerican Journals

Welcome and presentation

On behalf of the planning committee, we welcome you to the Sixth Symposium on Biomedical Research organized jointly by the Instituto de Investigaciones Biomédicas “Alberto Sols” (CSIC-UAM) and the School of Medicine (UAM), Madrid. The Symposium will take place at the Campus of the School of Medicine on May 31, 2019 and will focus on the “Advances and Perspectives in Molecular Endocrinology” in memory of Gabriella Morreale. This highly advancing field is characterized by rapidly changing views of old paradigms contributing to a better understanding of the mechanisms behind the highly diverse hormonal signaling, the integration of their physiological effects and their failure leading to endocrine disorders. All these have led to the development and improvement of novel therapeutic strategies. The confluence of basic and clinical research will be emphasized to foster the transmission of new scientific findings into clinical practice. The Symposium will pay homage to the late Dr. Gabriella Morreale, as an internationally recognized leading figure in endocrinology research, whose work was crucial to deciphering the role of iodine and thyroid hormones on fetal and neonatal brain development. In addition, she and her husband Francisco Escobar del Rey made a major contribution to public health by preventing cognitive impairment in newborns due to congenital hypothyroidism.

Additionally, the meeting will be a stimulating gathering of researchers, graduate and post-graduate students, and industry sponsors. The Symposium will consist of invited lectures by distinguished speakers together with poster sessions, providing ample time for discussion both within and outside the scientific and poster sessions.

There will be prices to the best three poster communications, whose presenting authors will be awarded with free inscriptions to the next meeting of either SEBBM or SEEN.

Registration to the Symposium will be at no cost and attendance of undergraduate students will be certified with 1 ECTS by the UAM.

Abstracts will be published in IBJ Plus.

We hope you enjoy the Symposium,

Lisardo Boscá Gomar. Director of Instituto de Investigaciones Biomédicas “Alberto Sols” (CSIC-UAM)

Juan Antonio Vargas Núñez. Dean of the School of Medicine (UAM)

Committees

Organizing Committee

Symposium Direction

Lisardo Boscá Gomar. Director. Instituto de Investigaciones Biomédicas Alberto Sols CSIC-UAM

Juan Antonio Vargas Núñez. Dean. Facultad de Medicina. UAM

Symposium Secretary

Juan J. Aragón. Facultad de Medicina, UAM

Juan Bernal. Instituto de Investigaciones Biomédicas "Alberto Sols", CSIC-UAM

Ana Guadaño-Ferraz. Instituto de Investigaciones Biomédicas "Alberto Sols", CSIC-UAM

Susana Guerra. Facultad de Medicina, UAM

Oscar H. Martínez-Costa. Facultad de Medicina, UAM

Pilar Santisteban. Instituto de Investigaciones Biomédicas "Alberto Sols", CSIC-UAM

Scientific Committee

Ana Aranda. Instituto de Investigaciones Biomédicas "Alberto Sols", CSIC-UAM

Silvia Arribas. Facultad de Medicina, UAM

José González-Castaño. Facultad de Medicina, UAM

Ana M. Jiménez-Lara. Instituto de Investigaciones Biomédicas "Alberto Sols" CSIC-UAM

Aurora Sánchez. Facultad de Medicina, UAM

Technical Committee

Technical Secretariat
Sandra García
Esther Ramiro

Information Technologies
Francisco Vara
Susana Molina

Audiovisual Support
Juan Carlos Palomino

Supporting Personnel

Manuel Albert
Martina Becares
Michella Falqui
Carlos Fernández
Ángel García-Aldea
María del Carmen Grijota-Martínez
Marina Guillén-Yunta
Ana Montero
María Rojo
Víctor Valcárcel-Hernández

Invited Speakers

Antonio Castrillo
Instituto de Investigaciones Biomédicas "Alberto Sols" CSIC-UAM
Madrid, Spain

Luis de Lecea
Department of Psychiatry and Behavioral Sciences
Standford University School of Medicine
Standford, CA. USA

Mónica Marazuela
Hospital Universitario La Princesa
Facultad de Medicina UAM
Madrid, Spain

Marco Medici
Department of Internal Medicine
Erasmus Medical Center
Rotterdam. The Netherlands

Ángel Nadal
Instituto de Investigación, Desarrollo e Innovación en Biotecnología Sanitaria de Elche. Universidad Miguel Hernández de Elche y CIBERDEM
Alicante, Spain

Pilar Santisteban
Instituto de Investigaciones Biomédicas "Alberto Sols", CSIC-UAM y CIBERONC
Madrid, Spain

Manuel Tena-Sempere
Instituto Maimónides de Investigación Biomédica, Facultad de Medicina, Universidad de Córdoba y CIBEROBN
Córdoba, Spain

Antonio Vidal-Puig
Department of Clinical Biochemistry
BHF Cambridge Centre of Excellence
Cambridge, United Kingdom

Sponsors

Universidad Autónoma de Madrid
Vicerrectorado de Investigación
Fundación Universidad Autónoma de Madrid Decanato de la Facultad de Medicina www.uam.es

Consejo Superior de Investigaciones Científicas
Instituto de Investigaciones Biomédicas Alberto Sols
www.csic.es

Sociedad Española de Bioquímica y Biología Molecular
www.sebbm.es/web/es

Sociedad Española de Endocrinología y Nutrición
www.seen.es

Centro de Investigación Biomédica en Red Enfermedades Raras
www.ciberer.es

IberoAmerican Journals
www.ibjournals.com/

Italfarmaco
www.italfarmaco.es

Charles River Laboratories
www.criver.com

Merck
www.merckgroup.com

Acknowledgements

The Organizing Committee thanks the generous collaboration of the Dean's Office Secretariat, the Audio Visual Unit and the Information Technology Unit of the School of Medicine, Universidad Autónoma de Madrid and that from the Information Technologies and Scientific Imagen Services from the Instituto de Investigaciones Biomédicas "Alberto Sols" (CSIC-UAM).

IBJ Plus
IberoAmerican Journals

Programme

08:30-12.30. Registration / Recogida de documentación

AULA MAGNA. FACULTAD DE MEDICINA

09:00-09:10. Opening / Apertura

09:10-10:30. **Plenary Session 1 / Sesión Plenaria 1**.
Chairpersons / Moderadores: Juan Bernal and María Jesús Obregón

09:10-09:50. **Novel molecular pathways for the central control of puberty: basic aspects and translational implications**.
Manuel Tena, Córdoba, Spain

09:50-10:30. **To sleep or not to sleep: how the brain decides to wake us up.**
Luis de Lecea, Standford, CA. USA

10:30-11:10. Coffe & Poster viewing / Café y visita de paneles

11:10-12:30. **Plenary Session 2 / Sesión Plenaria 2**
Chairpersons / Moderadores: Belén Peral and Gema Medina

11:10-11:50. **Emerging genes and pathways in thyroid differentiation and tumorigenesis**
Pilar Santisteban
Madrid, Spain

11:50-12:30. **Adipose tissue expandability, lipotoxicity and the metabolic syndrome.**
Antonio Vidal-Puig, Cambridge, United Kingdom

12:30-13:15. Parallel poster sessions / Sesión simultánea de paneles

13:15-14:40. Lunch / Almuerzo

14:40-16:00. **Plenary Session 3 / Sesión Plenaria 3**
Chairpersons / Moderadores: Ana Aranda and Mercedes Ricote

14:40-15:20. **Regulation of tissue macrophage functions by LXR nuclear receptor dependent transcriptional pathways.**
Antonio Castrillo, Madrid, Spain

15:20-16:00. **Genetic determinants of thyroid function: novel insights and new approaches.**
Marco Medici, Rotterdam, The Netherlands.

16:00-16:40. Coffe & Poster viewing / Café y visita de paneles

16:40-18:00. **Plenary Session 4 / Sesión Plenaria 4**
Chairpersons / Moderadores: Antonio de la Vieja and Garcilaso Riesco-Eizaguirre

16:40-17:20. **The role of endocrine disruptors in the etiology of diabetes mellitus.**
Ángel Nadal, Alicante, Spain

17:20-18:00. **Pathogenesis of autoimmune thyroid diseases: role of cellular immunity.**
Mónica Marazuela, Madrid, Spain

18:00. Closing and Awards ceremony / Ceremonia de clausura y Premios

Invited Speakers Abstracts

Novel molecular pathways for the central control of puberty: Basic aspects and translational implications.

Manuel Tena-Sempere[1*]

[1]Department of Cell Biology, Physiology & Immunology, University of Córdoba; Maimónides Institute of Biomedical Research of Córdoba (IMIBIC); CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Córdoba, Spain; and FiDiPro Program, Institute of Biomedicine, Research Centre for Integrative Physiology and Pharmacology, University of Turku, Turku, Finland.
[*]Corresponding author:
Manuel Tena-Sempere, Department of Cell Biology, Physiology & Immunology, University of Córdoba; Maimónides Institute of Biomedical Research of Córdoba (IMIBIC); CIBER Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Córdoba, Spain; and FiDiPro Program, Institute of Biomedicine, Research Centre for Integrative Physiology and Pharmacology, University of Turku, Turku, Finland. E-mail: fi1tesem@uco.es.

Puberty is crucial developmental event, driven by a large set of sophisticated regulatory networks, which are capable to integrate internal and peripheral signals to precisely and timely activate the brain centers governing the reproductive axis. In humans and other mammalian species, the timing of puberty is genetically determined. Yet, puberty is also highly sensitive to numerous internal and external cues, among which metabolic and nutritional signals are especially prominent. Compelling epidemiological evidence suggests that alterations of the age of puberty are becoming more frequent in humans, via as yet unknown mechanisms; yet, the escalating prevalence of obesity and other metabolic/feeding disorders has been pointed out as major contributing factor. Notably, this phenomenon is likely to have translational implications, since alterations in the timing of puberty have been associated to adverse health outcomes later in life, including higher risk of earlier all-cause mortality. This urges for a better understanding of the neurohormonal basis of normal puberty and the mechanisms of its deviations.

In recently years, compelling evidence has documented the master role of hypothalamic neurons producing kisspeptins, which are encoded by the Kiss1 gene and operate via de G-protein coupled receptor, Gpr54, in the neuroendocrine pathways controlling puberty, with a particularly prominent function of Kiss1 neurons located in the arcuate nucleus (ARC). Other transmitters, such as tachykinins (e.g., Neurokinin B), opioids (e.g., dynorphin) and melanocortins, cooperate with kisspeptins in the precise regulation of puberty. In addition, Kiss1 neurons seemingly participate in transmitting at least part of the regulatory actions of the signals responsible for the metabolic control of puberty. In this context, recent work from our group has unveiled the important role of key cellular metabolic sensors, such as AMP-activated protein kinase (AMPK), the master cellular sensor activated in conditions of energy insufficiency, and the fuel-sensing deacetylase, Sirt1, as major components for the metabolic modulation of female puberty onset. Our data indicate that AMPK and Sirt1, acting in ARC Kiss1 neurons, are major molecular effectors for the metabolic control of Kiss1 and, thereby, puberty onset, whose alteration may contribute to the perturbations of pubertal timing frequently linked to conditions of metabolic stress, such as sub-nutrition and obesity.

Keywords: puberty; KISS1; kisspeptins; AMPK; Sirt1.
Published May, 2019.
Copyright: © 2019 Manuel Tena-Sempere. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Tena-Sempere, M. Novel molecular pathways for the central control of puberty: Basic aspects and translational implications. IBJ Plus 2019 S(3):e0001 doi: 10.24217/2531-0151.19v1s3.00001.
Funding: The authors declare that no fundings.
Competing Interests: The authors declare that no competing interests exit.

To sleep or not to sleep: how the brain decides to wake us up.

Luis de Lecea[1*]

[1]Department of Psychiatry and Behavioral Sciences, Standford University School of Medicine, Standford, CA. USA.
[*]Corresponding author:
Luis de Lecea, Department of Psychiatry and Behavioral Sciences, Standford University School of Medicine, Standford, CA. USA.
E-mail: llecea@stanford.edu

The arousal construct underlies a spectrum of behaviors that include sleep, exploration, feeding, sexual activity and adaptive stress. Pathological arousal conditions include stress, anxiety disorders, and addiction. In the past few years we have used optogenetics to identify and interrogate neuronal circuits underlying transitions between arousal states. In the first presentation, I will talk about how the hypocretin system coordinates and makes the decisions about when to mark the transition between sleep and wakefulness. The dynamics between arousal state transitions are also modulated by norepinephrine neurons in the locus coeruleus, histaminergic neurons in the hypothalamus, dopaminergic neurons in the mesencephalon and cholinergic neurons in the basal forebrain. I will introduce our own model of sleep/wake dynamics using probabilistic estimates of neurotransmitter function based on optogenetic stimulations. I will also discuss how these models can help characterize dissociated arousal states and develop treatments for neuropsychiatric disorders.

Keywords: arousal; hypothalamus; optogenetics; hypocretin; sleep; wakefulness; addiction; neuropsychiatric disorders.
Published May, 2019.
Copyright: © 2019 Luis de Lecea. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: de Lecea, L. To sleep or not to sleep: how the brain decides to wake us up. IBJ Plus 2019 S(3):e0002 doi: 10.24217/2531-0151.19v1s3.00002.
Funding: The authors declare that no fundings.
Competing Interests: The authors declare that no competing interests exit.

Emerging genes and pathways in thyroid differentiation and tumorigenesis.

Pilar Santisteban[1*]

[1]Instituto de Investigaciones Biomédicas, CSIC-UAM and Ciberonc, ISCIII Madrid, Spain.
[*]Corresponding author:
Pilar Santisteban, Instituto de Investigaciones Biomédicas, CSIC-UAM and Ciberonc, ISCIII Madrid, Spain. E-mail: psantisteban@iib.uam.es

Thyroid cancer remains the most common endocrine malignancy worldwide and its incidence and mortality has increased steadily over the last four decades. In general, it has a good outcome; however, some patients develop aggressive forms of thyroid cancer that are untreatable and the molecular bases are poorly understood. These aggressive forms have lost NIS (Na/I Symporter) function, one of the most important hallmarks during thyroid cancer progression, as it leads to radioiodine-resistant metastatic disease. Our work has contributed to understand the mechanisms involved in iodide uptake repression and tumor progression. We have found that BRAF activation decreases NIS expression and impairs NIS trafficking to the membrane of follicular thyroid cells, and accordingly causes (RAI)-refractory metastatic disease in patients with papillary thyroid cancer. We have demonstrated that the mechanism by which BRAF impairs NIS function is mediated by a TGFβ autocrine loop. Furthermore, by next-generation sequencing and gene expression analysis we have identified a master miRNA (miR) regulatory network involved in essential biological process such as thyroid differentiation. Among those miRNAs, the most abundantly expressed in thyroid tumors is the miR-146b and we found that it binds to the 3'-UTR region of thyroid differentiation genes such PAX8 and NIS, leading to impaired protein translation and subsequently a reduction of iodide uptake. Besides, we show that miR-146b and PAX8 regulate each other sharing common target genes, thus highlighting a novel regulatory circuit that govern differentiated phenotype in thyroid tumors. Furthermore, we have shown that the overexpression of miR-146b induces an hyperactivation of the PI3K/AKT pathway, via PTEN suppression, leading to a more aggressive tumoral behavior. In summary, our work described molecular determinants that may be exploited therapeutically to modulate thyroid cell differentiation and iodide uptake for improved treatment of advanced thyroid cancer.

Keywords: thyroid cancer; iodide; NIS; braf gene; microRNA146b; PAX8; PTEN; signaling.

Published May, 2019.
Copyright: © 2019 Pilar Santisteban. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Santisteban, P. Emerging genes and pathways in thyroid differentiation and tumorigenesis. IBJ Plus 2019 S(3):e0003 doi: 10.24217/2531-0151.19v1s3.00003.
Funding: Grants SAF2016-75531-R from MINECO, Spain (FEDER); B2017/BMD-3724 from CAM and GCB14142311CRES from AECC.
Competing Interests: The authors declare that no competing interests exit.

Adipose tissue expandability, lipotoxicity and the metabolic syndrome.

Antonio Vidal-Puig[1*]

[1]University of Cambridge, Metabolic Research Laboratories, Wellcome Trust-MRC Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, CB2 0QQ, United Kingdom.
[*]Corresponding author:
Antonio Vidal-Puig, University of Cambridge, Metabolic Research Laboratories, Wellcome Trust-MRC Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge, CB2 0QQ, United Kingdom. E-mail: ajv22@medschl.cam.ac.uk

The link between obesity and type 2 diabetes is clear on an epidemiological level, however the mechanism linking these two common disorders is not well defined. One hypothesis linking obesity to type 2 diabetes is the adipose tissue expandability hypothesis. The adipose tissue expandability hypothesis states that a failure in the capacity for adipose tissue expansion, rather than obesity per se is the key factor linking positive energy balance and type 2 diabetes. All individuals possess a maximum capacity for adipose expansion which is determined by both genetic and environmental factors. Once the adipose tissue expansion limit is reached, adipose tissue ceases to store energy efficiently and lipids begin to accumulate in other tissues. Ectopic lipid accumulation in non-adipocyte cells causes lipotoxic insults including insulin resistance, apoptosis and inflammation. This article discusses the links between adipokines, inflammation, adipose tissue expandability and lipotoxicity. Finally, we will discuss how considering the concept of allostasis may enable a better understanding of how diabetes develops and allow the rational design of new anti diabetic treatments.

Keywords: adipogenesis; obesity; type 2 diabetes; lipotoxicity; insulin resistance; immunometabolism ; inflammation.

Published May, 2019.
Copyright: © 2019 Antonio Vidal-Puig. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Vidal-Puig, A. Adipose tissue expandability, lipotoxicity and the metabolic syndrome. IBJ Plus 2019 S(3):e0004 doi: 10.24217/2531-0151.19v1s3.00004.
Funding: The authors declare that no fundings.
Competing Interests: The authors declare that no competing interests exit.

Regulation of tissue macrophage functions by LXR nuclear receptor dependent transcriptional pathways.

Antonio Castrillo[1*]

[1]Instituto de Investigaciones Biomédicas "Alberto Sols" CSIC-UAM, Madrid, Spain.
[*]Corresponding author:
Antonio Castrillo, Instituto de Investigaciones Biomédicas "Alberto Sols" CSIC-UAM, Madrid, Spain. E-mail: antonio.castrillo@iib.uam.es

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. We have 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, LXRα and 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. In this symposium, we will discuss our recent advances in LXR biology. With a combination of functional assays, expression profiling and ChIP-sequencing data, we will shed light on our understanding of LXR´s cell-specific targets and the specific actions of LXRα and LXRβ in macrophage immune responses. Collectively we will discuss the current view of LXR transcription factors in immune processes and their impact in macrophage biological processes.

Keywords: LXR; liver X receptor; nuclear receptor; gene expression; transcription; inflammation; macrophage; immunology.
Published May, 2019.
Copyright: © 2019 Antonio Castrillo. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Castrillo, A. Regulation of tissue macrophage functions by LXR nuclear receptor dependent transcriptional pathways. IBJ Plus 2019 S(3):e0005 doi: 10.24217/2531-0151.19v1s3.00005.
Funding: The authors declare that no fundings.
Competing Interests: The authors declare that no competing interests exit.

Genetic determinants of thyroid function: novel insights and new approaches.

Marco Medici[1*]

[1]Department of Internal Medicine, Erasmus Medical Center, Rotterdam. The Netherlands.
[*]Corresponding author:
Marco Medici, Department of Internal Medicine, Erasmus Medical Center, Rotterdam. The Netherlands. E-mail: m.medici@erasmusmc.nl

In the last few years studies have shown that subtle variations in thyroid function, including subclinical thyroid dysfunction, and even variation in thyroid function within the normal range, are associated with morbidity and mortality. It is estimated that 40-65% of the inter-individual variation in serum TSH and FT4 levels is determined by genetic factors. To identify these factors, various linkage and candidate gene studies have been performed in the past, which have identified only a few genes. In the last decade, genome-wide association studies identified >100 genetic variants, while whole exome and whole genome sequencing studies are expected to further clarify the genetic basis of thyroid function in the near future. The identification of these genes has paved the way for various lines of research. Examples of follow-up in vitro characterization studies of these genes include the identification of SLC17A4 as a novel thyroid hormone transporter and AADAT as a novel thyroid hormone metabolizing enzyme. Furthermore, mendelian randomization studies are expected to clarify whether the observed associations between minor variations in thyroid function and clinical endpoints are causal or not, which is key when considering treatment for these mild variations in thyroid function. Finally, these genetic markers have been associated with normal range thyroid function as well as thyroid dysfunction, thereby possibly serving as predictive markers for the individual thyroid setpoint and for thyroid disease.

Keywords: thyroid; TSH; FT4; genome-wide association studies; SLC17A4.

Published May, 2019.
Copyright: © 2019 Marco Medici. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Medici, M. Genetic determinants of thyroid function: novel insights and new approaches. IBJ Plus 2019 S(3):e0006 doi: 10.24217/2531-0151.19v1s3.00006.
Funding: The authors declare that no fundings.
Competing Interests: The authors declare that no competing interests exit.

The role of endocrine disruptors in the etiology of diabetes mellitus.

Ángel Nadal[1*]

[1]Instituto de Investigación, Desarrollo e Innovación en Biotecnología Sanitaria de Elche. Universidad Miguel Hernández de Elche y CIBERDEM, Alicante, Spain.
[*]Corresponding author:
Ángel Nadal, Instituto de Investigación, Desarrollo e Innovación en Biotecnología Sanitaria de Elche. Universidad Miguel Hernández de Elche y CIBERDEM, Alicante, Spain. E-mail: nadal@umh.es

Keywords:
Published May, 2019.
Copyright: © 2019 Ángel Nadal. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Nadal, A. The role of endocrine disruptors in the etiology of diabetes mellitus. IBJ Plus 2019 S(3):e0007 doi: 10.24217/2531-0151.19v1s3.00007.
Funding: The authors declare that no fundings.
Competing Interests: The authors declare that no competing interests exit.

Pathogenesis of autoimmune thyroid diseases: role of cellular immunity.

Mónica Marazuela[1*]

[1]Hospital Universitario La Princesa, Facultad de Medicina UAM, Madrid, Spain.
[*]Corresponding author:
Mónica Marazuela, Hospital Universitario La Princesa, Facultad de Medicina UAM, Madrid, Spain. E-mail: monica.marazuela@uam.es

Autoimmune thyroid disease (AITD), which includes Hashimoto's thyroiditis (HT) and Graves' disease (GD) are one of the most prevalent organ-specific autoimmune diseases which are characterized by circulating antibodies and lymphocyte infiltration of the thyroid gland. The etiology of AITD is multifactorial due to a complex interplay of specific susceptibility genes and environmental exposures and is characterized by reactivity to self-thyroid antigens due to autoreactive lymphocytes escaping tolerance. Different adhesion molecules, cytokines and chemokines help lymphocyte migration to the thyroid in AITD.

