11th CIBERDEM ANNUAL MEETING

November 3-5, 2020

On-line

https://reunionanual.ciberdem.org/

Final programme

TUESDAY, NOVEMBER 3, 2020

16:00-16:10 OPENING AND WELCOME

Eduard Montanya, Scientific Director

16:10-18:00 SESSION 1

Chair: Josep Ribalta
Universitat Rovira i Virgili, IISPV, Tarragona

Olga Simó-Servat
Hospital Vall d'Hebron, Vall d'Hebron Research Institute (VHIR), Barcelona

16:10-16:40 STATE OF THE ART LECTURE

Favorable effects of nicotinamide supplementation on adiposity and inflammation in mice
Josep Julve
Instituto de Investigación del Hospital de la Santa Cruz y San Pablo, Barcelona

16:40-18:00 ORAL PRESENTATIONS

16:40 OP1 Lack of beneficial effect of iron tissue depletion on metabolic outcomes in women with polycystic ovary syndrome or idiopathic hyperandrogenism on standard treatment with combined oral contraceptives. A randomized clinical trial
Andrés Eduardo Ortiz-Flores[1], Mª Angeles Martínez-García[1,2], Lia Nattero-Chávez[1,2,3], Elena Fernández-Durán[1,2], Quintero-Tobar, A.[1,2] Héctor F. Escobar-Morreale[1,2,3], Manuel Luque-Ramírez M[1,2,3]
[1] Diabetes, Obesity, and Human Reproduction Research Group, Instituto Ramón y Cajal de Investigación Sanitaria, CIBERDEM; [2] Department of Endocrinology and Nutrition, Hospital Universitario Ramón y Cajal, Madrid; [3] University of Alcalá, Alcalá de Henares, Madrid

16:55 OP2 Relationship between serum vascular endothelium growth factor b levels and the development of metabolic syndrome in the Di@bet.es study
Eva García-Escobar[1,2], Ana Lago-Sampedro[1,2], Sergio Valdés[1,2], Natalia Colomo[1,2], Cristina Maldonado[1,2], Luis Castaño [1], Javier Chaves[1], Alfonso Calle1, Josep Franch[1], Elías Delgado[1], Federico Soriguer[3], Gemma Rojo-Martínez[1,2], Sara García-Serrano[1,2]
[1]CIBERDEM; [2]Biomedical Research Institute of Malaga (IBIMA), Endocrinology and Nutrition Department, Regional University Hospital of Malaga, Malaga; [3]Science Academy of Malaga, Málaga

17:10 OP3 Effects of Glucagon-like peptide-1 (GLP-1) in Diabetes-Induced Retinal Abnormalities: Involvement of Oxidative Stress
Hugo Ramos[1,2], Cristina Hernández C[1,2,3], Joel Sampedro [1], Jordi Huerta[1,2], Rafael Simó[1,2,3]* Patricia Bogdanov[1,2]*
[1]Diabetes and Metabolism Research Unit, Vall d'Hebron Research Institute, Barcelona; [2]CIBERDEM; [3]Department of Medicine, Universitat Autònoma de Barcelona

17:25 OP4 Subclinical macular edema and diabetic retinopathy: two entities evolving in parallel?
Olga Simó-Servat[1], Efraín Cordero-Vázquez[1], Alejandra Planas[1], Marc Ribas[1], Eva Sanz[1], Helena Brossa[2], José García-Arumí[2], Cristina Hernández[1], Rafael Simó[1]
[1]Endocrinology Department, Vall d'Hebron Hospital; Diabetes and Metabolism Unit, Vall d'Hebron Research Institute (VHIR); [2]Ophtalmology Department, Vall d'Hebron Hospital, Barcelona

17:40 OP5 Seasonal Stochastic Local Modelling: a new framework for accuracy improvement of glucose prediction in type 1 diabetes

