II YOUNG INVESTIGATORS SYMPOSIUM

October 20-21, online

MINISTERIO DE CIENCIA E INNOVACIÓN
Instituto de Salud Carlos III
Unión Europea
Fondo Europeo de Desarrollo Regional
"Una manera de hacer Europa"

Organizing Committee:

Maria Insenser

Eduard Montanya

Angel Nadal

Oscar Osorio

Izortze Santin

II YOUNG INVESTIGATORS SYMPOSIUM

Wednesday, October 20th

17:00-17:05 **WELCOME**

Eduard Montanya
Scientific Director, CIBERDEM

Angel Nadal
Training Program Coordinator, CIBERDEM

17:05-18:00 KEYNOTE LECTURE

The human Pancreas in Type 1 Diabetes: A Journey through Space and Time

Teresa Rodriguez-Calvo, Junior Group Leader. Institute of Diabetes Research (IDF). Helmholtz Zentrum Munich

18:00- 20:00 **SESSION 1**

Chairs:

Ana Isabel Rojas
Centro Andaluz de Biología Molecular y Medicina Regenerativa (CABIMER), Universidad Pablo de Olavide (Sevilla)

Ainara Castellanos
Asociación Instituto de Investigación Sanitaria de Biocruces (Barakaldo)

18:00 Translational metabolomics in diabetes research: how far are we?

María Vinaixa
Institut d'Investigació Sanitària Pere Virgili (IISPV), Metabolomics Platform (Reus)

18:30 An inter-organ crosstalk mediates the therapeutic effect of a dual GLP-1/glucagon receptor agonist in diet-induced obesity

Pilar Valdecantos
Instituto de Investigaciones Biomédicas Alberto Sols, CSIC-UAM (Madrid)

19:00 Biomarkers for incident type 2 diabetes and related metabolic diseases in the Di@bet.es

Sara García Serrano
Instituto de Investigación Biomédica de Málaga (IBIMA), UGC Endocrinología y Nutrición. Hospital Regional Universitario de Málaga (Málaga)

19:30 Exosomal miRNAs in the diagnosis and treatment of Type 2 Diabetes

Carlos Castaño
Instituto de Investigaciones Biomédicas August Pi i Sunyer (IDIBAPS) (Barcelona)

Thursday October 21st

17:00 -19:05 **SESSION 2**

Chairs:

Herminia González
Fundación Centro de Investigación Príncipe Felipe (Valencia)

Clara Meana
Instituto de Biología y Genética Molecular, Consejo Superior de Investigaciones Científicas (CSIC), Universidad de Valladolid (Valladolid)

17:00 Identification of new therapeutic targets for the treatment of type 1 diabetes based on the survival strategies of pancreatic alpha cells

Laura Marroquí
Instituto de Investigación, Desarrollo e Innovación en Biotecnología Sanitaria de Elche (IDiBE), Universidad Miguel Hernández de Elche (Elche)

17:30 Hypothalamic deficiency of Alx3 in the arcuate nucleus correlates with altered body composition and muscle weakness

Mercedes Mirasierra
Instituto de Investigaciones Biomédicas Alberto Sols (CSIC/UAM) (Madrid)

18:00 Hyperactivation of mTORC1, aging and pancreatic β cells

Carlos Guillén
Diabetes and Obesity Group, Biochemistry and Molecular Biology Department; Pharmacy School, UCM (Madrid)

18:30 Unveiling the role of the Fatty Acid Binding Protein 4 in the non-alcoholic fatty liver disease

Ricardo Rodríguez-Calvo
Fundación Instituto de Investigación Sanitaria Pere Virgili, Universitat Rovira i Virgili (Reus)

19:00-19:05 **CLOSING REMARKS**

ABSTRACTS

SESSION 1: Wednesday, October 20th

Translational metabolomics in diabetes research: how far are we?