Although humoral and cellular mechanisms have been classically considered separately in AITD, recent research suggests a close reciprocal relationship between these two immune pathways. The simple dichotomy Th1/Th2 has been outweighed by the recently described T cells subtypes Treg and Th17 have an essential role in the pathogenesis of AITD. Although several types of CD4 Treg cells (Foxp3, CD69, Tr1), which are able to prevent the appearance of autoimmune diseases, are found in peripheral blood and thyroid tissue from patients with AITD, these cells are apparently unable to put down the autoimmune process. In addition, many reports indicate the involvement of different Th17 cells in AITD. Recently, specific miRNA have been involved in the disregulation of immune mechanisms in AITD probably through differential Treg and Th17 differentiation. Nowadays, both Treg and Th17 cells must be considered as key elements in the pathogenesis of AITD as well as plausible potential targets for the next generation of therapeutic options of this condition.

Keywords: autoimmune thyroid disease; lymphocyte differentiation; immunity; immunometabolism; inflammation.

Published: May, 2019.

Copyright: © 2019 Mónica Marazuela. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Cite as: Marazuela, M. Pathogenesis of autoimmune thyroid diseases: role of cellular immunity. IBJ Plus 2019 S(3):e0008 doi: 10.24217/2531-0151.19v1s3.00008.

Funding: The authors declare that no fundings.

Competing Interests: The authors declare that no competing interests exit.

Poster Session Abstracts

Urinary concentration of Iodotyrosines correlates with the severity of iodine deficiency in Dehal1 knockout mice.

Cristian González-Guerrero[1*], Marco Borso[2], Jorge García-Giménez[1], Federico Salas-Lucia[1], Pouya Alikhani[1], Alessandro Saba[2], Riccardo Zucchi[2], José C. Moreno[1].

[1]Thyroid Molecular Laboratory. Insitute for Medical and Molecular Genetics-INGEMM. La Paz University Hospital. Autonomous University of Madrid. Spain.
[2]Mass Spectrometry Laboratory. Department of Pathology. University of Pisa. Pisa, Italy.
[*]Corresponding author:
Cristian González Guerrero, INGEMM-Universitary Hospital of la Paz, Madrid, Spain. Email: cristian.gonzalez.guerrero@gmail.com

Thyroid hormone (TH) synthesis requires iodine, a scarce element whose recycling is mediated by DEHAL1 through deiodination of iodotyrosines MIT and DIT. In humans, DEHAL1 defects lead to severe congenital hypothyroidism (CH) non-detected by neonatal screening programs, which involves the risk of mental retardation in infants. The timing for establishment of this hypothyroidism remains unknown, but environmental iodine deficiency may represent a triggering factor. While urinary loss of iodotyrosines could represent early biomarkers for the disorder, its determination in fluids remains a technical challenge.
To measure urinary concentrations of iodotyrosines and test their correlation with urinary iodide in Dehal1 knockout mice under experimentally controlled iodine deficiency.

Dehal (-/-) and wild type (wt) mice were subjected to normal, low, and very low iodine diets (NID, LID, VLID) containing 5.6, 1 and 0.25µgI/day, for 28 days. At d0, d15 and d28, urinary iodine concentration (UIC) was determined by Kolthoff method and MIT, DIT determined in urine using a novel LC/MS-MS protocol.

At baseline and NID, MIT and DIT urinary levels were statistically higher in Dehal1(-/-) (5 and 8ng/ml) than in wt (1 and 0.5ng/ml), respectively ($p<0.02$). Accordingly, UIC was increased in Dehal1 (-/-) (30mg/dl) compared to wt (15mg/dl) ($p<0.05$), suggesting that iodide content of iodotyrosines is freed during Kolthoff procedure and adds to the general iodide pool in the urine. This situation persists in time till d28. Under LID, MIT and DIT concentrations remain elevated in Dehal1(-/-) (5.5 and 8ng/ml) compared to wt (0.5 and 0.5ng/ml) ($p<0.05$) at d15, but start to decrease in both genotypes at d28. UIC was still higher in Dehal1(-/-) (4 mg/dl) versus wt (1mg/dl) ($p<0.05$) at d15 and d28, but decreased with respect to NID. Under VLID, MIT and DIT levels were still remained significantly higher in Dehal1 (-/-) (4 and 3ng/ml) compared to wt (0.5 and 0.25ng/ml ($p<0.05$) at d15. At d28, iodotyrosines lowered to barely detectable levels in wt mice. Finally, UIC levels in Dehal1(-/-) were intensely decreased (0.5 mg/dl) at d15 and d28, while wt mice showed undetectable levels, reflecting stringent iodine restriction.

Our data strongly suggest that the accurate measurement of increased urinary loss of MIT and DIT correlates with UIC increment in Dehal1 deficient mice, which is triggered by iodine deficient intake. Therefore, urinary iodotyrosines may represent pre-clinical biomarkers for early detection and treatment of DEHAL1 deficiency and prevention of mental retardation risks related to late diagnosis of CH.

Keywords: Dehal1, Iodotyrosines, Iodine deficiency.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: González-Guerrero C., Borso M., García-Giménez J., Salas-Lucia F., Alikhani P., Saba A., Zucchi R., Moreno JC.. Urinary concentration of Iodotyrosines correlates with the severity of iodine deficiency in Dehal1 knockout mice. IBJ Plus 2019 S(3):e0009 doi: 10.24217/2531-0151.19v1s3.00009.
Funding: The research Project PI16/00830 is funded by the Carlos III Health Institute (ISCIII) from the Spanish Ministry of Education and European FEDER funds.
Competing Interests: The authors declare that no competing interests exit.

3D mapping and in silico predictions of the DEHAL1 enzyme as a tool to discriminate pathogenic mutations from non-functional variants in hypothyroidism.

Jorge García-Giménez[1], Ángel González Wong[2], Cristian González-Guerrero[1*], Ainhoa Iglesias[1], Emily Styers[1], José Cocho[3], Leonardo Pardo[2], José C. Moreno[1].

[1]Thyroid Molecular Laboratory. Insitute for Medical and Molecular Genetics-INGEMM. La Paz University Hospital. Autonomous University of Madrid. Spain.
[2]Computational Medicine Laboratory. Biostatistics unit. Autonomous University of Barcelona, Barcelona, Spain.
[3]Congenital Metabolomic Pathology Unit. Clinical hospital of Santiago de Compostela, Santiago de Compostela, Spain.
[*]Corresponding author: Cristian González Guerrero, INGEMM-Universitary Hospital of la Paz, Madrid, Spain.
Email: cristian.gonzalez.guerrero@gmail.com

Next Generation Sequencing (NGS) is becoming widely used for genetic diagnosis. While its capacity for detection of human genetic variations (GV) is outstanding, drawbacks is the identification of numerous GV of which functional significance cannot be predicted in silico by computer programs (variants of uncertain significance, VUS). Currently, only sensitive (but also expensive and time-demanding) in vitro cell assays, can trustfully ascertain pathogenicity of VUSs, generally of selected proteins o signalling pathways, seriously hampering efficiency of genetic diagnostic for the clinic.

To apply 3D mapping and in silico predictions as tools to inform pathogenicity of GVs identified in hypothyroid patients with alleged iodotyrosine deiodinase deficiency, as compared with in vitro dehalogenation assays.
Nine missense DEHAL1 variants identified in goitrous hypothyroid patients were subjected to both in vitro functional testing and in silico 3D modelling and docking with substrates (MIT, DIT) and cofactor (FMN), using available X-Ray crystallographic information of dimeric DEHAL1. Three (K258N, V265M and R279S) were identified in patients with undisputed diagnosis of iodotyrosine deiodinase deficiency through in vivo 123I-MITdeiodination test. The rest (N108S, A202T, R246Q, L260P and E271K) are harboured by patients with clinical suspicion of DEHAL1 defect. The functional assay involved mutagenesis of DEHAL1 variants in expression vectors, transfection in HEK293 cells, addition of MIT, FMN and NADPH to culture medium and determination of % MIT decrease by LC/MS-MS.
The functional assay showed significant decrease of deiodination for K258N (60%) and R279S (58%) versus WT. However, V265M did not, suggesting limitations of our assay to detect less severe mutations. The rest of variants showed normal deiodination with the exception of L260P, which behaved as deleterious (10%).Interestingly, in silico studies on K258N, R279S, V265M and L260P revealed that the amino acids changes had damaging effects on the structural stability, electrostatic properties or interaction with cofactor and substrates (FMN and MIT) on the DEHAL1, and provide a structural explanation for the iodotyrosine deiodinase deficiency (Figure 1). Besides, the peripheral location of N108S, A202T, R246Q, and E271K variants in the model correlates with the benign nature of such changes in the assay (Figure 1).
Structural modelling and molecular dynamics is a valuable tool to discriminate pathogenic versus VUS changes in human DEHAL1, showing consistency with the in vitro assay and superior sensitivity to detect some pathogenic changes. An additional advantage of this filtering approach is the prediction of the intrinsic molecular mechanism driving the functional damage of mutations.

Keywords: Dehal1, 3D-mapping, massive-sequencing.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: García-Giménez J., González Wong A., González-Guerrero C., Iglesias A., Styers E., Cocho J., Pardo L., Moreno JC. 3D mapping and in silico predictions of the DEHAL1 enzyme as a tool to discriminate pathogenic mutations from non-functional variants in hypothyroidism. IBJ Plus 2019 S(3):e0010 doi: 10.24217/2531-0151.19v1s3.00010.
Funding: The research Project PI16/00830 is funded by the Carlos III Health Institute (ISCIII) from the Spanish Ministry of Education and European FEDER funds.
Competing Interests: The authors declare that no competing interests exit.

Mice deficient in Mct8 and Dio2 as a new tool to go in depth in the neuropathology of human MCT8 deficiency and to explore new therapeutic strategies.

Soledad Bárez-López[1,2], Carmen Grijota-Martínez[1,2], Eva Ausó[1,3], Mario Fernández-de Frutos[1,4], Ana Montero-Pedrazuela[1] and Ana Guadaño-Ferraz[1,2*]

[1]Instituto de Investigaciones Biomédicas Alberto Sols, Consejo Superior de Investigaciones Científicas (CSIC)-Universidad Autónoma de Madrid (UAM), Arturo Duperier 4, E-28029 Madrid, Spain.
[2]Center for Biomedical Research On Rare Diseases (Ciberer), Unit 708, Instituto de Salud Carlos III, Madrid, Spain.
[3]Universidad de Alicante, Departamento de Óptica, Farmacología y Anatomía. Carretera San Vicente del Raspeig s/n, 03690 Alicante, Spain.
[4]Present adress: IMDEA Research Institute on Food and Health Sciences. 28049 Madrid, Spain.
[*]Corresponding author:
Ana Guadaño-Ferraz, Instituto de Investigaciones Biomédicas Alberto Sols, Consejo Superior de Investigaciones Científicas (CSIC)-Universidad Autónoma de Madrid (UAM), and Center for Biomedical Research On Rare Diseases (Ciberer), Unit 708, Instituto de Salud Carlos III, Madrid, Spain.
E-mail: aguadano@iib.uam.es

Allan-Herndon-Dudley syndrome is a rare disease caused by mutations in the specific thyroid hormone transporter monocarboxylate transporter 8 (MCT8). Defects in this transporter cause peripheral hyperthyroidism and profound psychomotor alterations in humans. Mice lacking Mct8 were the first murine model used for the study of this disease; they presented peripheral hyperthyroidism but unfortunately no gross neurological abnormalities. This seems to be due to a compensatory mechanism in brain involving the enzyme deiodinase type 2 (Dio2) which converts T4 into T3. Therefore, a new animal model has been proposed: mice lacking both Mct8 transporter and Dio2 enzyme. Here we have analysed the endocrine and neurologic phenotype of these mice at 3 and 6 months of age. Our results show that these animals present peripheral hyperthyroidism and brain hypothyroidism that seems to be permanent and to vary across regions, being the striatum the most sensitive area. Immunohistochemical studies in brain show alterations compatible with thyroid hormone deficiency. We have also found alterations in motor skills evaluations. All these data support the potential of Mct8/Dio2-deficient mice as a new tool to understand the mechanism underlying the pathophysiology of human Mct8 deficiency and to explore new therapeutic strategies.

Keywords: thyroid hormone; Allan-Herndon-Dudley syndrome; MCT8; Dio2; hyperthyroidism.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Bárez-López S., Grijota-Martínez C., Ausó E., Fernández-de Frutos M., Montero-Pedrazuela A., Guadaño-Ferraz A., Mice deficient in Mct8 and Dio2 as a new tool to go in depth in the neuropathology of human MCT8 deficiency and to explore new therapeutic strategies. IBJ Plus 2019 S(3):e0011 doi: 10.24217/2531-0151.19v1s3.00011.
Funding: Supported by grants BFU2007-62979 from the Spanish Ministry of Science, Innovation and Universities and from the Sherman Foundation.
Competing Interests: The authors declare that no competing interests exit.

Interplay between TGFβ and the Hippo mediator TAZ leads to Sodium-iodide symporter inhibition.

Celia Fernández-Méndez[1], Pilar Santisteban[1, 2*]

[1]Instituto de Investigaciones Biomédicas "Alberto Sols"; Consejo Superior de Investigaciones Científicas (CSIC), Universidad Autónoma de Madrid (UAM), Madrid, Spain.
[2]Centro de Investigación Biomédica en Red de Cáncer (CIBERONC) Instituto de Salud Carlos III (ISCIII), Madrid, Spain.
[*]Corresponding author:
Pilar Santisteban, Instituto de Investigaciones Biomédicas "Alberto Sols"; Consejo Superior de Investigaciones Científicas (CSIC), Universidad Autónoma de Madrid (UAM), Madrid, Spain. Centro de Investigación Biomédica en Red de Cáncer (CIBERONC) Instituto de Salud Carlos III (ISCIII), Madrid, Spain. E-mail: psantisteban@iib.uam.es.

TAZ is a well-known coactivator downstream of the Hippo signaling pathway. Together with its paralogous YAP and the transcription factors of the TEAD family, TAZ plays a key role in the regulation of differentiation, among other cellular processes. Little is known about the involvement of this signaling pathway in the function of the thyroid gland, although TAZ has been described as a coactivator of Pax8 on the thyroglobulin promoter. Pax8 has a predominant role in thyroid differentiation by regulating the transcription of many crucial genes, such as sodium-iodide symporter (NIS). The aim of this work was to study the role of the Hippo pathway, and particularly its mediator TAZ, in NIS expression, and hence in thyroid differentiation.

By western blot and immunofluorescence, we show TAZ nuclear expression is promoted by TGFβ signalling through its downstream mediator p38. We demonstrated that nuclear TAZ exerts a marked role as NIS repressor, decreasing its expression levels, affecting its presence in the celular membrane and thus impairing iodide uptake. By chromatin immunoprecipitation (ChIP) and luciferase reporter assays, we demonstrated that TAZ strongly suppresses Pax8 activation of the NIS promoter by decreasing its binding to the NIS Upstream Enhancer (NUE). In fact, the absence of TAZ directly increases Pax8 nuclear levels. RNAi assays of other Hippo effectors were performed in order to check their participation in this process. Although YAP and TEAD1 could have additive effects, TAZ seems to be the main requirement for NIS downregulation.

TGFβ role in thyroid differentiation is well establish, however here we describe a novel crosstalk with the Hippo Pathway and its mediator TAZ, remarkably involved in the control of the sodium iodide symporter expression.

Keywords: TGFβ, Hippo pathway, TAZ, thyroid, NIS.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Fernández-Méndez C., Santisteban P., Interplay between TGFβ and the Hippo mediator TAZ leads to Sodium-iodide symporter inhibition. IBJ Plus 2019 S(3):e0012 doi: 10.24217/2531-0151.19v1s3.00012.
Funding: SAF2016-75531-R
Competing Interests: The authors declare that no competing interests exit.

Molecular Basis of Deafness Caused by Insulin-like Growth Factor Type 1 Deficiency.

Lourdes Rodríguez-de la Rosa[*1,2,3], Jose M. Bermúdez-Muñoz[1,2], Marina López[1], Almudena Sanz[1], Melanie Mertens[1], Adelaida M. Celaya[1], Jose M. Morales[3,4], Miryam Calvino[3,4], Luis Lassaletta[1,2,3,4], Rafael Cediel[1,2,5], Julio Contreras[1,2,5], Isabel Varela-Nieto[1,2,3] and Silvia Murillo-Cuesta[1, 2, 3].

[1]Instituto de Investigaciones Biomédicas "Alberto Sols" (IIBm). Consejo Superior de Investigaciones Científicas (CSIC) y Universidad Autónoma de Madrid (UAM). Madrid, Spain.
[2]Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER). Instituto de Salud Carlos III (ISCIII). Madrid, Spain.
[3]Instituto de Investigación Sanitaria del Hospital Universitario La Paz (IdiPAZ). Madrid, Spain.
[4]Servicio de Otorrinolaringología. Hospital Universitario La Paz. Madrid, Spain.
[5]Facultad de Veterinaria. Universidad Complutense de Madrid (UCM). Madrid, Spain.
[*]Corresponding author:
Lourdes Rodríguez-de la Rosa E-mail: lrodriguez@iib.uam.es

World Health Organization estimates that around 466 million people worldwide have disabling hearing loss (HL), and 34 million of these are children (1). The most common is sensorineural hearing loss (SNHL), a heterogeneous disorder which is produced mainly by the irreversible loss of sensory cells or neurons in the cochlea.
Insulin like growth factor type 1 (IGF-1) is a neurotrophic factor key for the regulation of postnatal cochlear growth and differentiation. Human IGF-1 deficiency is a rare disease (ORPHA73272) associated with growth retardation, microcephaly and SNHL. The mouse model lacking the Igf1 gene reproduces the syndrome and presents dwarfism and SNHL (2). IGF-1 deficiency causes important cellular alterations in the mouse cochlea, such as the early apoptosis of auditory neurons and the deficit in myelination (3). Analysis of downstream signalling in the Igf1-/- cochlea has shown the activation of p38 MAPK pathway, involved in response to stress, whereas ERK1/2 and AKT pathways, which regulate proliferation and survival, are impaired (4). A transcriptomic study carried out in the Igf1-/- showed the altered expression of the cell cycle modulator Foxm1 and of the myocyte enhancer factor-2 (Mef2), a key factor for cellular differentiation, during inner ear development and early postnatal ages (4).
IGF-1 haploinsufficiency has been also associated with growth retardation and HL in human genetic disorders such as Laron syndrome (5). In contrast, the Igf1+/- mouse does not show congenital HL, but adult mice hearing thresholds progressively increase with ageing and mice show increased susceptibility to noise insult (6). Adult Igf1+/- cochleae show unbalanced redox and inflammation biomarkers, as well as altered IGF-1 downstream signalling, which have been proposed as molecular mechanism underlying susceptibility (7).

Mouse models of IGF-1 deficiency constitute a valuable tool to study the molecular bases of deafness and to identify potential targets to develop new HL therapies.

(1) World Health Organization. https://www.who.int/pbd/deafness/estimates/en/. Published 2018.
(2) Cediel et al., Eur J Neurosci. 2006 Jan;23(2):587-90.
(3) Camarero et al., J Neurosci. 2001 Oct 1;21(19):7630-41.
(4) Sanchez-Calderon et al., PLoS One. 2010 Jan 25;5(1):e8699.
(5) Varela-Nieto et al., Ped Endocrinol Rev. 2013; 10(4):460-72.
(6) Rodríguez-de la Rosa et al., Neurobiol Dis. 2012 May;46(2):476-85.
(7) Celaya et al., 2019. Submitted.

Keywords: IGF-1, hearing loss, AKT, p38, MEF2.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Rodríguez-de la Rosa L., Bermúdez-Muñoz JM., López M., Sanz A., Mertens M., Celaya AM., Morales JM., Calvino M., Lassaletta L., Cediel R., Contreras J., Isabel Varela-Nieto I., Murillo-Cuesta S., Molecular Basis of Deafness Caused by Insulin-like Growth Factor Type 1 Deficiency. IBJ Plus 2019 S(3):e0013 doi: 10.24217/2531-0151.19v1s3.00013.
Funding: This work was supported by grants from the Spanish MINECO/FEDER (SAF2014-53979-R and SAF2017-86107-R) and FP7-PEOPLE-2013-IAPP TARGEAR to IVN. SMC and LRdR holds a contract supported by CIBERER (Institute of Health Carlos III) co-financed with FEDER funds.
Competing Interests: The authors declare that no competing interests exit.

Insulin-like growth factor-1 regulates survival and differentiation in otic cells.

Sara Pulido[1,2*], Ángela García-Mato[1,2], Blanca Cervantes[1,2], Marina López[1], Yolanda León[1,3], Isabel Varela-Nieto[1,2,4], Marta Magariños[1,2,3], Lourdes Rodríguez de la Rosa[1,2,4]

[1] "Alberto Sols" Biomedical Research Institute (CSIC-UAM), Madrid, Spain.
[2]CIBERER Unit 761, Institute of Health Carlos III, Madrid, Spain.
[3]Department of Biology, Autonomous University of Madrid, Madrid, Spain.
[4]IdiPAZ, La Paz Hospital Institute for Health Research, Madrid, Spain.
[*]Corresponding author:
"Alberto Sols" Biomedical Research Institute (CSIC-UAM), Madrid, Spain. E-mail: spulido@iib.uam.es

Insulin-like growth factor-1 (IGF-1) is a key element in chicken otic development, and its deficit causes syndromic deafness in mice and men (1). Early steps of inner ear development involve the formation of an autonomous embryonic structure, the otic vesicle or otocyst. Otic vesicle development requires the coordinated actions of apoptosis, proliferation, senescence, cell differentiation and autophagy (2). Autophagy is a catabolic process essential for vertebrate development and homeostasis. We have reported that autophagy is required to facilitate the clearance of apoptotic cells and neuronal differentiation during early otic development (3). In other cellular context, IGF-1 has been shown to regulate autophagy (4). To better understand the molecular actions of IGF-1 and its potential modulation of autophagy in otic cells, we have used the cell line HEI-OC1 (derived from the auditory organ of the transgenic mouse Immortomouse™) and ex vivo cultures of chicken otocysts.
IGF-1 signaling pathway was studied by Western blotting of main IGF-1 targets. Proliferation was measured by incorporation of EdU. Apoptosis was assessed by TUNEL labelling and flow cytometry. Autophagy flux was analyzed by measuring LC3 and p62 relative protein levels.
Our results show that IGF-1 promotes cell survival and cell proliferation while reduces cell death in both experimental models. IGF-1 is also playing a role in neuronal differentiation in the otic vesicle, maintaining otic neuroblasts in an undifferentiated and proliferative state. Furthermore IGF-1 actions include the downregulation of autophagy, which is induced in response to starvation and is essential for development and differentiation of otic cells.