Eslam Montaser[1], José Luis Díez[1,2], Jorge Bondia[1,2]
[1]Universitat Politècnica de València, València; [2]CIBERDEM

18:15-19:20 SESSION 2 – RAPID COMUNICATIONS

ROOM 1

Chair: Héctor Escobar
Hospital Universitario Ramón y Cajal, Universidad de Alcalá, Instituto Ramón y Cajal de Investigación Sanitaria IRYCIS, Madrid

Laura Piqueras
Institute of Health Research-INCLIVA, University of Valencia, Valencia

18:15 RC1 Influence of obesity and sex hormones on surrogate markers of gut permeability after glucose, lipid and protein oral challenges

Mª Ángeles Martínez-García, María Insenser, Alejandra Quintero-Tobar, Elena-Fernández-Durán, Manuel Luque-Ramírez, Héctor F. Escobar-Morreale.
Diabetes, Obesity and Human Reproduction Research Group, Department of Endocrinology & Nutrition, Hospital Universitario Ramón y Cajal, Universidad de Alcalá, Instituto Ramón y Cajal de Investigación Sanitaria IRYCIS, CIBERDEM, Madrid

18:22 RC2 Acute-phase glycoprotein profile responses to different 1 oral macronutrient challenges: Influence of sex, functional hyperandrogenism and obesity.

Samuel Moncayo, María Insenser, M. Ángeles Martínez-García, Rocío Fuertes-Martín, Núria Amigó-Grau, Francisco Álvarez-Blasco, Manuel Luque-Ramírez, Xavier Correig-Blanchar, Héctor F. Escobar-Morreale
Diabetes, Obesity and Human Reproduction Research Group, Hospital Universitario Ramón y Cajal & Universidad de Alcalá & Instituto Ramón y Cajal de Investigación Sanitaria IRYCIS & CIBERDEM, Madrid. BiosferTeslab SL; Universitat Rovira i Virgili, IISPV; CIBERDEM, Reus. Metabolomics platform, DEEEA-Universitat Rovira i Virgili, IISPV; CIBERDEM, Tarragona.

18:29 RC3 Gut Microbiota in Non-Obese Adolescent Girls with Polycystic Ovary Syndrome: Effects of Randomized Treatments

Cristina Garcia-Beltran[1,2], Rita Malpique[1,2], Belen Carbonetto[3], Pedro González-Torres[3], Desirée Henares[4,5], Pedro Brotons[4,5,6], Carmen Muñoz-Almagro[4,5,6], Abel López-Bermejo[7], Francis de Zegher[8], Lourdes Ibáñez[1,2]
[1] Endocrinology Department, Pediatric Research Institute Hospital Sant Joan de Déu, University of Barcelona, Esplugues, Barcelona; [2] CIBERDEM; [3] Microomics Systems S.L., Barcelona Biomedical Research Park (PRBB), Barcelona; [4] Molecular Microbiology Department, Pediatric Research Institute Hospital Sant Joan de Déu, Esplugues, Barcelona; [5] CIBERESP; [6] School of Medicine, Universitat Internacional de Catalunya, Barcelona; [7] Pediatric Endocrinology Research Group, Girona Institute for Biomedical Research (IDIBGI) and Dr. Josep Trueta Hospital, Girona, Spain; [8] Department of Development & Regeneration, University of Leuven, Leuven, Belgium

18:36 RC4 Upregulation of CCL22 is related to insulin resistance in morbidly obese subjects

Luisa Hueso[1,3], Rebeca Ortega[1,3], Esther Benito[1,2,5], Marta Peiró [1,5] Joaquín Ortega[4], Miguel Civera[1,2], Maria-Jesus Sanz[1,3,5], José T Real[1,2,5], Laura Piqueras[1,3,5]
[1]Institute of Health Research-INCLIVA, Valencia; [2]Endocrinology and Nutrition Service, University Clinic Hospital of Valencia, Valencia; [3]Department of Pharmacology, Faculty of Medicine, University of Valencia, Valencia; [4]Surgery Service, University Clinic Hospital of Valencia, Valencia; Department of Surgery, University of Valencia, Valencia; [5]CIBERDEM

18:43 RC5 Up-regulation of nuclear retinoid-related orphan receptor RORα in adipose tissue from diabetic obese patients.