Maria Vinaixa

Metabolomics Interdisciplinary Laboratory (MIL@b), Institut d'Investigació Sanitària Pere Virgili (IISPV), Reus (Tarragona)

It is being more than two decades now since the term metabolomics was first coined. Metabolomics popularity and applicability has increased ever since. Initially, the focus of metabolomics was mainly on biomarkers discovery with diagnostic or prognostic markers of pre-diabetes or early T2DMbeing proposed so far. However, these markers have not yet made their way to the clinical practice. Here we will discuss the practical needs to be addressed to move forward discovery-based studies to the clinics. On the other hand, gaining mechanistic insights is another major asset of discovery-based metabolomics studies. Tracking the metabolic fate through different pathways using isotope stable tracers has become a particularly well-suited approach to this end. We will illustrate and discuss our latest development in such methodologies and their applications to diabetes research.

An inter-organ crosstalk mediates the therapeutic effect of a dual GLP-1/glucagon receptor agonist in diet-induced obesity.

Pilar Valdecantos

Instituto de Investigaciones Biomédicas Alberto Sols, CSIC-UAM (Madrid)

Bariatric surgery is an effective surgery for treatment of obesity and type 2 diabetes mellitus remission and pharmacological approaches which exert similar metabolic adaptations are needed. This study addresses how G49, an oxyntomodulin (OXM) analog and dual glucagon/GLP-1 receptor (GCGR/GLP-1R) agonist, initiates a metabolic rewiring, the target tissues involved, and the specific contribution of each receptor to body weight loss. We demonstrated that G49 triggers an inter-organ crosstalk between adipose tissues (WAT and BAT), pancreas, and liver initiated by a rapid release of free fatty acids by epididymal WAT in a GCGR-dependent manner. This interactome leads to elevations in adiponectin and FGF21, resulting in WAT beiging, BAT activation, increased energy expenditure and body weight loss. Elevation of the native dual agonist OXM under basal and post-meal test and similar metabolic adaptations were found in plasma from obese patients at an early stage after metabolic bariatric surgery. In conclusion, obesity treatment with G49 represents a potential pharmacological alternative to bariatric surgery.

Biomarkers for incident type 2 diabetes and related metabolic diseases in the Di@bet.es study.

Sara García Serrano
Instituto de Investigación Biomédica de Málaga (IBIMA), UGC Endocrinología y Nutrición. Hospital Regional Universitario de Málaga (Málaga), (CIBERDEM), (Madrid)

Several evidences indicate that metabolic disorders, including type 2 diabetes (T2DM), obesity, or non-alcohol fatty liver disease, are the leading cause of disability and death. The pathogenesis of these metabolic disorders and their chronic complications involves multiple biological pathways and is largely unknown. In view of the high incidence of T2DM and related metabolic diseases, the identification of early diagnostic/therapeutic markers has become an urgent objective.

The Di@bet.es study is a national epidemiological study designed to determine the prevalence and incidence of diabetes, obesity and other cardiovascular risk factors in Spain. The first phase of the study comprised 5072 persons in 100 clusters (health centers or their equivalents). The participation was 57%, and data were gathered the following: clinical and demographic characteristics and lifestyle survey, physical examination and oral-glucose tolerance test. Collection of serum, urine and DNA samples from each individual have been stored. A follow-up examination of the cohort was completed in 2015-2017.

In the present lecture, we will discuss some of the latest results of the study, with a focus on new projects testing the association of VEGFb, miRNAs and nutrition with the incidence of glucose metabolism related disorders.

Exosomal miRNAs in the diagnosis and treatment of Type 2 Diabetes

Carlos Castaño
Instituto de Investigaciones Biomédicas August Pi i Sunyer (IDIBAPS) (Barcelona)

Maintenance of metabolic homeostasis requires the coordinated action of many tissues, and may be disturbed under physiological or pathological contexts. It has recently been shown that release of exosomes enriched in miRNAs is a novel form of cell communication. Interestingly, there is a reciprocal relationship between exosomal miRNAs and metabolic homeostasis, so that the metabolic context influences the pattern of exosomal miRNAs, and these then modify the function of acceptor cells, either favoring or delaying the onset and progression of metabolic disease. Hence, we have been exploring the role of exosomal miRNAs as both novel informative biomarkers in humans and therapeutic targets in mice.