(1) Rodríguez-de la Rosa, L., Lassaletta, L., Calvino, M., Murillo-Cuesta, S., & Varela-Nieto, I. (2017). The Role of Insulin-Like Growth Factor 1 in the Progression of Age-Related Hearing Loss. Frontiers in aging neuroscience, 9, 411. doi:10.3389/fnagi.2017.00411
(2) Varela-Nieto, I., Palmero, I., Magariños, M. (2019). Complementary and distinct roles of autophagy, apoptosis and senescence during early inner ear development. Hearing Research, 376, 86-96. doi: 0.1016/j.heares.2019.01.014
(3) Aburto, M. R., Sánchez-Calderón, H., Hurlé, J. M., Varela-Nieto, I., & Magariños, M. (2012). Early otic development depends on autophagy for apoptotic cell clearance and neural differentiation. Cell death & disease, 3(10), e394. doi:10.1038/cddis.2012.132
(4) Renna, M., Bento, C. F., Fleming, A., Menzies, F. M., Siddiqi, F. H., Ravikumar, B., … Rubinsztein, D. C. (2013). IGF-1 receptor antagonism inhibits autophagy. Human molecular genetics, 22(22), 4528–4544. doi:10.1093/hmg/ddt300

Keywords: IGF-1, inner ear, autophagy, otic cells.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Pulido S., García-Mato A., Cervantes B., López M., León Y., Varela-Nieto I., Magariños M., Rodríguez de la Rosa L., Insulin-like growth factor-1 regulates survival and differentiation in otic cells. IBJ Plus 2019 S(3):e0014 doi: 10.24217/2531-0151.19v1s3.00014.
Funding: This work was supported by FEDER/SAF2017-86107-R-HEARCODE. SP holds an FPI predoctoral fellowship (BES-2015-071311; European Social Fund/MINECO). AGM holds a MECD FPU fellowship (FPU16/03308). LR-R holds a contract supported by CIBERER (Institute of Health Carlos III) co-financed with FEDER funds.
Competing Interests: The authors declare that no competing interests exit.

Ghrelin modulates hippocampal plasticity changing density and morphology of dendritic spines.

Perea Vega ML[1], Sánchez M.[2], De Barioglio S. R.[1]

[1]Dpto. de Farmacología, Universidad Nacional de Córdoba - IFEC- Conicet; Haya De La Torre Y Medina Allende S/n, Córdoba, Argentina.
[2]Instituto de Investigaciones Médicas Mercedes y Martín Ferreyra (INIMEC-CONICET-UNC); Friuli 2434, Colinas de Vélez Sarsfield, X5016NST Córdoba, Argentina.
*Corresponding author:
Perea Vega ML, Depto Farmacología, Universidad Nacional de Córdoba - IFEC- Conicet; Haya De La Torre Y Medina Allende S/n, Córdoba, Argentina.
E-mail: mlperea@unc.edu.ar

Ghrelin (Gr) is a peptide involved in the modulation of various biological processes. In previous works we have demonstrated that intracerebroventricular or hippocampal (Hp) Gr administration improves memory retention in a dose-dependent manner in rats and mice using different behavioral paradigms that evaluate memory. In addition, we also showed that Gr decreases the threshold for inducing long-term potentiation (LTP, a process underlying memory formation), increases glutamate release and the expression of the NR2B subunit of NMDA receptor.

It is well known that neuronal plasticity correlated with changes on the level of the dendritic spines (DS). It has been demonstrated a correlation between the structure and number of DS and mechanisms related to learning and memory. The density of DS is related to the amount of connectivity between neurons and indicates the numbers of synaptic excitatory inputs onto a particular neuron. DS are largely heterogeneous and can be classified into three classes according the morphology: stubby, thin, and mushroom spines. DS are highly dynamic in the mature nervous system and could be modulated by inputs from the environment in the form of synaptic activity which is central to memory formation. Investigating the molecular mechanisms that underlie structural plasticity of synapses will therefore be crucial not only in understanding the brain functions but should also provide important insights on identifying therapeutic targets for various neurological disorders.

Taking into account the functional effects of Gr previously described, the purpose of this study was to investigate morphological and quantitative changes in DS after Gr administration (2 different doses) in primary hippocampal cultures from rats.

The analysis of the DS showed that Gr increases the total density of DS (+150%) in relation to non-treated cells (control). In relation to the morphology the mushroom type was the most increased type. These results indicate that Gr promotes the formation of new spines as well as the enlargement and stabilization of these spines.

Keywords: Ghrelin, neuronal plasticity, memory

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Perea Vega ML., Sánchez M., De Barioglio S. R., Ghrelin modulates hippocampal plasticity changing density and morphology of dendritic spines. IBJ Plus 2019 S(3):e0015 doi: 10.24217/2531-0151.19v1s3.00015.
Funding: This work was supported by grants from Consejo Nacional de Investigación Científica y Técnica (CONICET), Secretaría de Ciencia y Técnica de la Universidad Nacional de Córdoba, Argentina (SECyT-UNC), Fondo para la Investigación Científica y Tecnológica, Agencia Nacional de Promoción Científica y Tecnológica (FONCyT), and the Swedish Research Council (VR, Medicine). The authors thank Estela Salde and Lorena Mercado (CONICET and UNC technicians) for their technical assistance
Competing Interests: The authors declare that no competing interests exit.

Identification of primary cilia targeting sequences in HTR6 and SSTR3.

Pablo Barbeito[1,3], Paula Moreno[1,3], Raquel Martin-Morales[1,3], Maria Belen Sierra-Rodero[1,3] and Francesc R. Garcia-Gonzalo[1-3,*].

[1] Departamento de Bioquímica, Facultad de Medicina, Universidad Autónoma de Madrid (UAM), Calle Arzobispo Morcillo 4, 28029, Madrid, Spain
[2]Instituto de Investigaciones Biomédicas Alberto Sols UAM-CSIC, Calle Arturo Duperier 4, 28029, Madrid, Spain
3Instituto de Investigación Hospital Universitario de La Paz, Edificio IdiPAZ, Paseo de la Castellana 261, 28046, Madrid, Spain
[*]Corresponding author:
Francesc R. Garcia-Gonzalo, Departamento de Bioquímica, Facultad de Medicina UAM, Madrid, Spain. E-mail: francesc.garcia@uam.es

Serotonin receptor 6 (Htr6) is a neuronal G protein-coupled receptor (GPCR) involved in multiple aspects of brain pathophysiology. Htr6 localizes to primary cilia, microtubule-based plasma membrane protrusions that act as signaling platforms. Htr6 contains a ciliary targeting sequence (CTS) in its third intracellular loop. This CTS (CTS1) is sufficient to confer cilia localization to non-ciliary proteins such as Htr7, a non-ciliary GPCR, or CD8, a single pass transmembrane protein. Surprisingly, however, CTS1 is not required for Htr6 itself to localize to cilia, suggesting that Htr6 contains another CTS. Here, we have identified a second CTS (CTS2) in the C-terminal tail of Htr6. Like CTS1, the novel CTS2 is sufficient but not necessary for cilia localization. When both CTS1 and CTS2 are mutated, Htr6 no longer accumulates in cilia. Thus, CTS1 and CTS2 act redundantly and are, in combination, both necessary and sufficient for Htr6 ciliary targeting. Furthermore, we have found that the same pattern applies to another ciliary GPCR, namely, Somatostatin receptor 3 (Sstr3). We are now elucidating the mechanisms of action of these novel CTSs.

Keywords: primary cilia, G protein-coupled receptor, ciliary targeting sequence, Serotonin, Somatostatin.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Barbeito P., Moreno P., Martin-Morales R., Sierra-Rodero MB. and Garcia-Gonzalo FR., Identification of primary cilia targeting sequences in HTR6 and SSTR3. IBJ Plus 2019 S(3):e0016 doi: 10.24217/2531-0151.19v1s3.00016.
Funding: This work was funded by MINECO/FEDER (SAF2015-66568-R) and Ramón y Cajal (RYC2013-14887) grants from the Spanish Ministry of Economy and Competitiveness to F.R.G.G.
Competing Interests: The authors declare that no competing interests exit.

Oxidative stress, altered dopamine neurotransmission and increased susceptibility to nigrostriatal neurodegeneration in diabetic mice.

Pérez-Taboada, I[1], Moratalla, R[2] and Vallejo, M.[1,*]

[1]Instituto de Investigaciones Biomédicas Alberto Sols, CSIC/UAM, CIBER de Diabetes y Enfermedades Metabólicas Asociadas (Ciberdem)
[2]Instituto Cajal, CSIC and Ciberned

*Corresponding author:
Mario Vallejo, Madrid, Spain. Email: mvallejo@iib.uam.es

Diabetes has been associated with increased risk of neurodegenerative diseases in a number of epidemiological studies, but the underlying mechanisms are unknown. In the case of Parkinson's disease, this association has been confirmed in an increasing number of reports, although other fail to find a link. Here, using a mouse model of diabetes, we describe oxidative stress and neurotransmission alterations in the nigrostriatal system, and investigate whether diabetes increases the vulnerability of substantia nigra neurons to neurodegeneration. We used C57BL/6 mice rendered diabetic by streptozocin injections. Dopaminergic neuron and oxidative stress markers were determined by RT-qPCR or western blot. Striatal neurotransmitter and related metabolite levels were monitored by HPLC. Oxidative stress in the striatum was determined using commercial tests. [3H]-Dopamine uptake was assessed using striatal synaptosomes. After unilateral striatal injections of a sub-threshold dose of 6OHDA, motor performance was assessed using standard tests and neurodegenerative damage was histologically studied. The expression of genes involved in the regulation of the defense response against oxidative stress, including Nrf2, Keap1, Foxo1, catalase and SOD2 was altered in the substantia nigra of diabetic mice. SOD2 protein levels were unaffected, but catalase levels and activity were reduced. Oxidative stress was confirmed by elevated 4-HNE in the striatum. Diabetes resulted in decreased levels of dopamine and their metabolites in the striatum, without affecting those of noradrenaline or serotonine. Functional changes in neurotransmission were documented by reduced levels of the dopamine transporter DAT, the potassium channel Girk2, and the presynaptic vesicle markers VMAT2 and Syb2. However, dopamine reuptake was not significantly affected in diabetic animals. Finally, histological and motor performance tests revealed increased damage and motor impairment after 6OHDA injections in diabetic mice. Our data indicate that diabetic mice develop striatal oxidative stress and present altered striatal dopaminergic neurotransmission as well as increased vulnerability of nigrostriatal neurons to neurodegenerative damage, providing new insights into the pathophysiology of a possible relationship between diabetes and Parkinson's disease.

Keywords: Diabetes; Parkinson's disease; Dopaminergic neurons.

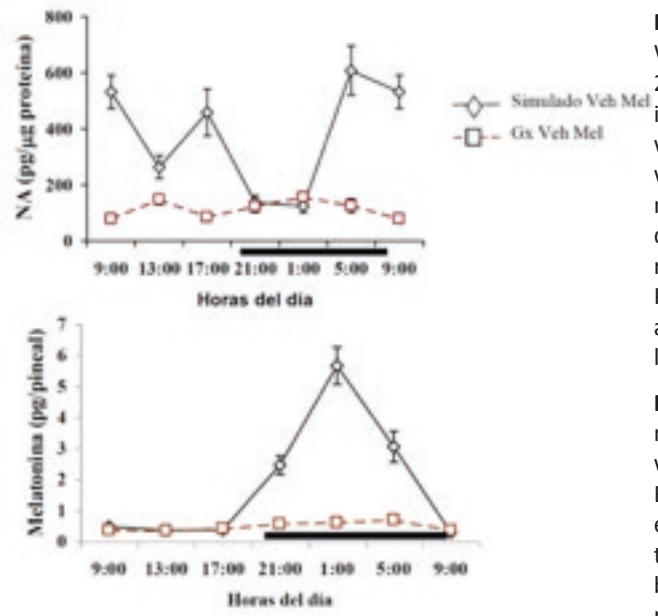
Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Pérez-Taboada I., Moratalla R., Vallejo M., Oxidative stress, altered dopamine neurotransmission and increased susceptibility to nigrostriatal neurodegeneration in diabetic mice. IBJ Plus 2019 S(3):e0017 doi: 10.24217/2531-0151.19v1s3.00017.
Funding: (BFU2014-52149-R and BFU2017-89336-R to M.V.; SAF2016-78207-R and PCIN-2015-098 to R.M; FPU 14/04457 to I.P.T.).
Competing Interests: The authors declare that no competing interests exit.

Effect of melatonin administration on the 24-hour variations of prolactin secretion in bilaterally gangliectomized adult male rats.

Diego Fajardo-Puig[1], Pilar Fernández-Mateos[2,3], Vanesa Jiménez-Ortega[1,3], Pilar Cano-Barquilla[1,3], Juliana Pérez-Miguelsanz[3,4] and Esquifino AI[1,3*]

[1]Departmental Section of Biochemistry and Molecular Biology, Medicine Faculty, Complutense University of Madrid, Madrid, Spain.
[2]Departmental Section of Cell Biology, Medicine Faculty, Complutense University of Madrid, Madrid, Spain.
[3]Instituto de Investigación Sanitaria del Hospital Clínico San Carlos (IdISSC), Madrid, Spain.
[4]Department of Human Anatomy and Embriology, Medicine Faculty, Complutense University of Madrid, Madrid, Spain.
[*]Corresponding author:
Ana Isabel Esquifino, Departmental Section of Biochemistry and Molecular Biology, Medicine Faculty, Complutense University of Madrid, Madrid, Spain. E-mail: pelayos@ucm.es

Introduction: The superior cervical ganglion (SCG) is responsible of innervating intracranial which includes the hypothalamus or pineal gland. Its surgical removal leaves these areas without sympathetic innervation. Unilateral denervation does not generate important effects on noradrenergic function because the non-operated side can partially compensate its loss. However, if the extirpation is bilateral (SCGx), it does generate alterations in pituitary and pineal hormone secre-tion. The bilateral SCGx generates a decrease in the production of melatonin by the pineal gland due to the decreased noradrenaline arrival to the gland, which is the key role for its synthesis. This lack of melatonin leads to changes in the daily patterns of secretion of hormones like prolactin, ACTH or GH. Also neurotransmitters involved in pituitary hormones such as serotonin, GABA or dopamine may be changed as well. With all data mentioned above, this work was designed to analyse whether the administration of melatonin in vivo is able to reverse the alterations observed in the hypothalamic-pituitary axis in SCGx male rats in autumn.



Material and methods: Eight 60 days old male rats of the Wistar strain, SCGx, per group were used at 09:00, 13:00, 17:00, 21:00, 01:00 and 05:00. 30µg of melatonin were administered in 200µL of vehicle one hour before lights switch off for 11 days with the subsequent slaughter of the animals by decapitation without previous anaesthesia, to avoid stress conditions that may interfere with the prolactin secretory mechanism, at the different times studied throughout the day. Control and SCGx rats were administered either with the vehicle or melatonin. Plasma prolactin levels were measured by radioimmunoassay and dopamine was by HPLC, both techniques in routine in our laboratory.

Results and conclusions: Bilateral gangliectomy effectively reduced both noradrenalin arrival to the pineal gland together with a marked decrease in melatonin secretion (see fig.). Besides, it did not modify the 24-h pattern of prolactin. However, when melatonin is exogenous replaced, a phase advance in the secretory rhythm of prolactin occurs, showing a plat-eau between 5:00 and 9:00 p.m., that resembles the circadian rhythm of summer for this hormone. Melatonin induced an increase in dopamine content in median eminence ($p<0.05$) with respect to control SCGx rats, with a plateau between 01:00 and 05:00 similar to prolactin. In addition, there is an interaction between the factors time, surgery and administra-tion of melatonin for both dopamine ($p <0.0001$) and prolactin ($p <0.0115$). It may be concluded that the presence of the autonomic innervation is a key factor for melatonin effect at the hypothalamus pituitary axis.

Keywords: Gangliectomy, dopamine, prolactin and melatonin.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Fajardo-Puig D., Fernández-Mateos P., Jiménez-Ortega V., Cano-Barquilla P., Pérez-Miguelsanz J., Esquifino AI., Effect of melatonin administration on the 24-hour variations of prolactin secretion in bilaterally gangliectomized adult male rats. IBJ Plus 2019 S(3):e0018 doi: 10.24217/2531-0151.19v1s3.00018.
Funding: Ministerio de Ciencia y Tecnología (2001-2003), Madrid, Spain.
Competing Interests: The authors declare that no competing interests exit.

Role of the Prolactin Releasing Peptide (PrRP) in the neuroendocrine regulation of thermogenesis.

Diego Fajardo Puig[1*], David Bolado López de Andújar[2*], Lorena Caballero Sánchez[3], Francisco Javier Martínez Picabea[4]

[1]Departmental Section of Biochemistry and Molecular Biology, Medicine Faculty, Complutense University of Madrid, Madrid, Spain.
[2]Hospital Universitario 12 de Octubre, Medicine Faculty, Complutense University of Madrid, Madrid, Spain.
[3]Hospital Clínico San Carlos, Medicine Faculty, Complutense University of Madrid, Madrid, Spain.
[4]Escuela Técnica Superior de Ingeniería Agronómica, Alimentaria y de Biosistemas, Politechnic University of Madrid, Madrid, Spain.

[*]Both authors should be considered as corresponding authors.
Diego Fajardo Puig, Departmental Section of Biochemistry and Molecular Biology, Medicine Faculty, Complutense University of Madrid, Madrid, Spain. E-mail: dfajardo@ucm.es
David Bolado López de Andújar, Hospital Universitario 12 de Octubre, Medicine Faculty, Complutense University of Madrid, Madrid, Spain. E-mail: davidbol@ucm.es

The prolactin-releasing peptide (PrRP) is involved in the regulation of appetite and regulates prolactin secretion. This molecule was discovered as a ligand of the orphan GRP10 / hGR3 receptors in man and UHR1 in the rat, in the year 1998 and it was very important to identify new functions of prolactin.

This molecule is synthesized in the ventromedial, ventrolateral hypothalamus and in the nucleus of the solitary tract and is involved in the regulation of energy expenditure. PrPR interacts with the hypothalamic-hypophysis-adrenal axis exerting a similar effect on energy metabolism, producing an anorectic effect. Likewise, PrRP also interacts with melanocortin alfa and beta (MSH), reducing the intake. The PrRP is directly related to an increase in energy expenditure, through an increase in oxygen consumption, producing a decrease in weight or preventing its increase. The increase in energy expenditure would be related to the increase in the degree of expression of UCP1 in brown adipose tissue (BAT). In fact, as already known, the intra-cerebro-ventricular administration (ICV) of PrRP at a concentration of 4 nmolar generated a hyperthermia that correlates with the increased expression of the UCP1 gene. Likewise, the dietary intake of rats treated with PrRP is significantly reduced, which would confirm its anorexigenic effect, its maximum effects being in the first 24 hours after its administration, producing a gradual refractoriness to the administration of this peptide. This desensitization seems to be mediated by the neuroendocrine changes produced by PrRP on cholecystokinin and leptin. It is also possible that, due to continuous injections to administer PrPR, the mouse raised its stress level noticeably and any minimal modification generated by the hormone could have been masked. In addition, in situations of stress, the decrease in secretion of PrRP from the nucleus of the solitary tract attenuates ACTH / corticosterone, prolactin and oxytocin responses due to a lack of interaction with the amygdala and, therefore, its anorexic effect. This effect could be potentiated because its stimulating effect on the hypothalamic-pituitary-adrenal axis is attenuated, since, as previously mentioned, ACTH produces an anorexigenic effect. It should be noted that, in addition to the aforementioned hormones, the existence of mechanisms of interaction between leptin and PrRP has been demonstrated. This is due to the fact that both leptin and PrRP produce an anorectic effect and are involved in the regulation of responses to cold and heat. The blocking of the PrRP gene annuls the thermoregulatory effect of leptin, so its presence is essential for leptin to exert its thermoregulatory role. In these effects, the interactions between the mechanisms of secretion of cholecystokinin, leptin and PrRP for the control of intake and thermoregulation must be taken into account.

Keywords: PrRP, prolactin, thermogenesis, BAT, leptin.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Fajardo Puig D., López de Andújar DB., Caballero Sánchez L., Martínez Picabea FJ., Role of the Prolactin Releasing Peptide (PrRP) in the neuroendocrine regulation of thermogenesis. IBJ Plus 2019 S(3):e0019 doi: 10.24217/2531-0151.19v1s3.00019.
Funding: The authors declare that no fundings.
Competing Interests: The authors declare that no competing interests exit.

Investigating the role of molting hormones in adult stages.

Gil-Marti B[1], Barredo CG.[2], Rodríguez-Navas C.[3], Martín F.A. [4*]

[1, 2, 3, 4]Instituto Cajal, Avenida Dr. Arce,37, Madrid, Spain.

[*]Corresponding author:
Francisco A Martín, Instituto Cajal, Madrid, Spain. E-mail: famartin@cajal.csic.es

Juvenile forms of insects express the non-steroid Prothoracicotropic Hormone (PTTH) (1). As documented in Drosophila, the established function takes place during metamorphosis triggering the molt throughout larval and pupal stages (2). However, the expression of both ptth and its receptor torso in the adult brain suggests additional functions beyond the larval stage. Indeed, the observation that PTTH immune-signal is detected in the antennal lobe indicates that this hormone could play a role in olfaction. Thus, our biological question in this project is: does Drosophila need PTTH to smell?

Using individual Y-maze and collective T-maze assays, we analyze the response of control and ptth mutant flies to different odors. Current results indicate that adult PTTH modulates olfaction. In particular, it modulates OR (typical from insects) and IR (present in all protostomes) olfactory subsystems (3).

Further odorants and ages are now under analysis. We hypothesize that this study will provide a novel insight to neurohormone mediated olfaction, and its evolution given the functional homology between fly PTTH and vertebrate Gonadotropin Release Hormone (GnRH).

Keywords: Olfaction, Prothoracicotropic Hormone, Neuromodulation.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Gil-Marti B., Barredo CG., Rodríguez-Navas C., Martín FA., Investigating the role of molting hormones in adult stages. IBJ Plus 2019 S(3):e0020 doi: 10.24217/2531-0151.19v1s3.00020.
Funding: This work has been supported by grants from the Spanish Ministry of Economy (Ministerio de Economía y Competitividad) BFU2014–54346-JIN. FAM is a recipient of a Ramon y Cajal Contract (RyC-2014–14961). BGM is a reciepient of the “Ayuda para el Fomento de la Investigacion” 2017-2019, from UAM.
Competing Interests: The authors declare that no competing interests exit.

Uncovering sexual dimorphism in type 2 diabetes by redox proteomics.

María Gómez-Serrano[1,2], Emilio Camafeita[1,2], Jesús Vázquez[1,2], Belén Peral[3*].

[1]Centro Nacional de Investigaciones Cardiovasculares (CNIC), Melchor Fernández Almagro 3, Madrid, Spain.
[2]Centro de Investigación Biomédica en Red sobre Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain.
[3]Instituto de Investigaciones Biomédicas, Alberto Sols, (IIBM). Consejo Superior de Investigaciones Científicas & Universidad Autónoma de Madrid (CSIC-UAM), Arturo Duperier 4, Madrid, Spain.
[*]Corresponding author:
Belén Peral, Instituto de Investigaciones Biomédicas, Alberto Sols, (IIBM). Consejo Superior de Investigaciones Científicas & Universidad Autónoma de Madrid (CSIC-UAM), Arturo Duperier 4, Madrid, Spain. E-mail: bperal@iib.uam.es

The prevalence of type 2 diabetes (T2DM) is rising globally due to, among other factors, obesity, physical inactivity, and aging superimposed on a genetic predisposition. Despite that the NIH recently highlighted the importance of sexual dimorphism and dictated inclusion of both sexes in clinical trials and basic research, little is known about the role of gender in adipose tissue biology.

We have recently validated that antioxidant response is one of the gender-specific hallmarks of sexual dimorphism in adipose tissue. Since mitochondria is recognized as the main source of oxidative stress, in this work we aimed to better understand the impact of gender on adipocyte mitochondria by quantitating not only protein abundance changes, but also redox alterations undergone by Cys protein residues.

Mitochondrial samples were obtained from adipocytes previously isolated from visceral adipose tissue biopsies collected from morbidly obese patients (BMI > 35 kg/m2) suffering T2DM who were submitted for bariatric surgery. Protein abundance and redox differences between women and men suffering T2DM were assessed following a high-throughput approach encompassing differential alkylation of reduced and reversibly oxidized Cys (FASILOX), isobaric labelling (iTRAQ) and LC-MS/MS.

LC-MS/MS analysis allowed the identification of 15,763 peptides at 1% FDR, corresponding to 2,895 proteins in the mitochondrial extracts. Of note, 754 proteins were annotated in the current version of Human MitoCarta v.2 (68% coverage). FASILOX technology allowed the identification of 277 oxidized and 1990 reduced Cys-containing peptides. Cys oxidation was globally increased in diabetic men compared to women. Enrichment analyses showed that oxidation was focus on the oxidative phosphorylation (OXPHOS) system, especially in Complex I ($p < 0.001$, FDR 1%) which showed diminished abundance in men as compared to women.

In conclusion, male patients displayed higher oxidation than females in adipocyte mitochondria under T2DM, most likely revealing a substantial oxidative stress on OXPHOS machinery. These results provide the first evidence for a decreased efficiency in the antioxidant response of diabetic men as compared to women. The identification of gender-matched oxidation targets in T2DM may help to improve the therapeutic approaches currently available for these patients.

Keywords: adipocyte, gender, mitochondria, proteomics, redox, type 2 diabetes.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Gómez-Serrano M., Camafeita E., Vázquez J., Belén Peral B., Uncovering sexual dimorphism in type 2 diabetes by redox proteomics. IBJ Plus 2019 S(3):e0021 doi: 10.24217/2531-0151.19v1s3.00021.
Funding: This work was supported by grant SAF2012-33014 from MINECO, Spain (B.P). The CNIC is supported by the Ministerio de Ciencia, Innovación y Universidades (MCNU) and the Pro CNIC Foundation, and is a Severo Ochoa Center of Excellence (SEV-2015-0505).
Competing Interests: The authors declare that no competing interests exit.

The new role of RXR in podocytes: implications in renal disease associated to obesity and Type 2 diabetes.

Almudena García-Carrasco[1], Borja Lanzón-García[1], Adriana Izquierdo-Lahuerta[1], Daniel Horrillo-Novero[1], Mercedes Ricote[2] , Manuel Ros-Pérez1 Gema Medina-Gómez[1*]

[1]National Centre for Biotechnology (CNB-CSIC), Madrid, Spain.
[2]CIBERER-ISCIII, Madrid, Spain.
*Corresponding author:
montoliu@cnb.csic.es

Background: Obese patients show other comorbidities such as hypertension, heart disease, dyslipidemia, type 2 diabetes and renal disease. Recently, evidences suggest that renal lipid accumulation leads to glomerular damage and more specifically, whether this accumulation produces podocyte dysfunction. Nuclear receptors (NRs) are ligand-dependent transcription factors, which can activate or suppress the transcription of target genes in lipid metabolism and inflammation. We have shown that the mice with specific deletion of isoform gamma 2 of Peroxisome proliferator-activated receptor (PPARγ2KO) in an obese background, exhibits IR, an alteration of lipid metabolism and glomeruli damage associated with significantly increased inflammation. RXRs are ligand-dependent NRs that play an important role as a heterodimeric partner for other NRs, including PPARs. The aim of this study was to analyze the role of RXR isoforms in the integrity of the podocyte and the involvement in the maintenance of Glomerular Filtration Barrier.

Methods: Mice with specific deletion of RXRα and β in podocyte (podRXRKO) were generated. At 3 months of age, serum and urine were collected; kidneys were removed for histological and molecular studies.

Results: Lack of RXR induced a reduction of the glomerulus size associated to the presence of fibrosis. No changes in blood pressure were shown. Podocyte effacement was observed in 3-month-old males. Moreover, females also showed a decrease in the urine volume.

Conclusion: This study suggests a crucial role of RXR in the integrity of the podocyte and its possible implication as a target in renal disease.

Keywords: RXR, nuclear receptor, podocytes, PPAR.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: García-Carrasco A., Lanzón-García B., Izquierdo-Lahuerta A., Horrillo-Novero D., Ricote M., Manuel Ros-Pérez M., Gema Medina-Gómez G. The new role of RXR in podocytes: implications in renal disease associated to obesity and Type 2 diabetes. IBJ Plus 2019 S(3):e0022 doi: 10.24217/2531-0151.19v1s3.00022.
Funding: BFU2016-78951-R, B2017BMD-3684, BFU2017-90578-REDT.
Competing Interests: The authors declare that the research was conducted in the abscence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

Bioavailability of the multitasking hormone melatonin from lentil sprouts and its role on plasmatic antioxidant status in rats.

Miguel Rebollo-Hernanz[1,2], Yolanda Aguilera[1,2], Teresa Herrera[2], L. Tábata Cayuelas[2], Pilar Rodríguez-Rodríguez[3], David Ramiro[3], Ángel L. López de Pablo[3], Silvia M. Arribas[3], María A. Martín-Cabrejas[*1,2]

Affiliations:
[1]Department of Agricultural Chemistry and Food Science, School of Science, Universidad Autónoma de Madrid, 28049, Madrid, Spain
[2]Institute of Food Science Research, CIAL (UAM-CSIC), 28049, Madrid, Spain
[3]Department of Physiology, School of Medicine, Universidad Autónoma de Madrid, 28029, Madrid, Spain

[*]Corresponding author:
María A. Martín-Cabrejas, Universidad Autónoma de Madrid, Madrid, Spain. E-mail: maria.martin@uam.es

Melatonin is an endogenous antioxidant neurohormone present in the organism in decreasing concentrations with aging. These low plasmatic concentrations are associated with diverse chronic diseases, including hypertension, type 2 diabetes, and obesity. Plant foods could serve as sources of this indolamine, being legumes a sustainable and healthy option for this purpose. Germination of legumes enhances melatonin concentration, which renders sprouts as a suitable food source of this hormone.

Since little information on melatonin bioavailability from food sources has been generated to date, we aimed to evaluate the effect lentil sprouts intake on the plasmatic levels of melatonin and metabolically related compounds (plasmatic serotonin and urinary 6-sulfatoxymelatonin), total phenolic compounds, and plasmatic antioxidant status and compare it with synthetic melatonin bioavailability.

Male young Sprague Dawley rats (n = 10 per group) were used. Pharmacokinetic profile of melatonin was investigated after oral administration of lentil sprouts at a dose 50 µg of melatonin/kg of body weight. Blood samples were drawn before and sequentially within the 4 h period after ingestion of the extract. Likewise, blood and urine samples were obtained from rats before four experimental conditions (Control: ad libitum feeding; Fasting: 12h fasting; Lentil Sprouts: 12h fasting + gavage administration of lentil sprouts extract; and MEL: 12h fasting + gavage administration of melatonin solution). Melatonin and its related biomarkers were determined by ELISA; antioxidant capacity of the plasma was measured using colorimetric/fluorimetric techniques (FRAP and ORAC).

Melatonin showed maximum concentration 1.5 h (Tmax) after lentil sprouts administration (Cmax = 45.4 pg/mL); mean residence time was 3.2 h. Moreover, variations of the plasmatic antioxidant capacity measure by FRAP followed a similar behavior. The plasmatic melatonin concentration increased after lentil sprouts intake (70%, $p < 0.05$) respect to the control, 1.2-fold more than after synthetic melatonin ingestion. These increments correlated with the urinary 6-sulfatoxymelatonin content ($p < 0.05$), a key biomarker of plasmatic melatonin, as well as with plasmatic serotonin concentration ($p < 0.05$). Nonetheless, the phenolic compounds content did not exhibit any significant variation. Plasmatic antioxidant status evidenced increases in the antioxidant capacity upon both lentil sprouts and synthetic melatonin administration.

For the first time, we investigated the bioavailability of melatonin from lentil sprouts and its role plasmatic antioxidant status. From results, we conclude that lentils sprouts are a good source of bioavailable dietary melatonin which intake could attenuate plasmatic oxidative stress and protect the organism against aging among other potential health benefits.

Keywords: melatonin, antioxidant status, lentil sprouts.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Rebollo-Hernanz M., Aguilera Y., Herrera T., Tábata Cayuelas L., Rodríguez-Rodríguez P., Ramiro D., López de Pablo A.L., Arribas S.M., Martín-Cabrejas M.A., Bioavailability of the multitasking hormone melatonin from lentil sprouts and its role on plasmatic antioxidant status in rats. IBJ Plus 2019 S(3):e0023 doi: 10.24217/2531-0151.19v1s3.00023.
Funding: This research was financially supported by the Second Call for Interuniversity Cooperation Projects University Autónoma de Madrid and the Santander Bank with the United States (2013–2014). M. R. H. thanks Ministry of Science, Innovation, and Universities for his FPU contract (FPU15/04238).
Competing Interests: The authors declare that no competing interests exit.

Phenolic compounds from cocoa shell prevent inflammation, mitochondrial dysfunction, and insulin resistance via activation of insulin/PI3K/AKT signaling pathways in 3T3-L1 adipocytes.

Miguel Rebollo-Hernanz[1,2,3], Qiaozhi Zhang[3,4], Yolanda Aguilera[1,2], Elvira González de Mejía[3], María A. Martín-Cabrejas[*1,2]

[1]Department of Agricultural Chemistry and Food Science, School of Science, Universidad Autónoma de Madrid, 28049, Madrid, Spain
[2]Institute of Food Science Research, CIAL (UAM-CSIC), 28049, Madrid, Spain
[3]Department of Food Science and Human Nutrition, University of Illinois at Urbana-Champaign, IL 61801, United States
[4]College of Food Science, Northeast Agricultural University, Harbin, 150030, China

[*]Corresponding author:
María A. Martín-Cabrejas, Universidad Autónoma de Madrid, Madrid, Spain. E-mail: maria.martin@uam.es

The incidence of these metabolic disorders is increasing worldwide primarily due to poor lifestyle habits. Obesity is caused by the imbalance between energy intake and expenditure and entails the storage of excess amounts of triglycerides, associated with the production of adipokines involved in inflammation. Likewise, the accumulation of macrophages in the adipose tissue results in the secretion of a variety of pro-inflammatory cytokines and chemokines. This inflammation triggers mitochondrial dysfunction and insulin resistance.

We aimed to investigate the effect of an aqueous extract from cocoa shell (CAE) and its main phenolic compounds (protocatechuic acid, procyanidin B2, and epicatechin) on the prevention of obesity-induced mitochondrial dysfunction and insulin resistance, targeting the inflammatory crosstalk between macrophages and adipocytes in vitro.

CAE and its main phenolic compounds were tested in cell culture of RAW264.7 macrophages and 3T3-L1 mature adipocytes. Macrophages were stimulated with lipopolysaccharide (LPS, 1 µg/mL) and the media was recovered as macrophages-conditioned media (CM). Adipocytes were treated with CM in the presence/absence of CAE and pure phenolics. Biomarkers for inflammation, mitochondrial dysfunction, and insulin resistance were determined after 24 h co-treatment with CAE or pure phenolics and CM using chemical and immunochemical techniques.

The inflammatory crosstalk created by stimulating adipocytes with CM was arrested by the treatment with CAE and pure phenolics. CAE reduced tumor necrosis factor-α (TNF-α, 67%, $p < 0.05$) and highly stimulate adiponectin secretion (12.3-fold, $p < 0.05$). Mitochondrial dysfunction, measured through reactive oxygen species production, mitochondrial content, and activity, was attenuated in CM-treated adipocytes via the up-regulation of peroxisome proliferator-activated receptor gamma coactivator 1-α expression (PGC1-α, 46%, $p < 0.05$). Significant increases in insulin receptor (INSR, 9-fold, $p < 0.05$), phosphoinositide 3-kinase (PI3K, 3-fold, $p < 0.05$), protein kinase B (AKT, 4-fold, $p < 0.05$) phosphorylation and a diminished insulin receptor substrate 1 serine phosphorylation promoted glucose uptake (IRS-1, 34%, $p < 0.05$) and glucose transporter 4 translocation (GLUT4, 14-fold, $p < 0.05$) in 3T3-L1 adipocytes under CM-triggered inflammatory conditions.

Cocoa shell aqueous extract and its main phenolic compounds blocked macrophages-adipocytes inflammatory interplay preventing mitochondrial dysfunction and insulin resistance via activation of insulin/PI3K/AKT signaling pathways in 3T3-L1 adipocytes. For the first time, CAE phenolics exhibited a positive effect on inflammatory obesity-related disorders.

Keywords: phenolic compounds, cocoa shell, adipocytes inflammation.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Rebollo-Hernanz M., Zhang Q., Aguilera Y., González de Mejía E., Martín-Cabrejas M.A., Phenolic compounds from cocoa shell prevent inflammation, mitochondrial dysfunction, and insulin resistance via activation of insulin/PI3K/AKT signaling pathways in 3T3-L1 adipocytes. IBJ Plus 2019 S(3):e0024 doi: 10.24217/2531-0151.19v1s3.00024.
Funding: This study was funded by UAM-Banco Santander project 2017/EEUU/01 and the USDA-NIFA-HATCH project 1014457. M. Rebollo-Hernanz, thanks to the FPU program of the Ministry of Science, Innovation, and Universities for his predoctoral fellowship (FPU15/04238) and the support for the international research stay (EST17/00823).
Competing Interests: The authors declare that no competing interests exit.

PTP1B deficiency protects mice against metabolic dysfunction in glucose homeostasis upon Olanzapine intraperitoneal treatment.

Vítor Ferreira[1,2*], Patrícia Rada[1,2], Diana Grajales[1,2], Irma García-Martinez[1,2], Ángela M. Valverde[1,2]

[1]IIBm Alberto Sols (CSIC-UAM), Madrid, Spain.
[2]CIBER de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), ISCIII, Spain.

*Corresponding author:
Vitor Ferreira, Madrid, Spain. E-mail: vdasilva@iib.uam.es

Schizophrenia is a chronic mental disorder that affects approximately 50 million people worldwide. Also, it is associated with psychotic experiences that not allow patients to have a normal life. Fortunately, treatments used can suppress the symptomatology and lead to a productive life and integration in the society. According to the current guidelines, the first line in schizophrenia's therapy are the second generation antipsychotic drugs (SGA). Besides being D2 receptors antagonists/partial agonists, the SGAs have the ability to interact also with serotonergic, histaminergic and other receptors; minimizing the symptomatology and not resulting in neurological side effects (contrarily to first generation antipsychotic drugs). Nevertheless, recent clinical observations show a variety of metabolic dysfunctions in patients under SGAs treatment, such as abnormal gain weight, hyperglycemia and dyslipidemia. However, the molecular mechanisms behind these alterations are still very poorly understood. Having this in consideration, the objective of this work was to study the effect of Olanzapine administration in wild-type (WT) and PTP1B-deficient (KO) mice on glucose homeostasis and the mechanisms involved. Of interest, PTP1B is the main tyrosine phosphatase of the insulin receptor, and PTP1B KO mice are protected against insulin resistance and development of type 2 diabetes mellitus. After administration of 10 mg/kg/day of Olanzapine for 8 weeks to WT and PTP1B-KO mice, the glucose homeostasis tests suggest that Olanzapine induced insulin resistance only in WT mice. Also, primary hepatocytes from WT mice treated with Olanzapine showed lower glucose uptake than those from non-treated WT mice. In contrast, Olanzapine treatment of PTP1B KO mice significantly increased hepatocyte glucose uptake, suggesting that Olanzapine-induced insulin resistance is at least in part dependent on PTP1B. These results support the relevance of PTP1B in Olanzapine-induced insulin resistance in hepatocytes.

Keywords: Insulin sensitivity; Insulin resistance; Liver; Second generation antipsychotics.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Ferreira V., Rada P., Grajales D., García-Martinez I., Valverde A.M., PTP1B deficiency protects mice against metabolic dysfunction in glucose homeostasis upon Olanzapine intraperitoneal treatment. IBJ Plus 2019 S(3):e0025 doi: 10.24217/2531-0151.19v1s3.00025.
Funding: European Union's EU Framework Programme for Research and Innovation Horizon 202. ITN-TREATMENT under Grant Agreement No GA 721236.
Competing Interests: The authors declare that no competing interests exit.

TGFβ3 as a novel target in obesity-associated kidney failure.

Elia Escasany[1], Adriana Izquiero-Lahuerta[1], Patricia Corrales[1], Almudena García-Carrasco[1], Lucía Torres[1], Yamila López[1,2], Paul Petrus[3], Estela Maldonado[2], Concha Martínez Álvarez[2], Manuel Ros[1], Peter Arner[3], Miakel Ryden[3], Gema Medina-Gómez[1]

[1]Universidad Rey Juan Carlos. Dpto. de Ciencias Básicas de la Salud. Avda. de Atenas s/n. 28922. Alcorcón. Madrid. Spain
[2]Departamento de Anatomía y Embriología Humanas, Facultad de Medicina, Universidad Complutense. 28040. Madrid. Spain.
[3]Department of Medicine, Karolinska Institutet, Karolinska University Hospital, Huddinge, 141 86, Stockholm, Sweden

*Corresponding author:
Gema Medina-Gómez, Universidad Rey Juan Carlos. Dpto. de Ciencias Básicas de la Salud. Avda. de Atenas s/n. 28922. Alcorcón. Madrid. Spain.
E-mail: gema.medina@urjc.es

Obesity is associated with development of lipotoxicity in metabolically important organs such as the kidney leading to apoptosis and dedifferentiation, which contributes to fibrosis and chronic kidney diseases progression. Glomerulosclerosis and tubulointerstitial fibrosis are the reversible common final pathological features of chronic kidney diseases (CKD), regarding the aetiology making it an appealing target of study for both finding new biomarkers and developing therapeutic strategies for CKD. Transforming growth factor β (TGFβ) is involved in differentiation, apoptosis and fibrosis. TGFβ1 has long been associated with renal fibrosis; however, the role for TGFβ3 is not so clear.

Our aim was to unravel the role of TGFβ3 in the pathophysiology of the kidney. We have used in vivo and in vitro lipotoxic models. Regarding the in vitro model, we have used heterozygous (HZ) TGFβ3 mice, due to lethality of the homozygous TGFβ3 mutant mice. These mice were subjected to either a control (CD) or a high fat diet (HFD) and sacrificed at 16 weeks of age.

In HZ mice, lower levels of TGFβ3 did not affect body weight; however, under HFD, HZ mice showed glucose intolerance but no insulin resistance, with higher basal levels of glucose and insulin. Despite similar renal hypertrophy index, glomerular area or blood pressure, HZ mice under CD already showed decreased 24h urine volume and a tendency towards higher albumin/creatinine ratio under both diets, which was aggravated under HFD.

Histological analysis (PAS and α-SMA IHC) showed renal fibrosis in HZ mice under both diets confirmed by increased fibronectin, osteopontin and N-cadherin and decreased E-cadherin and β-catenin mRNA levels. Partial lack of TGFβ3 lead to higher oxidative stress (ROS), thickening of the glomerular basement membrane (GBM), foot process effacement and loss of podocytes, as observed by electronic microscopy and flow cytometry.

Kidneys of HZ mice showed altered expression of lipid metabolism genes, with an increase in lipid synthesis genes (ACC and SREBP1) and a decrease in β-oxidation genes (PPARα, CPT1, PGC1α and PGC1β). This translated into an accumulation of lipids inside the kidney as observed histologically (Oil Red) and by flow cytometry experiments (Bodipy staining).

Altogether, these data suggest a tight link between TGFβ3 and lipid metabolism at the renal levels as well as a possible important role of TGFβ3 as anti-fibrotic in the development of renal fibrosis under lipotoxic conditions.

Keywords: kidney, fibrosis, TGFβ3, lipotoxicity, podocytes, CKD, obesity

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Escasany E., Izquiero-Lahuerta A., Corrales P., García-Carrasco A., Torres L., López Y., Petrus P., Maldonado E., Martínez Álvarez C., Ros M., Arner P., Ryden M., Medina-Gómez G., TGFβ3 as a novel target in obesity-associated kidney failure. IBJ Plus 2019 S(3):e0026 doi: 10.24217/2531-0151.19v1s3.00026.
Funding: BFU2016-78951-R, B2017BMD-3684, BFU2017-90578-REDT and Karolinska Institutet.
Competing Interests: The authors declare that no competing interests exit.

Initial age-associated metabolic alterations in white and brown fat depots: effect of long-term caloric restriction.

Patricia Corrales[1], Yurena Vivas[1], Adriana Izquierdo-Lahuerta[1], Daniel Horrillo[1], Patricia Seoane-Collazo[2], Ismael Velasco1, Lucia Torres[1], Yamila Lopez[1], Carmen Martínez[1], Miguel López[2], Manuel Ros[1], Maria Jesús Obregón[3], Gema Medina-Gómez[1].

[1]Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain.
[2]Universidad Santiago de Compostela-Instituto de Investigación Sanitaria, Santiago de Compostela, Spain.
[3]Instituto de Investigaciones Biomédicas (IIB), Centro Mixto CSIC-UAM, Madrid, Spain.
*Corresponding author:
Patricia Corrales, Universidad Rey Juan Carlos, Alcorcón, Madrid, Spain. Email: patricia.corrales@urjc.es

Changes in the body composition such as high adiposity and sarcopeny occur during aging. These changes are usually associated to metabolic alterations like insulin resistance, type 2 diabetes and metabolic syndrome. Adipose tissue is not homogeneous and dysfunction of white adipose tissue (WAT) and brown adipose tissue (BAT) can develop differently during aging. Our aim is to study different WAT and BAT depots at middle-age to detect the initial signals of alteration. Moreover, we have studied the effect of the long-term caloric restriction (CR) and its benefits.

Sv129 mice 3 and 12-month-old mice fed ad libitum and 12-month-old mice fed with a 20% CR (3m, 12m and 12mCR, respectively) have been used. RT-PCR has been employed to study lipid metabolism gene expression in eWAT, scWAT and BAT. Moreover, circulating serum and BAT thyroid hormones levels were measured by radioimmunoassay (RIA).