In particular, we have shown that the profile of exosomal miRNAs can be used as biomarker to monitor the progression of Type 2 Diabetes. Moreover, using an animal model of glucose intolerance, we have demonstrated that obesity-associated exosomal miRNAs are active players in the first stages of the metabolic syndrome. On the other hand, we also show that exercise triggers the release of exosomes by the muscle, carrying a specific miRNA signature that induces gene expression changes in the liver, leading to improved insulin sensitivity.

The study of the influence of exosomal miRNAs in metabolic homeostasis might provide us with a deeper knowledge of the mechanisms driving metabolic dysfunction, ultimately leading to the development of novel and more effective therapeutic approaches.

SESSION 2: Thursday, October 21st

Identification of new therapeutic targets for the treatment of type 1 diabetes based on the survival strategies of pancreatic alpha cells

Laura Marroqui, Athenea Pérez-Serna, Regla Maria Medina-Gali, Reinaldo S. dos Santos

Instituto de Investigación, Desarrollo e Innovación en Biotecnología Sanitaria de Elche (IDiBE) and CIBERDEM, Universidad Miguel Hernández de Elche, (Elche)

Background and aims: Type 1 diabetes is an autoimmune disease characterized by progressive beta cell loss. During type 1 diabetes progression, both pancreatic alpha and beta cells are exposed to the same stressors, such as proinflammatory cytokines (e.g. IL-1β, IFN-γ, and TNFα), but only alpha cells survive to this environment. Of note, the mechanisms underlying this alpha cell resistance are yet to be clarified. In the present study we sought to identify proteins highly expressed in alpha cells that could protect alpha cells against proinflammatory cytokines.

Materials and methods: An unbiased bioinformatics analysis was performed using mouse or human RNA sequencing data from purified alpha and beta cells obtained from four different studies. Candidate genes were selected based on the following selection criteria: 1) mean expression (RPKM) ≥ two; 2) expression in alpha cells ≥ 2-fold the expression in beta cells; 3) the gene should be expressed in all samples; 4) the gene should be confirmed in the four selected RNA sequencing data. mRNA expression was measured in FACS-purified rat alpha and beta cells as well as in alphaTC1-9 and MIN-6 cell lines by quantitative RT-PCR. Small interfering RNAs (inhibition of >50%) were used to inhibit gene expression. Cell viability was evaluated by Hoechst/Propidium iodide staining.

Results: Twenty-five candidate genes met the established selection criteria; from these 25 genes, four genes were selected based on their known functions, namely *Itpr1* (Inositol 1,4,5-trisphosphate receptor type 1), *Pdk4* (Pyruvate dehydrogenase kinase 4), *Vim* (Vimentin), and *Ttr* (Transthyretin). In FACS-purified rat cells, all four genes presented higher mRNA expression in alpha cells than in beta cells (8- to 266-fold change; n=4-7; $p<0.05$). In cell lines, *Itpr1*, *Pdk4*, and *Vim* expression was higher in alphaTC1-9 than in MIN-6 cells (n=6-12; $p<0.05$), whereas *Ttr* expression was lower in alphaTC1-9 than in MIN-6 cells (n=7-12; $p<0.05$). Interestingly, silencing of *Itpr1*, *Pdk4*, *Vim*, or *Ttr* exacerbated apoptosis under basal condition in alphaTC1-9 cells (1.5- to 3-fold increase; n=3-8, $p<0.05$). Upon exposure to the cytokines IL-1β + IFNγ, a similar increase in apoptosis was still observed.

Conclusions: These findings suggest that our bioinformatics analysis is a valid approach for the identification of genes that may play important roles in alpha cell survival during the development of type 1 diabetes.

This project has received support from by Generalitat Valenciana (fondos SEJI/2018/023).

Hypothalamic deficiency of Alx3 in the arcuate nucleus correlates with altered body composition and muscle weakness.