12m animals showed insulin resistance and lower adiponectin levels in plasma compared with 3m. Expression of insulin pathway (Glut4, Irs1), lipogenesis (Fas, Scd1) and lipolysis (Hsl, Atgl, Pparα) genes was decreased in scWAT of 12m animals, but not in eWAT. Furthermore, UCP-1 expression was significantly lower in scWAT of aged mice compared with younger mice, suggesting a decrease in beige adipose tissue associated to aging. On the other hand, we found decreased expression of some BAT-selective genes12m animals such as Ucp1, βAr. CR recovered the expression levels to those of 3m mice. Thyroxine (T4) in plasma did not reach significance among middle-aged and young animals, however triiodothyronine (T3) levels were lower in 12m than 3m and 12mCR mice. Dio2 expression, T4 and T3 concentrations in BAT followed a similar pattern, a decrease in 12m mice and an increase in CR mice.

Although eWAT has been described as the most dangerous tissue from the metabolic point of view, our data could suggest an earlier metabolic alteration in scWAT than in eWAT. Our findings prompt that CR could revert the initial age-related alterations in scWAT. In agreement, we point to alteration of thyroid axis status with age is an important factor contributing to BAT dysfunction at middle-age, which can be ameliorated by CR.

Keywords: aging, caloric restriction, adipose tissue, thyroid hormone.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Corrales P., Vivas Y., Izquierdo-Lahuerta A., Horrillo D., Seoane-Collazo P., Velasco I., Torres L., Lopez Y., Martínez C., López M., Ros M., Obregón MJ., Medina-Gómez G., Initial age-associated metabolic alterations in white and brown fat depots: effect of long-term caloric restriction. IBJ Plus 2019 S(3):e0027 doi: 10.24217/2531-0151.19v1s3.00027.
Funding: BFU2016-78951-R, B2017BMD-3684, BFU2017-90578-REDT, Fundacion Mapfre, CAMS210/BMD-2433.
Competing Interests: The authors declare that no competing interests exit.

Microsomal Prostaglandin E Synthase-1 (mPGES-1) mediates the development of metabolic and cardiovascular alterations associated to obesity.

Ballesteros-Martinez C[1], Rodrigues-Diez R[1,2,3], Gonzalez-Amor M[1], Salaices M[1,2,3], Briones AM[1,2,3]

[1]Department of Pharmacology and Therapeutics, Faculty of Medicine, Universidad Autónoma de Madrid, Madrid, Spain.
[2]Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain.
[3]CIBER Cardiovascular Diseases, Madrid, Spain.
*Corresponding author:
Briones AM1,2,3, Madrid, Spain. E-mail: ana.briones@uam.es

Introduction: Obesity is linked to chronic low-grade inflammation. Adipose tissue responds to metabolic signals, being also metabolically active secreting peptides, hormones and adipokines that, under obesity situation, participate in the development of cardiovascular and metabolic alterations such as endothelial dysfunction, arterial stiffness and insulin resistance. Microsomal prostaglandin E Synthase-1 (mPGES-1) is an inducible isomerase responsible for the production of prostaglandin E2 (PGE2) under inflammatory conditions. PGE2 is a key lipid mediator implicated in the regulation of adipose tissue homeostasis. It is also involved in vascular remodeling in different inflammatory pathologies.

Objective: To evaluate the role of mPGES-1 in the development of obesity and in the metabolic and cardiovascular alterations associated.

Methods: We have developed a model of high fat diet (HFD, 60% fat)-induced obesity in mPGES-1-/- and their control littermates mPGES-1+/+ mice. Body weight was measured twice a week and organs and adipose tissue weights were measured at the end of the experiment. The glycemic profile was studied by the glucose tolerance test (GTT) and insulin tolerance test (ITT). Arterial pressure was measured by tail-cuff plethysmography. Aortic vascular function and structural and mechanical properties of mesenteric resistance arteries where evaluated by isometric and perfusion myographs respectively. Histological analysis was also performed. Changes in mRNA expression were studied by q-RT- PCR.

Results: Our results show that mPGES-1-/- mice fed with a HFD are protected against body weight gain and present reduced adiposity with less grade of macrophage infiltration. In addition, mPGES-1 deficient mice have better glycemic profile compared to wild type mice. At cardiovascular level, mPGES-1+/+ but not mPGES-1-/- mice on HFD, develop an increase in the size of cardiomyocytes, which results in cardiac hypertrophy, show aortic endothelial dysfunction and vascular insulin resistance, and show structural alterations in resistance arteries.

Conclusion: Our data suggest that the lack of mPGES-1 protects against some of the cardiovascular and metabolic alterations associated to obesity.

Keywords: obesity, mPGES-1, vascular function, adipose tissue.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Ballesteros-Martinez C., Rodrigues-Diez R., Gonzalez-Amor M., Salaices M., Briones AM., Microsomal Prostaglandin E Synthase-1 (mPGES-1) mediates the development of metabolic and cardiovascular alterations associated to obesity. IBJ Plus 2019 S(3):e0028 doi: 10.24217/2531-0151.19v1s3.00028.

Funding: This project was supported by the Spanish Ministerio de Economía, Industria y Competitividad (SAF2016-80305P); Instituto de Salud Carlos III (PI13/01488; CIBER de Enfermedades Cardiovasculares, CB16/11/00286) and Comunidad de Madrid (B2017/BMD-3676).

Competing Interests: The authors declare that no competing interests exit.

Lack of improvement in sperm quality and changes in reproductive hormones in obese mice and patients males after obesity surgery and diet.

Casado ME[1,2], Calderón B[2,4], Huerta L[1], Botella-Carretero JI[2,3] and Martín-Hidalgo A[1,2]

[1]Servicio de Bioquímica-Investigación, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRyCIS), Madrid, Spain.
[2]CIBER de la Fisiopatología de la Obesidad y Nutrición (CIBERobn), ISCIII, Madrid, Spain.
[3]Servicio de Endocrinología y Metabolismo, Hospital Universitario Ramón y Cajal, E-28034 Madrid, Spain.
[4]Instituto Tecnológico de Santo Domingo (INTEC), Santo Domingo, Republica Dominicana.

*Corresponding author:
Martín-Hidalgo A, Servicio de Bioquímica-Investigación, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRyCIS), Ctra. Colmenar Km 9.1, 28034-Madrid, Spain. E-mail: antonia.martinl@hrc.es

Obesity in men is associated with a decrease in sperm concentration, motility, alterations in sperm morphology, chromatin integrity and hormonal profile that leads to infertility. Even though obesity surgery normalizes circulating testosterone concentrations in males with obesity-associated secondary hypogonadism, its impact on spermatogenesis remains controversial. We aimed to evaluate sperm characteristics and changes in reproductive hormones in obese men after bariatric surgery and obese mice after low fat diet.

Methods: Twenty severely obese men (body mass index (BMI) ≥ 35 kg/m2) were evaluated before and 2 years after bariatric surgery. We assayed insulin, leptin, kisspeptin, and inhibin B in the serum of the patients. The obese mice model included the following experimental groups: 1) LFD 10 weeks; 2) HFD 10 weeks; 3) LFD 18 weeks; 4) HFD 18 weeks; 5) HFD 10 weeks and LFD 8 weeks. The seminal fluid was get from epididymis for spermatozoa counts and motility. We studied the mice at 10 and 18 weeks after the different diets. We assayed glucose, insulin and testosterone in plasma. Homeostasis model assessment of insulin resistance (HOMA-IR) was estimated. We used World Health Organization reference values for sperm analysis.

Results: Before surgery, serum total testosterone, calculated free testosterone, leptin, glucose and fasting insulin, HOMA-IR, increased in obese patients. After surgery, serum total testosterone, calculated free testosterone, inhibin B, and kisspeptin increased, whereas fasting insulin, HOMA-IR, and leptin concentrations decreased in the patients. Despite these improvements, sperm volume showed a small decrease after surgery, while the rest of sperm characteristics remained mostly unchanged. Abnormal sperm concentration persisted in 60% of the obese patients. In mice, plasma glucose and insulin increased in HFD compared with LFD at 10 and 18 weeks. These values decreased in the group of HFD+LFD at 18 weeks. The HFD mice have insulin resistance compared with LFD mice. Plasma testosterone decreased in HFD compared to LFD at 10 and 18 weeks; and remained low in HFD+LFD. There was not reversion of plasma testosterone levels with the change of the diet. Spermatozoa concentration decreased in HFD compared to LFD mice, and there was not reversion of sperm concentration after the change of HFD to LFD at 18 weeks.

Conclusions: Sperm characteristics may not improve after bariatric surgery despite the beneficial changes of reproductive hormones in obese patients. There is not improvement in sperm quality and testosterone in obese mice after diet.

Keywords: Obesity, bariatric surgery, testosterone, kisspeptin, leptin, semen analysis, male infertility.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Casado ME., Calderón B., Huerta L., Botella-Carretero JI. and Martín-Hidalgo A., Lack of improvement in sperm quality and changes in reproductive hormones in obese mice and patients males after obesity surgery and diet. IBJ Plus 2019 S(3):e0029 doi: 10.24217/2531-0151.19v1s3.00029.
Funding: CIBEROBN. Financed by PI16/00154. Instituto de Salud Carlos III. Ministerio de Economía y Competitividad, Spain.
Competing Interests: The authors declare that no competing interests exit.

The short-term dietary impact on the central and circulating IGF systems in rats.

Santiago Guerra-Cantera[1,2,3*], Francisca Díaz[2,3], Purificación Ros[1,4], Alejandra Freire-Regatillo[1,2,3], Laura M. Frago[1,2,3], Vicente Barrios[2,3], Jesús Argente[1,2,3,5], Julie Chowen[2,3,5]

[1]Department of Pediatrics, Universidad Autónoma de Madrid, Madrid, Spain.
[2]Department of Endocrinology, Hospital Infantil Universitario Niño Jesús, Research Institute "La Princesa", Madrid, Spain.
[3]Centro de Investigación Biomédica en Red de la Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain.
[4]Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain.
[5]IMDEA Food Institute, CEI UAM + CSIC, Madrid, Spain.

[*]Corresponding author:
Santiago Guerra-Cantera, Madrid, Spain. E-mail: santiguerra8@gmail.com

The insulin-like growth factor system (IGF) exerts a wide range of functions in the organism, participating in linear bone growth, metabolism and neuroprotection. Poor nutrition and obesity can alter this system; however, little is known regarding the effects of short-term dietary changes on the IGF axis. Our aim was to determine if a 1-week high-fat diet (HFD) or a low-fat diet (LFD) modifies the central and peripheral IGF systems.

Adult male and female Wistar rats were given a HFD (60% fat, 8.9% sucrose, 5.1 kcal/g), LFD (10% fat, 33.1% sucrose, 3.76 kcal/g) or standard rodent chow (3.1% fat, 0.9% sucrose, 3.41 kcal/g) for 1 week. Serum hormone levels were measured by ELISA and tissue gene expression by RT-qPCR. Hepatic glucose-6-phosphate dehydrogenase (G6PDH) activity was evaluated (Sigma-Aldrich) and malic enzyme activity was determined as described by Geer et al (1).

HFD increased body weight ($p<0.05$) exclusively in males. In serum, males had higher levels of free and total IGF1, IGF-binding protein (IGFBP) 3, IGFBP5, insulin, leptin and triglycerides compared to females ($p<0.001$) and pregnancy-associated plasma protein-A2 (PAPP-A2) was higher in females ($p<0.05$), with no dietary effect on these parameters. In females, serum IGF2 levels increased on the LFD ($p<0.01$). Hepatic IGF1 and IGFBP3 mRNA levels were affected by both sex and diet ($p<0.01$) and IGF2 mRNA levels were increased in response to HFD, reaching significance in females ($p<0.01$). Hepatic IGFBP2 mRNA levels were increased in response to HFD in both sexes ($p<0.001$) with sex differences, as levels were higher in females than males ($p<0.001$). Liver G6PDH activity was higher on the LFD compared to chow in both sexes ($p<0.001$), whereas in females HFD also increased G6PDH activity. Liver malic enzyme activity was increased in response to LFD compared to chow in both sexes ($p<0.001$).

Hypothalamic mRNA levels of IGF2 ($p<0.01$) and IGFBP2 ($p<0.001$) increased after LFD intake, but only in males. No effects were found on the remaining members of the IGF system. In males, LFD also increased the mRNA levels of neuropeptide-Y ($p<0.01$) and Agouti-related peptide ($p<0.05$), with no changes in proopiomelanocrotin or cocaine- and amphetamine-regulated transcript mRNA levels.

In conclusion, a short-term dietary change can modify both the systemic and central IGF systems, with these modifications differing between males and females. Thus, this system could be involved in the sex difference in weight gain in response to poor dietary habits. Further investigation is warranted to determine the role of IGF2 and IGFBP2 in metabolism.

(1) Geer et al., Comp. Biochem. Physiol., 1980. Vol. 65B, pp. 25-34.

Keywords: Obesity, IGF1 system, neuropeptides, HFD, LFD.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Guerra-Cantera S., Díaz F., Ros P., Freire-Regatillo A., Frago L.M., Barrios V., Argente J., Chowen J., The short-term dietary impact on the central and circulating IGF systems in rats. IBJ Plus 2019 S(3):e0030 doi: 10.24217/2531-0151.19v1s3.00030.
Funding: This work was funded by CIBEROBN, PI16/00485, and BFU2017-82565-C2-1-R, fondos FEDER.
Competing Interests: The authors declare that no competing interests exit.

Myeloid SAPKs in the control of obesity and BAT thermogenesis.

Maria Crespo[1], Ivana Nikolic[1], Aránzazu Pintor[1], Alfonso Mora[1], Elena Rodríguez[1], Luis Leiva-Vega[1], Magdalena Leiva[1*], Guadalupe Sabio[1*].

[1]Centro Nacional de Investigaciones Cardiovasculares (CNIC), Melchor Fernandez Almagro 3, Madrid, Spain
[*]Corresponding author:
Magdalena Leiva, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain. E-mail: magdalena.leiva@cnic.es
Guadalupe Sabio, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain. E-mail: guadalupe.sabio@cnic.es

Chronic inflammation of white adipose tissue during obesity is a main driver of insulin resistance and type 2 diabetes (T2D). Among this inflammatory scenario, macrophages play important roles. Stress activated kinases (SAPKs) are key members of the signaling pathways implicated in inflammatory response, function and cytokine production in macrophages. Brown adipose tissue (BAT) is a potential therapeutic target for obesity because of its capacity to burn fat during thermogenesis, thus increasing energy expenditure. M1 (pro-inflammatory or classically activated) and M2 (anti-inflammatory or alternatively activated) macrophages are important for the control of BAT thermogenic activity, by blocking or promoting it, respectively. Using a mice model lacking the main upstream activators of some SAPKs in the myeloid lineage we found that this pathway is crucial for M2, but not M1 macrophage polarization. Moreover, this mice model is more sensitive to high-fat diet (HFD)-induced obesity as they have more body weight and liver steatosis, they are more insulin resistant. This correlates with the less energy expenditure, BAT thermogenic activity and subcutaneous browning found in this mice model. Accordingly with this, we found there is a significant depletion of M2 macrophage population in BAT from these mice. All this data suggests the crucial role of myeloid SAPKs in the protection against obesity and in the control of BAT thermogenesis during HFD.

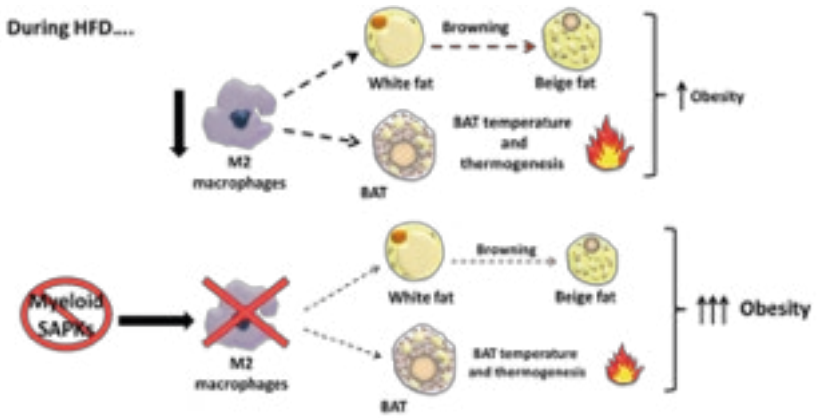


Figure 1. The lack of SAPKs in the myeloid lineage leads to impaired BAT thermogenesis and browning of white adipose tissue and contributes to the development of obesity during HFD.

Keywords: macrophages, SAPKs, obesity, BAT, thermogenesis.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Crespo M., Nikolic I., Pintor A., Mora A., Rodríguez E., Leiva-Vega L., Leiva M., Sabio G., Myeloid SAPKs in the control of obesity and BAT thermogenesis. IBJ Plus 2019 S(3):e0031 doi: 10.24217/2531-0151.19v1s3.00031.
Funding: FPI 2018 Ministerio de Ciencia, Innovación y Universidades.
Competing Interests: The authors declare that no competing interests exit.

Intermittent Hypoxia a powerful stimulus of the endocrine system: Anabolic/Catabolic Hormone response in Athletes.

Fernández-Lázaro Diego[1], Fernández-Lázaro César Ignacio[1,2], Mielgo-Ayuso Juan[3], Caballero García Alberto[4], Pascual Fernández Jorge[5], Córdova Martínez Alfredo[3]

[1]Department of Cell Biology, Histology and Pharmacology, Faculty of Physiotherapy, University of Valladolid, Campus de Soria, Soria. (Spain).
[2]Department of Preventive Medicine and Public Health, Faculty of Medicine, University of Navarra, Pamplona (Spain).
[3]Department of Physiology, Faculty of Physiotherapy, University of Valladolid, Soria Campus, Soria (Spain)
[4]Department of Anatomy, Faculty of Physiotherapy, University of Valladolid, Soria Campus, Soria (Spain)
[5]García Orcogen Hospital, Estella, Navarra (Spain)
*Corresponding author:
Dr. Diego Fernández Lázaro, Department of Cell Biology, Histology and Pharmacology Faculty of Physiotherapy, University of Valladolid, Campus of Soria, Spain. E-mail: diego.fernandez.lazaro@uva.es

Introduction: Exposure to intermittent hypoxia (IH), that is used as a complement to training to increase sports performance, affects the function on the hypothamulus-pitutary-adrenal axis, increases the corticotroph number and the levels of plasma ACTH and stimulates the expression of the steroidogenic acute regulatory protein and enhances the secretion of glucocorticoids as cortisol (C) (1). Also, the extreme physical effort induces a powerful stimulus of the endocrine system, that generates a hormonal response (2,3). Therefore, we investigated the effects of acute short duration IH along a macrocycle of training, over variations and behavior of anabolic/catabolic hormones. In this context we wont to evaluate also the influence of IH on specific test of performance. Material and Methods: We investigated the effects of IH along 4 weeks training on endocrine response by anabolic/catabolic hormones, Testosterone (T) and C. We studied professional male athletes exposed (PA) (n=12) or not (n=12) to IH, at three different moments: baseline (M1) (i.e., under resting conditions immediately before start the study); after two weeks of IH (M2); and at the end of the 4-week IH exposure period (M3). Physical performance was assessed by individual test: aerobic power, lactic power and speed were performed in the athletics track, over distances of 1000 meters (m), 400m and 60m respectively. For the strength test, force of the quadriceps with a dynamometer was measured. The tests were performed on M1 and M3. Results: Significant differences were observed throughout the study (M1 to M3) in T and T/C between groups. In PA group T increase significantly ($P<0.001$), however the tendency of C was to increase but no significantly. With respect T/C ratio increase ($p<0.01$) along of study (M1 to M3). In CG both, T and T/C were showed a significant decrease along the study ($p<0.05$), and T/C ratio decrease significantly in M2 and M3 with respect baseline (M1). The stepwise discriminant function analysis resulted indicated athletes who use hypoxia (centroid = 1,793) had higher Δ T values, whereas the athletes who use normoxia (centroid = -1,569) had lower Δ T values. The results, of physical parameters, were better in PA group that in CG, being significant the differences in anaerobic ($P=0.003$) and aerobic ($P>0.001$) power between both groups. Conclusion: We have observed that IH might potentially stimulate performance through an anabolic effect. The testosterone is a determinant informative to evaluate the answer to exercise in PA. For all this we recommended performing the resistance training under the intermittent hypoxia to induce anabolic hormone responses and after improve the physical performances.

References:

1.Kujala UM, Alen M, Huhtaniemi IT. Gonadotrophin-releasing hormone and human chorionic gonadotrophin tests reveal that both hypothalamic and testicular endocrine functions are suppressed during acute prolonged physical exercise. Clin Endocrinol (Oxf). 1990; 33: 219-225.

2.Cordova A, Fernandez-Lazaro D, Mielgo J, Seco J, Caballero A. Effect of magnesium supplementation on muscular damage markers in basketball players during a full season. Magnes Res. 2017; 1; 30: 61-70.

3.Navarrete-Opazo A, Mitchell GS. Therapeutic potential of intermittent hypoxia: A matter of dose. Am J Physiol Regul Integr Comp Physiol. 2014; 307: 1181-1197.

Keywords: Intermittent Hypoxia, endocrine system, athletes.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Fernández-Lázaro D., Fernández-Lázaro César I., Mielgo-Ayuso J., Caballero García A., Pascual Fernández J., Córdova Martínez A., Intermittent Hypoxia a powerful stimulus of the endocrine system: Anabolic/Catabolic Hormone response in Athletes. IBJ Plus 2019 S(3):e0032 doi: 10.24217/2531-0151.19v1s3.00032.
Funding: No conflict of interest authors has related to the work presented.
Competing Interests: The authors recognize the Institute of Studies of Health Sciences of Castilla y León (ICSCYL) for their support and collaboration throughout the research process of this study.

Influence of malnutrition during pregnancy on maternal and fetus plasmatic corticosterone concentrations.

Andrea Gila-Diaz[1*] , Cynthia Guadalupe Reyes-Hernández[1], David Ramiro-Cortijo[1], Pilar Rodríguez-Rodríguez[1], Angel Luis López de Pablo[1], Mª del Rosario López-Giménez[2], Mª del Carmen González[1], Silvia M. Arribas[1].

[1]Department of Physiology, Faculty of Medicine, University Autónoma of Madrid, Spain.
[2]Department of Epidemiology, Public Health & Microbiology, Faculty of Medicine, University Autónoma of Madrid, Spain.

*Corresponding author:
Andrea Gila Díaz, Department of Physiology, Madrid, Spain. E-mail: andrea.gila@estudiante.uam.es

Introduction: Exposure to stress factors during gestation can negatively influence fetal development leading to low birth weight (LBW), which has been associated with later development of cardiometabolic diseases (fetal programming). Malnutrition and exposure to excess glucocorticoids during gestation are some of the stress factors that negatively influence fetal development. In situations of maternal undernutrition, the stress induced by reduced nutrient availability may elevate maternal cortisol levels. Under normal conditions, cortisol concentrations in the fetus are low due to the placental enzymatic barrier (11-β-HSD2) that converts cortisol to inactive cortisone. However, this barrier may be inhibited in malnutrition situations.

Hypothesis: Maternal undernutrition during gestation may induce a poor fetal development, in part due to increased access of cortisol to the fetus.

Objective: To analyze if undernutrition during gestation in the rat increases fetal corticosterone levels and to assess the relationship with fetal growth.

Material and methods: Dams were fed ad libitum (Control) or with 50% of the control diet (Maternal undernutrition, MUN) during the second half of gestation. At the end of gestation (gestational day 20) a blood sample was obtained from the dam and the fetuses were extracted. The fetuses were weighted, and blood was collected after decapitation. Plasma corticosterone levels were assessed by ELISA; maternal protein levels by Bradford and glucose levels with a glucometer. Mann-Whitney U and Student's t test were used for statistical analysis, as appropriate.

Results: In MUN dams, plasma protein levels were significantly lower, glycaemia was not statistically different and corticosterone levels were significantly higher compared to control dams. MUN fetuses exhibited significantly lower weight and length compared to controls, while plasma corticosterone was significantly higher.

Conclusions: Nutritional restriction during gestation in the rat produces a situation of stress that: 1) increases maternal plasma corticosterone, which can contribute to low protein availability through its catabolic effects; 2) increases passage of corticosterone to the fetus, which may contribute to the deficient fetal growth. Evaluation of 11-β-HSD2 enzymatic activity or protein expression in the placenta is needed to elucidate if these alterations are related to an alteration of this enzymatic barrier in situations of malnutrition.

Keywords: corticosterone, fetal programming, low birth weight, malnutrition, pregnancy, rat.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Gila-Diaz A., Reyes-Hernández C.G., Ramiro-Cortijo D., Rodríguez-Rodríguez P., López de Pablo A.L., López-Giménez M.R., González M.C., Arribas S.M., Influence of malnutrition during pregnancy on maternal and fetus plasmatic corticosterone concentrations. IBJ Plus 2019 S(3):e0033 doi: 10.24217/2531-0151.19v1s3.00033.
Funding: Plan Nacional I+D+I (FEM2015-63631-R) co-financed with FEDER funds.
Competing Interests: The authors declare that no competing interests exist.

Maternal cortisol in early pregnancy as potential biomarker of fetal complications.

David Ramiro-Cortijo[1], Andrea Gila-Diaz[1], Pilar Rodríguez-Rodríguez[1], Ángel L. López de Pablo[1], Mª Carmen González[1], María de la Calle[2], Rubén Gómez-Rioja[3], Silvia M. Arribas[1].

[1]Department of Physiology; Faculty of Medicine; Universidad Autónoma de Madrid, C/ Arzobispo Morcillo 2, Madrid, Spain.
[2]Obstetrics and Gynecology servicie, Hospital Universitario La Paz, Paseo de la Castellana, 261, Madrid, Spain.
[3]Laboratory Medicine, Hospital Universitario La Paz, Paseo de la Castellana, 261, Madrid, Spain.

*Corresponding author:
Dr. David Ramiro-Cortijo, Department of Physiology, Faculty of Medicine, Universidad Autónoma de Madrid, Spain. E-mail: david.ramiro@uam.es

Introduction: Maternity pattern has changed in Spain, leading to an increase in the age of first pregnancy and the used of assisted reproduction techniques (ART). A relevant consequence is the increase in fetal complications, such as small for gestational age (SGA) and preterm birth, both of which lead to low birth weight (LBW). LBW has a negative impact for both neonatal and long term health, being a risk factor for cardiometabolic disease. Delayed maternity and ART are associated with maternal psychological stress. We have evidenced that stress during pregnancy is associated with LBW. A possible mechanism could be an excess in the level of cortisol access to the fetus that may be deleterious for fetal growth. We hypothesized that maternal plasma cortisol at the beginning of pregnancy, associated with fetal complications and LBW and, therefore, it can be used as early diagnostic tool.

Material and Methods: The study included 200 healthy pregnant women, being attended at the Obstetrics and Gynecology Service from La Paz University Hospital (Madrid, Spain). Women were appointed for blood sample extraction at 10th week of gestation and followed-up until delivery, recording: 1) development of fetal complications including SGA (growth <p3th or <p10th with hemodynamic alterations by Echo-Doppler) and preterm birth (<37gestational age) and 2) offspring birth weight. Blood samples were centrifuged to obtain plasma and cortisol was assessed by competitive immunoassay using a direct chemiluminescent assay. Data were expressed as mean +- standard error of mean or relative frequencies (%). Statistical differences were assessed by Student´s t test with Confidence Interval at 95%. Pearson test (r) was used for correlation analysis, stablishing significance differences at p-value<0.05.

Results: Age of the pregnant women was 34.4+-0.33 years old. The prevalence of fetal complications was 26.5% and LBW was 28.8%. Both were significantly higher in older women (fetal complications=95% CI [-3.25; -0.18]; LBW=95% CI [-3.03; -0.11]). Maternal cortisol, in the first trimester of pregnancy, exhibited a positive correlation with maternal age (r=0.225; p=0.008) and a negative correlation with birth weight (r=-0.326; p=0.006). Plasma cortisol was significantly higher in women who developed fetal complications (95% CI [-5.24; -0.16]) and also in women with premature delivery (95% CI [-6.61; -1.44]).

Conclusions: Maternal plasma cortisol at the beginning of pregnancy is related to the age of maternity and fetal complications leading to LBW. Plasma cortisol could be used as potential biomarker to predict fetal complications particularly in delayed maternity context.

Keywords: birth weight, maternal plasma cortisol, pregnant, preterm birth, small for gestational age.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Ramiro-Cortijo D., Gila-Diaz A., Rodríguez-Rodríguez P., López de Pablo A.L., González M.C., De la Calle M., Gómez-Rioja R., Arribas S.M., Maternal cortisol in early pregnancy as potential biomarker of fetal complications. IBJ Plus 2019 S(3):e0034 doi: 10.24217/2531-0151.19v1s3.00034.
Funding: This work was supported by Ministerio de Economía y Competitividad (FEM2015-63631-R).
Competing Interests: The authors declare that no competing interests exist.

Metabolic response to diets enriched with sunflower seed oil or palm seed oil.

María Valencia-Avezuela[1], Victor Naranjo[2], Ana Conreras[2], Santiago Guerra-Cantera[1,3], Sandra Canelles[1,3], Jesús Argente[1,3,4], Nuria Del Olmo[2], Laura M. Frago[1,3], Mariano Ruiz-Gayo2, Julie Chowen[1,3,4]

[1]Department of Pediatrics, Universidad Autónoma of Madrid, Madrid, Spain. Department of Endocrinology, Hospital Infantil Universitario Niño Jesús, Instituto de Investigación La Princesa, Madrid, Spain.
[2]Department of Pharmaceutical and Health Sciences. Universidad CEU-San Pablo, Madrid, Spain
[3]Centro de Investigación Biomédica en Red de la Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain.
[4]IMDEA Food Institute, CEI UAM + CSIC, Carretera de Cantoblanco 8. 28049 Madrid, Spain.
*Corresponding author:
J. Chowen Madrid, Spain. E-mail: julieann.chowen@salud.madrid.org

The hypothalamus is the main integrating center for metabolic control, regulating the response to nutrients and other metabolic signals to maintain energy homeostasis. This response includes not only neuronal circuits that control appetite, but also glial cells that are involved in nutrient processing and inflammatory responses to high fat intake. However, it is now clear that the metabolic response is different depending on the type of fatty acid consumed. Our aim was to analyze the hypothalamic response to the consumption of a diet enriched with sunflower seed oil or palm seed oil.

Adult male C57/BL6J mice were given ad libitum access to a normal rodent chow diet enriched with sunflower seed oil with high oleic content (SO) or with palm seed oil (PO), or to a standard rodent chow (SD) for 8 weeks. Energy intake and body weight were monitored weekly. Relative protein expression was analyzed by Western blotting and relative gene expression by RT-PCR.

Both the SO and PO diets increased body weight and energy intake compared to SD ($p<0.01$). In the hypothalamus neuropeptide Y (NPY) mRNA levels were lower in mice consuming the SO diet compared to SD ($p<0.05$). No dietary effects were found on the neuropeptides Agouti-related peptide (AgRP) or pro-opiomelanocortin (POMC). Expression of the leptin receptor did not change. There was no change in the relative protein levels of ionized calcium-binding adaptor molecule 1 (Iba 1), a marker of microglia, or of glial fibrillary acidic protein (GFAP), a marker of astrocytes. We found no significant effect on hypothalamic mRNA levels of the cytokine interleukin-6 (IL-6), although there was a clear tendency to increase on the PO diet. There was also no change in the cytokine TNFα or the cell stress marker DNA damage-inducible transcript 3 (CHOP). No activation of c-Jun N-terminal kinases (JNK) was found. To explore hypothalamic fatty acid metabolism, we analyzed the relative expression of fatty acid synthase (FASn) and carnitine palmitoyltransferase (Cpt1a). PA decreased Cpt1a mRNA expression compared to SD ($p<0.01$), with no change in FASn.

In conclusion, although both diets enriched in fat induce weight gain, the central response to these diets differs. The mRNA levels of the orexigenic neuropeptide NPY were lower on the SO diet, which may suggest that this diet could be more effective in reducing food intake, at least at this time-point. In contrast, the PO diet decreased Cpt1a mRNA expression, indicating a possible reduction in hypothalamic fatty acid oxidation that could lead to stress of the system. Further studies are necessary to determine the secondary complications as a result of these specific high fat diets.

Keywords: Obesity, fatty acids, hypothalamus,

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Valencia-Avezuela M., Naranjo V., Conreras A., Guerra-Cantera S., Canelles S., Argente J., Del Olmo N., Frago L.M., Ruiz-Gayo M., Chowen J. Metabolic response to diets enriched with sunflower seed oil or palm seed oil. IBJ Plus 2019 S(3):e0035 doi: 10.24217/2531-0151.19v1s3.00035.
Funding: This work was funded by CIBEROBN, PI16/00485, and BFU2017-82565-C2-1-R, BFU2016-78556R and fondos FEDER.
Competing Interests: The authors declare that no competing interests exist.

Skeletal muscle kinases in the regulation of energy balance.

Leticia Herrera-Melle[1], Alfonso Mora[1], Juan Antonio López[2], Sara Cogliati[3], María Elena Rodríguez[1], Luis Leiva-Vega[1], Daniel Beiroa[4], Cintia Folgueira[4], José Antonio Enríquez[3], Jesús Vázquez[2], Rubén Nogueiras[4], Guadalupe Sabio[1*]

[1]Stress kinases in diabetes, cancer and cardiovascular disease Lab, Myocardial Pathophysiology Area, Centro Nacional de Investigaciones Cardiovasculares (CNIC), C/Melchor Fernández Almagro 3, 28029 Madrid, Spain.
[2]Cardiovascular Proteomics Unit, CNIC, C/Melchor Fernández Almagro 3, 28029 Madrid, Spain.
[3]Functional genetics of the oxidative phosphorylation system Lab, Myocardial Pathophysiology Area, CNIC, C/Melchor Fernández Almagro 3, 28029 Madrid, Spain.
[4]Department of Physiology, CiMUS, University of Santiago de Compostela-Instituto de Investigación Sanitaria, Santiago de Compostela 15782, Spain; CIBER Fisiopatología de la Obesidad y Nutrición (CIBERobn), 15706 Santiago de Compostela, Spain.

[*]Corresponding author:
Guadalupe Sabio, Stress kinases in diabetes, cancer and cardiovascular disease Lab, Myocardial Pathophysiology Area, CNIC, 28029 Madrid, Spain.
E-mail: guadalupe.sabio@cnic.es

Obesity is a well-known risk factor for several chronic diseases. Physical inactivity and changes in dietary habits have increased the incidence and prevalence of obesity in current societies, which has become a major health problem. Although several pharmacological treatments to lose weight through a reduction in food intake have been proposed, understanding the molecular mechanisms that lead to increased energy expenditure may help to find new therapies. In fact, exercise has the capacity to improve the metabolic status in obesity and type 2 diabetes, being skeletal muscle an important regulator of glucose homeostasis and an essential contributor to exercise-induced changes in metabolism.

In this work, using a conditional mouse model lacking a kinase in striated muscle, we have attempted to increase knowledge about the role of this protein both at the local and the systemic level. Our results show that the deficiency of this kinase in striated muscle decreases body weight and protects mice against high-fat diet (HFD)-induced obesity by increasing energy expenditure. The molecular alterations caused by this deficiency lead to skeletal muscle metabolic remodeling, increasing mitochondrial oxidative metabolism. Altogether, these molecular and metabolic changes in skeletal muscle are physiologically manifested as enhanced locomotor activity as well as improved glucose homeostasis, decreasing the risk of developing diabetes and liver steatosis, therefore linking local and systemic manifestations of the deficiency of this protein.

Keywords: skeletal muscle, obesity, kinase, energy balance.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Herrera-Melle L., Mora A., López J.A., Cogliati S., Rodríguez M.E., Leiva-Vega L., Beiroa D., Folgueira C., Enríquez J.A., Vázquez J., Nogueiras R., Sabio G., Skeletal muscle kinases in the regulation of energy balance. IBJ Plus 2019 S(3):e0036 doi: 10.24217/2531-0151.19v1s3.00036.
Funding: L.H-M. is a Ministry of Education, Culture and Sport (MECD) fellow. This study was funded by the following grants to G.S: ERC 260464, EFSD 2030, MICINN/SAF1305, Fundación BBVA, AstraZeneca and Comunidad de Madrid S2010/BMD-2326. The CNIC is supported by the Ministerio de Ciencia, Innovación y Universidades (MCNU) and the Pro CNIC Foundation, and is a Severo Ochoa Center of Excellence (SEV-2015-0505).
Competing Interests: The authors declare that no competing interests exist.

Role of pleiotrophin in hepatic metabolism: characterization in an aging model.

Begoña Zapatería[1], María Gracia Sánchez[1], Julio Sevillano[1], Gonzalo Herradón[2], María del Pilar Ramos[1].

[1]Regulation of Metabolism Group, Biochemistry and Molecular Biology Area, Chemistry and Biochemistry Department. School of Pharmacy. CEU-San Pablo University. Madrid. Spain.
[2]Department of Pharmaceutical and Health Sciences. School of Pharmacy. CEU-San Pablo University. Madrid. Spain.

*Corresponding author:
María del Pilar Ramos, CEU-San Pablo University, Madrid, Spain. E-mail: pramos@ceues.com

Pleiotrophin (PTN) belongs to a family of heparin-binding growth factors involved in regulation of cell growth and angiogenesis. Recently we have shown that PTN also modulates thermogenesis and adipose tissue plasticity. However, the function of this cytokine in hepatic metabolism is completely unknown.

Methods: To determine if pleiotrophin plays a role in the metabolism of the liver, we used a mouse model in which pleiotrophin has been deleted (Ptn-/-) and its corresponding controls (Ptn+/+). Glucose and lipid metabolism were studied including glucose intolerance, liver weight and lipid content, as well as gene expression of membrane transporters and key enzymes of glucose and lipid metabolic pathways in those mice at 3, 6, 12 and 15 months of age.

Results and discussion: Ptn-/- mice were smaller and present lower circulating triglycerides (TG). Both liver weight and total lipid content were significantly lower than in their corresponding controls. On the other hand, in Ptn+/+ mice, aging was accompanied by an increase in hepatic lipogenesis, while deletion of Ptn produces a marked reduction in the expression of all enzymes involved in fatty acid synthesis and esterification, which could be related with the reduced TG content in the liver of these animals. In addition, the expression of AQP 9 was clearly diminished in Ptn-/-, a fact that could suggest a lower uptake of glycerol in these animals than in the control mice.

Although, no significant changes were found in mRNA levels of most of the enzymes of glycolysis and gluconeogenesis, their enzymatic activity indicates that gluconeogenesis is significantly enhanced in Ptn-/- mice with aging, which correlates with the glucose intolerance of these animals. Finally, in the cycle of tricarboxylic acids, the activity of the enzymes involved is higher in Ptn-/- mice and in the oldest ones.

These results are the first ones showing the involvement of pleiotrophin in the control of hepatic homeostasis, which postulates pleiotrophin as a potential therapeutic target for the treatment of several metabolic disorders such as dyslipidaemia or NAFLD.

Keywords: Pleiotrophin, Glucose homeostasis, Metabolism, Lipogenesis, Beta-oxidation.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Zapatería B., Sánchez M.G., Sevillano J., Herradón G., Ramos M.P., Role of pleiotrophin in hepatic metabolism: characterization in an aging model. IBJ Plus 2019 S(3):e0037 doi: 10.24217/2531-0151.19v1s3.00037.
Funding: This work was funded by the Ministry of Economy and Competitiveness (SAF2014-56671-R) and by the Community of Madrid (B2017 / BMD-3684).
Competing Interests: The authors declare that no competing interests exist.

A possible role of Gonadotropin Releasing Hormone functional homolog, prothoracicotropic hormone (ptth), in metabolism.

Celia G. Barredo[1], Beatriz Gil-Marti[2], Carmen Rodriguez-Navas[3] and Francisco A. Martin[4].

[1,2,3,4] Affiliations Instituto Cajal (CSIC)
Celia G. Barredo, Instituto Cajal, Madrid, Spain. E-mail: c.barredo@cajal.csic.es

Besides its classical role on the control of adult transition, Gonadotropin Releasing Hormone (GnRH) influences sleep, memory and energetic metabolism during adulthood. However, mechanisms are not really known. We are interested in uncovering how GnRH regulates these behaviors. Functional GnRH homolog in Drosophila melanogaster is the prothoracicotropic hormone (ptth). Ptth might be involved in regulating the metabolic state, as suggested by its expression in two brain structures such as the Ellipsoid Body and the Mushroom body. Interestingly, torso (ptth receptor) is expressed in the pars intercerebralis and fat cells. Animals mutant for ptth are bigger in size. To assess ptth implications in starvation resistance, we used Drosophila Activity Monitors (DAMs-Trikinetics). DAMs quantify the movement of flies, so it can be used to determine when the animal stops moving for a long period of time, meaning that it is dead. We have also used the CAFE assay (CApillary FEeder assay) to quantify the feeding amount. Our results show that ptth mutant flies survive longer than controls under starvation. However, the way ptth mutant animals feed and move is indistinguishable from control flies. In conclusion, loss of ptth prolongs the survival of starving animals despite their normal activity and food ingestion, suggesting a role for ptth in regulating metabolism per se.

Keywords: ptth, Starvation resistance and metabolism

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Barredo, C.G. Gil-Marti B., Rodriguez-Navas C. and Martin F.A., A possible role of Gonadotropin Releasing Hormone functional homolog, prothoracicotropic hormone (ptth), in metabolism. IBJ Plus 2019 S(3):e0038 doi: 10.24217/2531-0151.19v1s3.00038.
Funding: F.A.M. is a recipient of a RyC-2014-14961 contract and supported by BFU2014-54346-JIN. Fomento a la investigación para estudios de Máster y Doctorado Grant.
Competing Interests: The authors declare that no competing interests exist.

Alx3 deficiency in the hypothalamic arcuate nucleus alters adipose tissue distribution, feeding and body mass composition.

M. Mirasierra, A. Fernández-Pérez and M. Vallejo*.

Instituto de Investigaciones Biomédicas Alberto Sols, Consejo Superior de Investigaciones Científicas/Universidad Autónoma de Madrid, and CIBER de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM).

*Corresponding author:
Mario Vallejo, Consejo Superior de Investigaciones Científicas, Madrid. E-mail: mvallejo@iib.uam.es

Alx3, an aristaless-type homeodomain transcription factor expressed in pancreatic islets, regulates glucose homeostasis by stimulating the expression of the insulin gene in beta cells, or by coordinately inhibiting that of the glucagon gene in alfa cells in a glucose-dependent manner. Our previous studies demonstrated that Alx3 deficiency leads to enhanced islet cell apoptosis and mild hyperglycemia without reaching levels characteristic of overt diabetes. Independently of its pancreatic functions, we have previously reported using data from positron emission tomography and diffusion-weighted magnetic resonance imaging that Alx3-deficient mice show signs of hypothalamic dysfunction. Indeed, the presence of Alx3 in neurons of the arcuate nucleus was demonstrated by immunofluorescence studies. In addition, Alx3-deficient mice exhibit decreased oxygen consumption, energy expenditure and respiratory exchange ratio. These studies strongly suggest that Alx3 may contribute to the systemic regulation of metabolic homeostasis by acting at the hypothalamic level independently of its functions in the pancreas. In the present study, we investigated whether the expression of genes regulating food intake in the arcuate nucleus of Alx3-deficient mice is altered, leading to changes in feeding and accumulation of fat.

Alx3-knockout and control mice of similar age and body weight were used. Gene expression was determined by RT-qPCR in freshly microdissected blocks of hypothalamic tissue containing the arcuate nucleus. Body mass composition was analyzed by magnetic resonance imaging. Muscle function was assessed by treadmill, rotarod and strength tests.

We found that Alx3-deficient mice exhibit reduced food intake but similar body weight relative to wild type animals. Expression of Alx3 in the arcuate nucleus was detected by immunofluorescence and confirmed by RT-qPCR. The expression of the orexigenic genes Npy and Agrp in response to fasting was similar in wild type and Alx3-deficient mice, but the expression of the anorexigenic genes Pomc and Cart was altered. Fasting and refeeding experiments showed that, after an overnight fasting, Alx3-deficient mice stopped eating shortly after the onset of the refeeding period. This coincided with elevated expression of Cart in the arcuate nucleus. Afterwards, Alx3-decicient animals proceeded to eat at a lower rate than controls. We found no differences in the hypothalamic expression of leptin, ghrelin and erythropoietin receptors. The expression of the alfaMSH receptor MC4R was similar in Alx3-mutant and in control mice, but the expression of MC3R was increased in Alx3-deficient animals. Relative to body weight, Alx3-deficient animals showed increased proportion of fat mass and reduced proportion of lean mass, as assessed by magnetic resonance imaging. In consonance with these results, muscle function (motor coordination and strength) was reduced in mutant mice relative to controls. Our results indicate that Alx3 in the arcuate nucleus of the hypothalamus regulates food intake and body mass composition.

Keywords: Arcuate nucleus; food intake; adipose tissue distribution.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Mirasierra M., Fernández-Pérez A. and Vallejo M., Alx3 deficiency in the hypothalamic arcuate nucleus alters adipose tissue distribution, feeding and body mass composition. IBJ Plus 2019 S(3):e0039 doi: 10.24217/2531-0151.19v1s3.00039.
Funding: Funded by MINECO (BFU2011-24245 (BFU2014-52149-R and BFU2017-89336-R) and CIBERDEM.
Competing Interests: The authors declare that no competing interests exist.

p38γ and p38δ control postnatal heart metabolism through glycogen synthase.