Mercedes Mirasierra

Instituto de Investigaciones Biomédicas Alberto Sols (CSIC/UAM), (Madrid)

The arcuate nucleus constitutes a primary site for the regulation of systemic metabolic homeostasis by controlling food intake and regulating energy expenditure. Defects in *Pomc*-expressing neurons in this nucleus result in altered body mass composition and obesity. We have previously shown that in pancreatic islets Alx3 coordinately regulates glucose-dependent expression of the insulin and glucagon genes. Here, we found that *Alx3* is expressed in the arcuate nucleus and that Alx3-deficiency results in systemic metabolic alterations independent of its function in pancreatic islets that indicate an important regulatory role in the hypothalamus.

Here we report that, despite reduced feeding, Alx3-deficient mice show no differences in body weight gain relative to wild type controls. Indirect calorimetry showed reduced energy expenditure and respiratory exchange ratio. In wild type animals, Alx3 was present in Pomc-Cart and NPY-AgRP neurons in the arcuate nucleus, but not in major metabolic peripheral organs including liver, adipose tissue and muscle. Arcuate nucleus response to fasting was altered in the absence of Alx3. Pomc-Cart mRNA levels in fed or fasted animals, responses to refeeding and expression of the MC3R aMSH receptor in the arcuate nucleus were altered in Alx3-deficient mice. Alx3-deficiency was associated with increased adiposity, decreased lean mass and impaired muscle and motor function. This correlated with markers of decreased motor and sympathetic innervation to muscles.

In conclusion our study identifies Alx3 in the arcuate nucleus as a novel factor regulating energy homeostasis and metabolic nutrient partitioning affecting body mass composition.

Hyperactivation of mTORC1, aging and pancreatic β cells

Carlos Guillén

Diabetes and Obesity Group, Biochemistry and Molecular Biology Department; Pharmacy School, UCM. (Madrid)

Type 2 Diabetes Mellitus (T2DM) is a complicated disorder representing a global epidemic related to other metabolic alterations, including obesity, defining the metabolic syndrome. T2DM is a progressive disease initially developing an insulin resistant, with a manifest pancreatic beta islets hyperplasia and hyperinsulinemia. Finally, pancreatic β cells fails in their capacity to compensate, and a decreased in cell number by apoptosis in the late stage of the disease is also observed. During the progression to T2DM there is a chronic activation of mTORC1 signaling pathway, which induces aging and acts as an endogenous inhibitor of autophagy. The complex 1 of mTOR (mTORC1) controls cell proliferation, cell growth as well as metabolism in a variety of cell types through a complex signaling network. Autophagy is involved in the recycling of cellular components for energy generation under nutrient deprivation, and serves as a complementary degradation system to the ubiquitin-proteasome pathway. Autophagy represents a protective mechanism for different cell types, including pancreatic β cells, and potentiates β cell survival across the progression to T2DM. Then, we have used both in vitro as well as in vivo approaches for trying to understand this complexity in the progression to T2DM.

Unveiling the role of the Fatty Acid Binding Protein 4 in the non-alcoholic fatty liver disease

Ricardo Rodríguez-Calvo

Fundación Instituto de Investigacion Sanitaria Pere Virgili, Universitat Rovira i Virgili (Reus)

Non-alcoholic fatty liver disease (NAFLD), the main cause of chronic liver disease worldwide, is a progressive disease ranging from non-alcoholic fatty liver (NAFL) to the non-alcoholic steatohepatitis (NASH). Nevertheless, it remains underdiagnosed due to the lack of effective non-invasive methods for its diagnosis and staging. Although NAFLD has been found in lean individuals, it is closely associated with obesity-related conditions. Adipose tissue is the main source of liver triglycerides and adipocytes act as endocrine organs releasing to bloodstream a large number of adipokines and pro-inflammatory mediators involved in the NAFLD progression. Among the adipocyte-derived molecules, the fatty acid binding protein 4 (FABP4) has been recently associated to fatty liver and additional features of advanced stages of NAFLD. Additionally, emerging data from preclinical studies propose FABP4 as a causal actor involved in the disease progression, rather than a mere biomarker for the disease. Therefore, the FABP4 regulation could be considered as a potential therapeutic strategy to NAFLD.

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