Bárbara González-Terán[1], Valle Montalvo-Romeral[1], Cristina Casanueva Benítez[1], Ayelén M. Santamans[1], Alfonso Mora[1], Elena Rodríguez[1], Rebeca Acín-Pérez[1], Luis Leiva-Vega[1], Jesús Jiménez-Borreguero[1], José Antonio Enríquez[1,2] and Guadalupe Sabio[1*]

[1]Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain
[2]Departamento de Bioquímica. Universidad de Zaragoza, Spain

[*]Corresponding author:
Guadalupe Sabio, Centro Nacional de Investigaciones Cardiovasculares Carlos III C/ Melchor Fernández Almagro, 3. 28029 Madrid (Spain)
E-mail: gsabio@cnic.es

Rationale– After birth, high-energy demand and increasing levels of circulating free fatty acids trigger a profound shift in cardiomyocyte metabolism to a predominant reliance on oxidative fatty acid metabolism, which consumes more oxygen but yields more ATP per molecule. This critical metabolic switch from glycolytic to oxidative metabolism is a key

transition in cardiomyocyte maturation during heart development. Stress-activated protein kinases (SAPK) p38g and p38d expression and activation increase after birth promoting cardiomyocyte hypertrophic growth and might be involved in these metabolic changes.

Objective– Understand whether p38g and p38d are implicated in the critical maturational changes that occur in cardiac energy metabolism during heart development.

Methods and Results– Using adeno-associated viral vectors, we have overexpressed in cardiomyocytes at postnatal day 1 (P1) the active forms of p38g and p38d. Cardiac function and whole body metabolism were evaluated. We found that postnatal p38γ and p38δ expression in the heart produces a reduction in glycogen content through the

phosphorylation and subsequent inhibition of the muscle-specific glycogen synthase 1 (GYS1), the main enzyme involved in cardiac glycogen production. Mice with reduced cardiac glycogen levels during the first two weeks after birth, showed increased lipid storage in the heart and developed dilated cardiomyopathy. Moreover, these changes in

cardiac energy metabolism resulted in whole body metabolism dysregulations. Interestingly, although the systemic metabolism is normalized after cardiac metabolic shift into fatty acid oxidation, the heart physiology alterations persisted in adult mice.

Conclusions– p38g and p38d function in a cooperative manner to inhibit GYS1 activity through phosphorylation, blocking glycogen production. Both kinases are involved in the metabolic switch of cardiomyocytes after birth. Our results point out these defects in cardiac fuel during the early postnatal development might cause cardiac dysfunction and deleterious metabolic consequences in whole body metabolism.

Keywords: Gys, heart metabolism, phosphorylation, p38, metabolic switch, glycogen

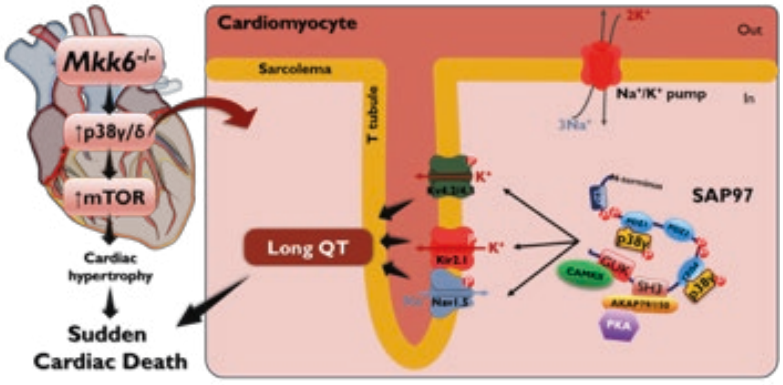
Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: González-Terán B., Montalvo-Romeral V., Casanueva Benítez C., Santamans A.M., Mora A., Rodríguez E., Acín-Pérez R., Leiva-Vega L., Jiménez-Borreguero J., Enríquez J.A. and Sabio G., p38γ and p38δ control postnatal heart metabolism through glycogen synthase. IBJ Plus 2019 S(3):e0040 doi: 10.24217/2531-0151.19v1s3.00040.
Funding: G.S. was an investigator of the Ramón y Cajal Program. B.G.T was a fellow of the FPI Severo Ochoa CNIC program (SVP-2013-067639). V.M.R is a FPI fellow (BES-2014-069332). This work was funded by the following grants supported in part by funds from European Regional Development Fund (ERDF): to G.S.: funding from the European Union's Seventh Framework Programme (FP7/2007-2013) under grant agreement n° ERC 260464, EFSD/Lilly European Diabetes Research Programme Dr Sabio, 2017 Leonardo Grant for Researchers and Cultural Creators, BBVA Foundation
(Investigadores-BBVA-2017) IN[17]_BBM_BAS_0066, MINECO-FEDER SAF2016- 79126-R, and Comunidad de Madrid IMMUNOTHERCAN-CM S2010/BMD-2326 and B2017/BMD-3733; The CNIC is supported by the Ministerio de Ciencia, Innovación y Universidades and the Pro CNIC Foundation, and is a Severo Ochoa Center of Excellence (SEV-2015-0505).
Competing Interests: The authors declare that no competing interests exist.

MKK6: a novel player in cardiac hypertrophy and sudden cardiac death.

Bárbara González-Terán[1#], Rafael Romero-Becerra[1#], Daniela Ponce-Balbuena[2], Roberto Ramos Mondragon[2], Eric Jimenez Vazquez[2], Elisa Manieri[1], Laura Sanz[1], Ivana Nikolic[1], María del Valle Montalvo[1], Ayelen Santamans[1], Maria Elena Rodriguez[1], Luis Leiva-Vega[1], Víctor Buendía[1], Guadalupe Guerrero Serna[2], David Filgueiras[1,3], Luis Jesús Jiménez Borreguero[1], José Jalife[1,2,3*] & Guadalupe Sabio[1*]

[1]Fundación Centro Nacional de Investigaciones Cardiovasculares Carlos III, 28029, Madrid, Spain
[2]Center for Arrhythmia Research, Department of Internal Medicine, University of Michigan, Ann Arbor, MI, USA
[3]Centro de Investigación Biomédica en Red Enfermedades Cardiovasculares (CIBERCV), 28029, Madrid, Spain
[#]Equal contribution
[*]Corresponding author: Guadalupe Sabio, Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid, Spain. E-mail: gsabio@cnic.es ; José Jalife, Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid, Spain. E-mail: jose.jalife@cnic.es

Knowledge about signaling pathways associated with hypertrophic cardiomyopathy and the risk of sudden cardiac death remains incomplete. Mitogen activated protein kinases kinases MKK6 and MKK3 have been suggested to be involved in cardiac growth. However, it is unclear how these kinases control the activation of the different p38 mitogen-activated protein kinase (MAPK) isoforms in cardiomyocytes and whether they are implicated in pathological cardiac hypertrophy and sudden cardiac death. Our results show that MKK3 is the main activator of p38γ and p38δ in the heart, whereas MKK6 activates cardiac p38α. Mice lacking MKK3 show a reduction in postnatal cardiac growth due to reduced p38γ and p38δ activation, while lack of MKK6-p38α activation leads to MKK3-p38γ/δ hyperactivation and increased mTOR signaling, resulting in physiological cardiac hypertrophy. Cardiac hypertrophy in Mkk6-/- mice can be reverted by knocking out MKK3, and by inhibiting mTOR signaling. Interestingly, when MKK6-deficient mice were challenged with chronic endurance training, the QT interval was prolonged and mice died prematurely during or just after exercise. In addition, Mkk6-/- mice showed cardiac ion channel dysfunction, prolonged action potential duration and increased arrhythmia susceptibility on programmed electrical stimulation, particularly in the presence of β-adrenergic stimulation. MKK6 deletion and p38γ activation also promotes the hyperphosphorylation of hDlg/SAP97, a scaffolding protein involved in the assembly and functionality of cardiac ion channels in the T tubule. SAP97 hyperphosphorylation results in altered levels and function of cardiac ion channels, likely because and increased phosphorylation of these channels by PKA and CAMKII, two other proteins that also interact with SAP97. These results indicate that the MKK3/6-p38γ/δ pathway is implicated in cardiac hypertrophy and cardiac ion channel dysfunction, which promotes QT prolongation and sudden cardiac death.



Keywords: MKK6, MKK3, p38MAPK, cardiac hypertrophy, mTOR, SAP97, sodium channels, potassium channels, Long QT, cardiac arrhythmia, sudden cardiac death.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: González-Terán B., Romero-Becerra R., Ponce-Balbuena D., Ramos Mondragon R., Jimenez Vazquez E., Manieri E., Sanz L., Nikolic I., Montalvo MV., Santamans A., Rodriguez M.E., Leiva-Vega L., Buendía V., Guerrero Serna G., Filgueiras D., Jiménez Borreguero L.J., Jalife J. & Sabio G., MKK6: a novel player in cardiac hypertrophy and sudden cardiac death. IBJ Plus 2019 S(3):e0041 doi: 10.24217/2531-0151.19v1s3.00041.

Funding: This work was funded by following grants to G.S.: ERC 260464, EFSD, MINECO-FEDER SAF2016-79126-R, and Comunidad de Madrid S2010/BMD-2326. Additional finding came from US National Heart, Lung, and Blood Institute (R01 Grant HL122352) and Fondos FEDER, Madrid, Spain, to J. Jalife. D. Ponce-Balbuena was supported by AHA Postdoctoral Fellowships 14POST17820005. The CNIC is supported by the Ministerio de Ciencia, Innovación y Universidades (MCNU) and the Pro CNIC Foundation, and is a Severo Ochoa Center of Excellence (SEV-2015-0505).

Competing Interests: The authors declare that no competing interests exist.

Nuclear receptors are required for transcriptional control of hematopoietic stem cells and myeloid differentiation.

Jesús Porcuna [1*], María Piedad Menéndez-Gutiérrez [1*] and Mercedes Ricote[1].

[1]Area of Myocardial Pathophysiology, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain.
Corresponding author:
Mercedes Ricote, CNIC, Madrid, Spain. E-mail: mricote@cnic.es

Hematopoietic stem cells (HSCs) maintain the hematopoietic system balance during the life of an organism. HSC fate and differentiation are based on gene expression, which is the result of an orchestrated transcriptional regulation. However, the transcription factors that govern HSC homeostasis remain poorly studied. Retinoid X Receptors (RXRs) are ligand-dependent transcription factors that respond to vitamin A derivatives. The Vitamin A signaling pathway activation has been demonstrated to regulate HSC differentiation and stem cell plasticity.

In this project, we aim to uncover the role of RXRs in the differentiation and identity of HSCs. We have generated conditional HSC RXRα and RXRβ knock out mice (KO) to study the RXRα and RXRβ specific contribution to HSCs. Our findings show that RXRs control myeloid differentiation and HSC survival. Flow cytometry analysis of bone marrow and spleen demonstrated an increase of myeloid progenitor cells LKs (Linage-/c-kit+/sca1-) and LSKs (Linage-/c-kit+/sca1+) in KO compared to WT mice. Interestingly, the myeloid-biased LSK subpopulation was largely increased indicating first, a tendency to myeloid differentiation and, second, a hematopoietic aged phenotype in these mice. Transplantation experiments suggested that KO-associated hematopoietic defects are serial and long-term transplantable, and showed that the effect of RXR in myelopoiesis is bone marrow niche-dependent. To further study the RXRs role in myeloid differentiation, we have developed conditional myeloid RXRα and RXRβ knock out mice. Flow cytometry data have proven that the lack of RXRs in myeloid cells led to the dysregulation of specific tissue resident macrophage populations.

In summary, we have proved that RXRα and RXRβ are novel and key regulators of HSC homeostasis, identity and differentiation, that the hematopoietic absence of RXRs leads to a myeloid-biased hematopoietic phenotype, and that RXRs are key controllers of specific tissue resident macrophages.

Keywords: Nuclear Receptors, RXRs, Hematopoietic Stem Cells, Differentiation, Tissue Macrophages.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Porcuna J., Menéndez-Gutiérrez MP. and Ricote M., Nuclear receptors are required for transcriptional control of hematopoietic stem cells and myeloid differentiation. IBJ Plus 2019 S(3):e0042 doi: 10.24217/2531-0151.19v1s3.00042.
Funding: This work was supported by grants from the Spanish Ministry of Economy and Competitiveness (SAF2012-31483) to M. Ricote and Formación de Profesorado Universitario (FPU17/01731) program from the Spanish Ministry of Education, Culture and Sports. The CNIC is supported by the Spanish Ministry of Economy and Competitiveness and the Pro-CNIC Foundation.
Competing Interests: The authors declare that no competing interests exist.

Quantitative analysis of cardiac receptors of the renin angiotensin system (RAS) in a fetal programming hypertension rat model.

Rodríguez-Rodríguez P[1], Vieira-Rocha MS[2], Quintana-Villamandos B[3], Monedero-Cobeta I[1], González MC[1], López de Pablo AL[1], Morato M[2], Diniz C[2], Arribas SM[1].

[1]Department of Physiology, Faculty of Medicine; Universidad Autónoma de Madrid, Madrid, Spain.
[2]LAQV/REQUIMTE, Laboratory of Pharmacology, Department of Drug Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal
[3]Department of Anesthesiology, Hospital Universitario Gregorio Marañón, Madrid.

*Corresponding author:
Pilar Rodríguez Rodríguez, Department of Physiology, Madrid, Spain. E-mail: pilar.rodriguezr@uam.es

Purpose. Maternal undernutrition during pregnancy is associated with low birth weight of the offspring, which in adult life develop hypertension and heart disease (fetal programming of cardiovascular diseases). We have evidence that male offspring from rats exposed to undernutrition during gestation (MUN) exhibits enlarged heart at weaning and cardiac dysfunction in ageing (Rodríguez-Rodriguez P. 2017). One of the potential mechanisms implicated in fetal programming is an alteration in renin angiotensin system (RAS).

Hypothesis. We hypothesized that perinatal alterations in RAS components are implicated in early cardiac hypertrophy and fibrosis, setting the basis for later occurrence of heart diseases.

Methods. Sprague Dawley rats were used. Control (C) dams were fed ad libitum during pregnancy and lactation. MUN dams were fed 50% of the calculated ad libitum daily intake during the second half of gestation and returned to ad libitum diet during lactation. All experimental procedures were performed at weaning (21 day-old) in male offspring from C and MUN groups. We analyzed : 1) plasma Ang II concentrations (by solid phase extraction and ELISA kit), 2) expression of AT1, AT2, Mas and MrgD receptors in myocardium and intramyocardial artery (immunohistochemistry), 3) intramyocardial artery (IMA) structure (histology), 4) Cardiac structure and function (echocardiography).

Results. Plasma concentration of Ang II was markedly higher in MUN rats compared to controls (Control=0.87±0.38 pg/ml; MUN=59.42±17.70 pg/ml, n=5; $p<0.05$).
Immunoreactivity against the AT1, AT2, Mas and MrgD receptors was observed in the myocardium from MUN and C rats. No statistical differences between C and MUN rats were detected in AT1, AT2, Mas receptors, while there was a lower expression of MrgD receptors in MUN rats. IMA from MUN rats exhibited a significantly higher wall/lumen ratio, collagen content and expression of AT1 and Mas receptors than controls. By contrast, AT2 and MrgD receptor expression was lower in MUN when compared to C rats.
Compared to C offspring, MUN rats exhibited an increased Left ventricular mass and reduced E/A ratio (parameter of diastolic function) but normal ejection fraction (EF, which evaluates systolic function. No statistical differences were detected in LVEF.

Conclusions. Fetal undernutrition induces perinatal alterations in RAS, which are implicated in heart hypertrophic responses and early signs of diastolic dysfunction. These findings indicate that fetal programming of cardiac dysfunction starts in perinatal life, suggesting that lactation period is an opportunity window for prevention, being the RAS a potential target.

Keywords: Angiotensin ll, maternal undernutrition, heart hypertrophy, AT1, AT2, Mas and MrgD receptors.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Rodríguez-Rodríguez P., Vieira-Rocha MS., Quintana-Villamandos B., Monedero-Cobeta I., González MC., López de Pablo AL., Morato M., Diniz C., Arribas SM., Quantitative analysis of cardiac receptors of the renin angiotensin system (RAS) in a fetal programming hypertension rat model. IBJ Plus 2019 S(3):e0043 doi: 10.24217/2531-0151.19v1s3.00043.
Funding: This work was supported by Ministerio de Economía y Competitividad-Spain (Grants FEM2012-37634-C03-01 and FEM2015-63631-R; 2015 co-financed with FEDER funds) to S.M. Arribas. This work was also supported by Fundação para a Ciência e Tecnologia, (project UID/QUI/50006/2013 - POCI/01/0145/FEDER/007265 with financial support from FCT/MEC through national funds and co-financed by FEDER, under the Partnership Agreement PT2020)
Competing Interests: The authors declare that no competing interests exist.

Modulation of mitochondrial activity in heart failure.

Ayelén M. Santamans[1*], Aránzazu Pintor Chocano[1], Alfonso Mora[2], Elena Rodríguez[1], Ainoa Caballero, María Villalba-Orero, Pablo Hernansanz-Agustín, José Antonio Enriquez[1], Mercedes Rincón[2], Guadalupe Sabio[1].

[1]Area of Myocardial Pathophysiology, Fundación Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid, Spain.
[2]University of Vermont, Vermont, United States.

*Corresponding author:
Ayelén M. Santamans. Area of Myocardial Pathophysiology, Fundación Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid, Spain.
E-mail: amsantamans@cnic.es

During cardiac hypertrophy it is vital for the heart to adapt to an increasing energy demand by improving mitochondrial activity and proliferation. The defective capacity of mitochondria to respond to these demands could result in heart failure. We found that modulation of mitochondria complex I activity during heart injury could be beneficial. Our results suggest that ATP availability decreases during heart injury. Genetic modification of the mice to increase this ATP availability resulted in protection against hypertrophy and left ventricle dilatation. Genetic modified animals are protected against diastolic dysfunction and showed less inflammation markers. In addition, the deposit of extracellular matrix is differential as there is an increase in the perivascular area in WT mice after cardiac injury, not observed in the genetically modified animals.

Altogether, these results suggest that mitochondria activity modulation could be a possible mechanism for the treatment or prevention of heart failure by improving cardiological parameters and leading to a differential cardiac remodeling by altering the mitochondrial metabolism.

Keywords: Heart failure, mitochondria, complex 1.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: M. Santamans A., Pintor Chocano A., Mora A., Rodríguez E., Caballero A., Villalba-Orero, M. Hernansanz-Agustín P., Enriquez JA., Rincón M., Guadalupe Sabio G., Modulation of mitochondrial activity in heart failure. IBJ Plus 2019 S(3):e0044 doi: 10.24217/2531-0151.19v1s3.00044.
Funding: There are no fundings to declare.
Competing Interests: The authors declare that no competing interests exist.

DICER1 downregulation and impaired miRNA processing in thyroid tumorigenesis.

Julia Ramírez-Moya[1,2], León Wert-Lamas[1,3], Garcilaso Riesco-Eizaguirre[1,2,3], Pilar Santisteban[1,2].

[1]Instituto de Investigaciones Biomédicas "Alberto Sols"; Consejo Superior de Investigaciones Científicas (CSIC); Universidad Autónoma de Madrid (UAM), Madrid, Spain.
[2]Centro de Investigación Biomédicas en Red de Cáncer (CIBERONC), Instituto de Salud Carlos III (ISCIII), Madrid, Spain.
[3]Departamento de Endocrinología y Nutrición, Hospital Universitario de Móstoles, Madrid, Spain.

*Corresponding author:
Pilar Santisteban, Instituto de Investigaciones Biomédicas "Alberto Sols"; Consejo Superior de Investigaciones Científicas (CSIC); Universidad Autónoma de Madrid (UAM), Madrid, Spain; Centro de Investigación Biomédicas en Red de Cáncer (CIBERONC), Instituto de Salud Carlos III (ISCIII), Madrid, Spain.
E-mail: psantisteban@iib.uam.es

Thyroid cancer is a common endocrine malignancy that has rapidly increased its global incidence in recent decades. Currently the important role of microRNAs (miRNAs) in cancer has been described, including thyroid neoplasms. It is known that miRNAs are important modulators of cancer progression and are globally downregulated in several human tumor types, through mechanisms that remain largely undefined. Functional maturation of most miRNAs requires processing of the primary transcript by DICER1, an RNAse III-type enzyme essential for both mammalian development and cell differentiation. Here we identified DICER1 and miRNA downregulation as sentinel events in thyroid cancer, providing a clear cut evidence of the molecular mechanisms underlying this effect. We demonstrated that this key miRNA-processing enzyme is a target of the most upregulated miRNAs in thyroid cancer. Specifically, miR-146b reduced DICER1 expression and DICER1 overexpression inhibited all the miR-146b-induced aggressive phenotypes, both in cells and in tumor models. Our analysis of The Cancer Genome Atlas revealed a general decrease in DICER1 expression in thyroid cancer and suggested a clinical association between DICER1 and patient prognosis. Notably, DICER1 downregulation promoted proliferation, migration, invasion and epithelial-mesenchymal transition in thyroid cancer cell lines, whereas it suppressed the expression of pro-differentiation transcription factors. Interestingly, these factors transcriptionally upregulated DICER1 expression, supporting the existence of a positive feedback loop. Finally, administration of the small molecule enoxacin to promote DICER1-complex activity reduced cell aggressiveness in vitro and tumor growth in vivo. Overall, our data establish DICER1 as a new tumor suppressor in thyroid cancer, and highlight a potential therapeutic approach of RNA-based therapies including antagomiRs and restoration of the biogenesis machinery may provide treatments for thyroid cancer and other cancers.

Keywords: Thyroid cancer, miRNAs, DICER1, miR-146b, antagomiR, Enoxacin.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Ramírez-Moya J., Wert-Lamas L., Riesco-Eizaguirre G., Santisteban P., DICER1 downregulation and impaired miRNA processing in thyroid tumorigenesis. IBJ Plus 2019 S(3):e0045 doi: 10.24217/2531-0151.19v1s3.00045.
Funding: There are no fundings to declare.
Competing Interests: The authors declare that no competing interests exist.

Antitumor activity of the ERK inhibitor DEL22379 against BRAF-like cells in thyroid cancer.

Adrián Acuña-Ruiz[1,2], Miguel Angel Zaballos[1,2], Garcilaso Riesco-Eizaguirre[2,3], Piero Crespo [2,4], Pilar Santisteban[1,2,*].

[1]Instituto de Investigaciones Biomédicas "Alberto Sols", Madrid, Spain.
[2]Instituto de Salud Carlos III (ISCIII), CIBERONC, Madrid, Spain.
[3]Hospital Universitario de Móstoles, Móstoles, Spain.
[4]Instituto de Biomedicina y Biotecnología de Cantabria, Santander, Spain.

*Corresponding author:
Pilar Santisteban, Instituto de Investigaciones Biomédicas "Alberto Sols", Madrid, Spain. E-mail: psantisteban@iib.uam.es

Thyroid cancer is the most prevalent human carcinoma of endocrine origin and its incidence is continuously increasing. Around 80% of all the somatic mutations are accumulated in only five driver genes (BRAF, H/N/K-RAS and RET) which converge in the hyperactivation of the MAPK signalling pathway. Given the central role of this pathway in thyroid tumorigenesis, thyroid cancer research is focused on the identification of new drugs that inhibit the different kinases of the pathway. DEL22379 is an inhibitor of ERK dimerization previously characterized in melanoma and colorectal cancer-derived cell lines as a new approach to partially inhibit ERK activation. It has been reported that ERK dimerization contributes to the activation of ERK cytoplasmic effectors, such as RSK, and enhances malignant cell features.

Our objective was to analyse the antitumor effect of the inhibitor of ERK dimerization DEL22379 as a possible therapeutic compound in thyroid cancer.

In vitro assays were made with different thyroid cancer cell lines with mutations in BRAF, H/N/K-RAS or RET. To evaluate cell proliferation, migration and invasion; we have used cell cycle, wound healing and matrigel invasion assays, respectively. We also have developed an orthotopic mouse model of anaplastic thyroid cancer by the generation of the 8505c-luc cell line. In vivo tumour progression was monitored by measuring luciferase activity.

Treatment with DEL22379 impairs ERK dimers formation in BRAF-like thyroid cells whereas Ras-like cells were unaffected. Unlike melanoma, phosphorylated ERK levels were substantially reduced after treatment with the inhibitor. Inhibition of ERK dimerization and phosphorylation correlated with diminished RSK phosphorylation. We also observed a decrease in cell proliferation, migration and invasion in the anaplastic thyroid cell lines 8505c and OCUT2. DEL22379 treatment significantly reduced tumour growth and formation of lung metastases in an orthotopic mouse model.

We propose DEL22379 as a new effective molecule for the inhibition of MAPK signalling and the reduction of cell malignant behaviour, tumour growth and metastasis in vivo, specifically in BRAF-like thyroid tumours. It promises to be another step forward in the achievement to cure thyroid cancer.

Keywords: Thyroid cancer, MAPK signaling, ERK, BRAF.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Acuña-Ruiz A., Zaballos MA., Riesco-Eizaguirre G., Crespo P., Santisteban P., Antitumor activity of the ERK inhibitor DEL22379 against BRAF-like cells in thyroid cancer. IBJ Plus 2019 S(3):e0046 doi: 10.24217/2531-0151.19v1s3.00046.
Funding: This work was supported by grants SAF2016-75531-R from Ministerio de Economía y Empresa (MINECO), Spain and PI14/01980 from ISCIII, Spain (FEDER) and GCB14142311CRES from Asociación Española contra el Cancer (AECC).
Competing Interests: The authors declare that no competing interests exist.

Role of the IQGAP1 scaffold protein in thyroid cancer.

Carlos Carrasco-López[1, 2], Miguel Angel Zaballos[1, 2], Pilar Santisteban1[, 2, *]

[1]Instituto de Investigaciones Biomédicas, C/ Arturo Duperier 4, Madrid, Spain.
[2]Instituto Carlos III, CIBERONC, Madrid, Spain.

*Corresponding author:
Pilar Santisteban, Instituto de Investigaciones Biomédicas, Madrid, Spain. E-mail: psantisteban@iib.uam.es

The IQGAP family of scaffold proteins comprises three members which have been described to interact with numerous proteins in several biological processes and participate in the signaling cascade of multiple pathways. Among these proteins IQGAP1 has been the most deeply studied, having characterized its function as a scaffold protein in the MAPK pathway and its interaction with actin leading to regulation of the cytoskeleton. Because of these functions it has been studied in multiple malignancies, where it has been assigned a tumorigenic effect.

We have studied IQGAP1 expression using different stablished cell lines of human thyroid carcinomas. Our results indicate that these carcinoma cell lines have variable levels of IQGAP1 but in general these levels are higher when compared to the normal thyroid cell line control. The results obtained are in agreement with the TCGA and Oncomine databases. Using IQGAP1 silenced cell lines we tried to elucidate how this protein was affecting tumor hallmarks such as proliferation, invasion, cell migration and epithelial mesenchymal transition. The effects of silencing IQGAP1 were different depending on the cell line and the oncogenic signature. While in some of them silencing produced an increase in the migration rate of the cells, others had the opposite behavior. We also found these differences when studying EMT markers such as E-cadherin and N-cadherin. Furthermore, cell viability was unaffected by IQGAP1 silencing and consequently the size of the primary tumor was not altered when cells were xenografted in a chicken embryo model. Importantly IQGAP1 silencing greatly decreased the ability of the tumor cells to intravasate and metastasize to distant organs such as lungs and brain.

Further studies will focus on trying to discover the underlying mechanisms responsible for the differences observed between cell lines. Our results indicate a role forIQGAP1 in thyroid tumorigenesis and underscore the importance of defining the oncogenic signature and particularities of a given tumor type in order to design effective therapeutic strategies.

Keywords: IQGAP1, Thyroid, Cancer

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Carrasco-López C., Zaballos MA., Santisteban P., Role of the IQGAP1 scaffold protein in thyroid cancer. IBJ Plus 2019 S(3):e0047 doi: 10.24217/2531-0151.19v1s3.00047.
Funding: Funding This work was supported by grants SAF2016-75531-R from MINECO, Spain and PI14/01980 from ISCIII, Spain (FEDER); B2017/BMD-3724 from CAM and GCB14142311CRES from AECC.
Competing Interests: The authors declare that no competing interests exist.

Proteomic analysis of fine-needle aspirates (FNA) for the molecular characterization of non-diagnostic follicular neoplasia.

Vanessa Arosa[1], Mikel Azkargorta[2,] Leire Isasa[1], Carmen Fernández[1], Leire Pérez[1], María Angeles Antón[1], Gonzalo Maldonado[1].

[1]Servicio de Endocrinología y Nutrición, Hospital Universitario Araba, Vitoria-Gasteiz.
[2]CIC bioGUNE-Proteomics Platform, ProteoRed---ISCIII, Derio, Bizkaia.

*Corresponding author:
Vanessa Arosa, Servicio de Endocrinología y Nutrición, Hospital Universitario Araba, Vitoria-Gasteiz. E-mail: vanessa.arosa@osakidetza.com

Thyroid cancer is the most prevalent malignant endocrine pathology. Differentiated thyroid cancer represents more than 90% of these cases, and 12% of these are follicular carcinomas. Currently, the diagnosis of thyroid nodules is based on the cytologic analysis of fine-needle aspirates (FNA) aided by echography. Around 10% of the cases provided are categorized as IV in the Bethesda system. Since malignancy cannot be ruled out, these cases are subjected to local surgery. The post-operatory analysis of these samples reveals that in 70-85% of them this intervention was not necessary. Given this, additional tools for sample categorization would be welcome.

Mass spectrometry-based proteomics provides a number of tools for the large-scale analysis of proteins in biological samples. Current technology allows the analysis of the presence and/or relative abundance of hundreds/thousands of proteins in a given sample; thus quantitative proteomics allows the comparison of protein levels between conditions (i.e.: healthy vs. disease). Further bioinformatics analyses help deepen into the molecular functions and pathways these proteins are involved in, providing additional information for the understanding of the disease. Thus, proteomics provides a very valuable tool for the molecular characterization of a disease, as well as for biomarker discovery.

In this work we present preliminary results on the analysis of FNA samples by proteomics. The aspirates were centrifuged, and both the resulting supernatant and the pellet containing aspirated cells and debris were processed and loaded into an LTQ Orbitrap XL-ETD mass spectrometer for protein identification. Identified proteins were further characterized using bioinformatic tools. The methods and results presented in this poster lay foundation for coming analyses in the context of the molecular characterization of these poorly defined cases, being our main goal the search for FNA markers that help distinguish follicular adenomas from carcinomas and thus avoid surgery.

Keywords: mass spectrometry, fine-needle aspirate (FNA), biomarker discovery, functional analysis.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Arosa V., Azkargorta M., Isasa L., Fernández C., Pérez L., Antón MA., Maldonado G., Santisteban P., Proteomic analysis of fine-needle aspirates (FNA) for the molecular characterization of non-diagnostic follicular neoplasia. IBJ Plus 2019 S(3):e0048 doi: 10.24217/2531-0151.19v1s3.00048.
Funding: No fundings to declare.
Competing Interests: The authors declare that no competing interests exist.

Radioiodide therapy in ovarian cancer.

Mielu Lidia Mirela[1,2], Fajardo-Delgado Dánae[2], Hortigüela Rafael[2], Diego-Hernández Cristina[3], García-Jiménez Custodia[4], Martín-Duque Pilar[5], and De la Vieja Antonio[1,2]

[1]CiberOnc (ISCIII), Spain
[2]Endocrine Tumors Unit. UFIEC (ISCIII), Majadahonda, Spain
[3]Hospital Universitario de Móstoles (HUM), Móstoles, Spain
[4]Universidad Rey Juan Carlos, Alcorcón, Spain
[5]Instituto Aragonés de Ciencias de la Salud, Spain
*Corresponding author:
Lidia Mirela Mielu, CiberOnc, Madrid, Spain, E-mail: mielulidia@gmail.com

Introduction: Ovarian cancer is the most lethal gynecological malignancy. Early diagnosis has a survival rate of 90%. Unfortunately, more than 70% of cases are diagnosed when the cancer has already metastasized, and survival rates do not exceed 30% in these cases. The sodium iodide symporter (NIS) mediates active transport of iodide into the thyroid as a fist steps in thyroid hormone biosynthesis, but also in others tissues like salivary gland, lactating mammary gland and stomach. Our group has demonstrated that NIS is expressed in ovarian surface epithelium and is overexpressed in human epithelial ovarian cancer, establishing NIS as a tumor marker. The aim of this study is to determine whether overexpression of NIS in ovarian cancer can be use as therapeutic tool using radioiodide therapy (RAI) in ovarian tumors.
Materials and Methods: serous ovarian cancer cell line (SKOV3) was transfected permanently with exogenous NIS (SKOV3-hNIS) and in vitro characterized by different techniques (western-blot, PCR, flow cytometry, immunofluorescence, iodide uptake and proliferation, migration, invasion, and adhesion assays). In vivo, NIS transfected cells and no transfected was injected into the flanks of nude and NSGs mice. Tumor growth was monitored by measurements with caliber and IVIS. The expression of NIS in tumors was analyzed by different molecular biology techniques and NIS functionality in animal models was measured by SPECT-CT.
Results: PCR and western-blot show NIS expression in both in vitro cancer cells and in vivo with xenotransplanted cells in animal models. Immunofluorescence and immunohistochemistry show that NIS expression occurs in plasma membrane, and iodide uptake assays show that the expression of NIS in plasma membrane is functional in vitro and in SPECT-CT assay in vivo. Additionally, NIS presence alters in vitro and in vivo proliferation, migration, invasion and adhesion of tumor cell properties.
Conclusion: NIS expression in human ovarian cancer cell lines is functional in vitro and in vivo, targeted to the plasma membrane and able to accumulate iodide. The high expression levels are correlated with worse prognosis pointing NIS as a future therapeutic approach in treatment of ovarian cancer.

Keywords: ovarian cancer, sodium/iodide symporter (NIS), Radioioide therapy (RAI), SPECT-CT

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Mielu Lidia M., Fajardo-Delgado D., Hortigüela R., Diego-Hernández C., García-Jiménez C., Martín-Duque P., and De la Vieja A., Radioiodide therapy in ovarian cancer. IBJ Plus 2019 S(3):e0049 doi: 10.24217/2531-0151.19v1s3.00049.
Funding: This work was supported by grants from the Ministerio de Economía y Competitividad and European Regional Development Fund (FEDER) SAF2015-69964-R and CiberOnc from the ISCIII.
Competing Interests: The authors declare that no competing interests exist.

Metabolic adaptations in spontaneously immortalized PGC-1α knock-out mouse embryonic fibroblasts increase their oncogenic potential.

Ignacio Prieto[1], Carmen Rubio-Alarcón[1], Raquel García-Gómez[1], Rebeca Berdún[2], Manuel Portero[2], Reinald Pamplona[2], Antonio Martínez-Ruiz[3,4], José Ignacio Ruiz-Sanz[5], Mª Begoña Ruiz-Larrea[5], Mariona Jove[2], Sebastian Cerdán[1], María Monsalve[1*].

[1]Instituto de Investigaciones Biomédicas "Alberto Sols" (CSIC-UAM). Arturo Duperier 4. 28029-Madrid (Spain).
[2]Institut de Recerca Biomédica Lleida. Avda. Alcalde Rovira Roure 80, 25198-Lleida (Spain).
[3]Unidad de Ivestigación, Hospital Universitario Santa Cristina, Instituto de Investigación Sanitaria Princesa (IIS-IP). Maestro Vives 3, 28009 – Madrid (Spain).
[4]Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain.
[5]Departamento de Fisiología, Facultad de Medicina y Enfermería. Universidad del País Vasco/Euskal Herriko Unibertsitea. Barrio Sarriena s/n. [4]8940-Leioa (Spain).

*Corresponding author:
María Monsalve, Instituto de Investigaciones Biomédicas Alberto Sols (CSIC-UAM), Madrid, Spain. E-mail: mpmonsalve@iib.uam.es

PGC-1α controls, to a large extent, the capacity of cells to respond to changing nutritional requirements and energetic demands. The key role of metabolic reprogramming in tumor development has highlighted the potential role of PGC-1α in cancer. To investigate how loss of PGC-1α activity in primary cells impacts the oncogenic characteristics of spontaneously immortalized cells, and the mechanisms involved, we used the classic 3T3 protocol to generate spontaneously immortalized mouse embryonic fibroblasts (iMEFs) from wild-type (WT) and PGC-1α knockout (KO) mice and analyzed their oncogenic potential in vivo and in vitro. We found that PGC-1α KO iMEFs formed larger and more proliferative primary tumors than WT counterparts, and fostered the formation of lung metastasis by B16 melanoma cells. These characteristics were associated with the reduced capacity of KO iMEFs to respond to cell contact inhibition, in addition to an increased ability to form colonies in soft agar, an enhanced migratory capacity, and reduced growth factor dependence. The mechanistic basis of this phenotype is likely associated with the observed higher levels of nuclear β-catenin and c-myc in KO iMEFs. Evaluation of the metabolic adaptations of the immortalized cell lines identified a decrease in oxidative metabolism and an increase in glycolytic flux in KO iMEFs, which were also more dependent on glutamine for their survival. Furthermore, glucose oxidation and tricarboxylic acid cycle forward flux were reduced in KO iMEF, resulting in the induction of compensatory anaplerotic pathways. Indeed, analysis of aminoacid and lipid patterns supported the efficient use of tricarboxylic acid cycle intermediates to synthesize lipids and proteins to support elevated cell growth rates. All these characteristics have been observed in aggressive tumors and support a tumor suppressor role for PGC-1α, restraining metabolic adaptations in cancer.

Keywords: PGC-1α, metabolism, cancer, tumor, metastasis.

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Prieto I., Rubio-Alarcón C., García-Gómez R., Berdún R., Portero M., Pamplona R., Antonio Martínez-Ruiz A., Ruiz-Sanz J.I., Ruiz-Larrea MB., Jove M., Cerdán S., Monsalve M., Santisteban P., Metabolic adaptations in spontaneously immortalized PGC-1α knock-out mouse embryonic fibroblasts increase their oncogenic potential. IBJ Plus 2019 S(3):e0050 doi: 10.24217/2531-0151.19v1s3.00050.
Funding: This work was funded by grants from the Spanish "Ministerio de Economía Industria y Competitividad" (MINEICO) and ERDF/FEDER funds, SAF2012-37693, SAF2015-63904-R, SAF2015-71521-REDC, to M.M., SAF2017-83043-R and B2017/BMD-3724 to S.C., PI15/00107 to A.M.R, the University of the Basque Country UPV/EHU grant GIU16/62) to J.I.R.S. and M.B.R.L., and the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement 721236-TREATMENT to M.M.
Competing Interests: The authors declare that no competing interests exist.

Gene regulatory and phenotypic effects of calcitriol and canonical WNT in human colon fibroblasts.

Gemma Ferrer-Mayorga[1,2,3], Núria Niell[1,4,^], Ramón Cantero[2,5], José Manuel González-Sancho1,3,4, Luis del Peso1,2,4,6, Alberto Muñoz[1,2,3,*] & María Jesús Larriba[1,2,3,*].

[1]Instituto de Investigaciones Biomédicas "Alberto Sols", Consejo Superior de Investigaciones Científicas, Universidad Autónoma de Madrid, Madrid, Spain.
[2]Instituto de Investigación Sanitaria Hospital Universitario La Paz, Madrid, Spain.
[3]CIBERONC, Instituto de Salud Carlos III, Madrid, Spain.
[4]Departamento de Bioquímica, Facultad de Medicina, Universidad Autónoma de Madrid, Madrid, Spain.
[5]Servicio de Cirugía General, Hospital Universitario La Paz, Madrid, Spain.
[6]CIBERES, Instituto de Salud Carlos III, Madrid, Spain.
[^]Present address: Departamento de Biología, Facultad de Ciencias, Universidad Autónoma de Madrid, Madrid, Spain.
[*]Corresponding authors:
Alberto Muñoz, Instituto de Investigaciones Biomédicas "Alberto Sols", Consejo Superior de Investigaciones Científicas, Universidad Autónoma de Madrid, Madrid, Spain. amunoz@iib.uam.es
María Jesús Larriba, Instituto de Investigaciones Biomédicas "Alberto Sols", Consejo Superior de Investigaciones Científicas, Universidad Autónoma de Madrid, Madrid, Spain. mjlarriba@iib.uam.es

Vitamin D3 (cholecalciferol) is synthesized in the skin by action of solar UV radiation or incorporated via diet, and is the inactive precursor of 1α,25-dihydroxyvitamin D3 (calcitriol), a major pleiotropic hormone in the human organism. By binding and activation of vitamin D receptor (VDR), a member of the superfamily of nuclear receptors, calcitriol regulates the expression of hundreds of genes in a tissue- and cell-type specific manner by transcriptional and posttranscriptional mechanisms.

Human WNT factors are a family of 19 members of secreted proteins that regulate crucial processes in many tissues and organs during development and adult life. Some (canonical) WNTs act by modulating the transcriptional activity of β-catenin whereas other (non-canonical) WNTs affect different signal transducers (Ca2+, Rho, JNK...) independently of β-catenin.

Colorectal cancer (CRC) is one of the most important neoplasias worldwide in terms of incidence and mortality. The key role of the constitutive activation of the WNT/β-catenin signaling pathway promoting CRC and the protective effect of VDR agonists, in part by antagonizing the WNT/β-catenin pathway, have been widely described. However, the effects of calcitriol and canonical WNTs on stromal fibroblasts, which are important players in CRC with protumorigenic action, remain mostly unknown.

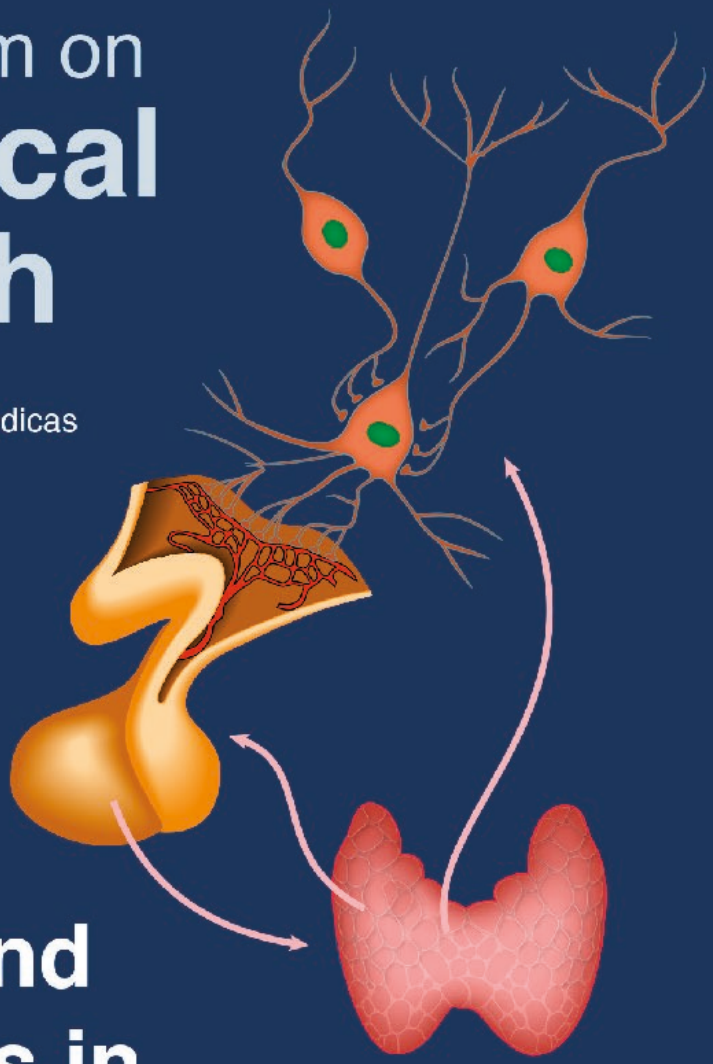
We have studied the effect of calcitriol and WNT3A on the human CCD-18Co colonic fibroblast cell line and on primary colon fibroblasts isolated from CRC patients. Data from global transcriptomic analyses by RNA-sequencing and also functional assays indicate that calcitriol and WNT3A exert a wide regulatory action on the gene expression and phenotype of colonic fibroblasts. Remarkably, a complex interplay exists between the two agents: while calcitriol and WNT3A act cooperatively in some effects, antagonistic actions are found in others.

Our results show that calcitriol and WNT3A are important modulators of human colon fibroblasts, with potential implications in colon homeostasis and neoplastic transformation.

Keywords: Calcitriol, vitamin D, WNT, colon fibroblasts, colorectal cancer

Published: May, 2019.
Copyright: © 2019 Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.
Cite as: Ferrer-Mayorga G., Niell N., Cantero R., González-Sancho J.M., Del Peso L., Muñoz A. & Larriba MJ., Gene regulatory and phenotypic effects of calcitriol and canonical WNT in human colon fibroblasts. IBJ Plus 2019 S(3):e0051 doi: 10.24217/2531-0151.19v1s3.00051.
Funding: Ministerio de Ciencia, Innovación y Universidades (SAF2016-76377-R, Nurcamein2) and Instituto de Salud Carlos III (CIBERONC) of Spain - Fondo Europeo de Desarrollo Regional.
Competing Interests: The authors declare that no competing interests exist.

6th Symposium on Biomedical Research



Instituto de Investigaciones Biomédicas
"Alberto Sols" CSIC-UAM
Facultad de Medicina UAM

May 31, 2019

Aula Magna, School of Medicine
Universidad Autónoma de Madrid
C/ Arzobispo Morcillo, 4
28029 Madrid, Spain

Advances and Perspectives in Molecular Endocrinology

"In Homage to Gabriella Morreale"

INVITED SPEAKERS

Antonio Castrillo
Luis de Lecea
Mónica Marazuela
Marco Medici
Ángel Nadal
Pilar Santisteban
Manuel Tena-Sempere
Antonio Vidal-Puig

Contact: 6sbr.endocrinology@gmail.com
Certified with 1 ECTS
https://eventos.uam.es/28633/detail/6th-symposium-on-biomedical-reserch-advances-and-perspectives-in-molecular-endocrinology.html