Rebeca Ortega[1,3], Luisa Hueso[1,3], Esther Benito[1,2,5], Marta Peiró [1,5] Joaquín Ortega[4], Miguel Civera[1,2], Maria-Jesus Sanz[1,3,5], Laura Piqueras[1,3,5], José T Real[1,2,5]

[1]Institute of Health Research-INCLIVA, Valencia; [2]Endocrinology and Nutrition Service, University Clinic Hospital of Valencia, Valencia; [3]Department of Pharmacology, Faculty of Medicine, University of Valencia, Valencia; [4]Surgery Service, University Clinic Hospital of Valencia, Valencia, Spain; Department of Surgery, University of Valencia, Valencia; [5]CIBERDEM

18:50 RC6 Mediterranean Diet and healthy eating in subjects with prediabetes of the Mollerussa prospective cohort study, a semi-rural area

Mireia Falguera[1,2], Minerva Granado-Casas[3,5], Maria Belén Vilanova[2,4], Jordi Real[5,6], Neus Miró[7], Cristina Cebrian[8], Àngels Molló[9], Manel Mata-Cases[5,6,10], Josep Franch-Nadal[5,6,11], Esmeralda Castelblanco[6,12], Didac Mauricio[6,12,13]

[1]Primary Health Care Centre Cervera, Gerència d'Atenció Primaria, Institut Català de la Salut, Lleida; [2]Department of Medicine, University of Lleida & Biomedical Research Institute of Lleida (IRBLleida), Lleida; [3]Department of Endocrinology & Nutrition, University Hospital Germans Trias I Pujol & Health Sciences Research Institute, Badalona; [4]Primary Health Care Centre Igualada Nord, Gerència d'Atenció Primaria, Institut Català de la Salut, Lleida; [5]DAP-Cat Group, Unitat de Suport a la Recerca Barcelona, Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona; [6]CIBERDEM, Barcelona; [7]Primary Health Care Centre Tàrrega, Gerència d'Atenció Primaria, Institut Català de la Salut, Lleida; [8]Primary Health Care Centre Mollerussa, Gerència d'Atenció Primaria, Institut Català de la Salut, Lleida; [9]Primary Health Care Centre Guissona, Gerència d'Atenció Primaria, Institut Català de la Salut, Lleida; [10]Primary Health Care Centre La Mina, Gerència d'Atenció Primària Barcelona, Institut Català de la Salut, Barcelona; [11]Primary Health Care Centre Raval Sud, Gerència d'Atenció Primaria Barcelona, Institut Català de la Salut, Barcelona; [12]Department of Endocrinology & Nutrition, Hospital de la Santa Creu i Sant Pau & Institut d'Investigació Biomédica Sant Pau (IIB Sant Pau),Barcelona;[13] Faculty of Medicine, University of Vic (UVIC/UCC), Vic

18:57 RC7 Fatty Acid Binding Protein 4 is associated with Fatty Liver in metabolic patients

Ricardo Rodríguez-Calvo, Juan Moreno, Josefa Girona, Daiana Ibarretxe, Neus Martínez-Micaelo, Nuria Plana, Lluís Masana

Vascular Medicine and Metabolism Unit, Research Unit on Lipids and Atherosclerosis, "Sant Joan" University Hospital, Universitat Rovira i Virgili, Institut de Investigació Sanitaria Pere Virgili (IISPV), Reus; CIBERDEM

19:04 RC8 Atherogenic dyslipidemia, but not hyperglycemia, is an independent risk factor for liver fibrosis in subjects with type 2 diabetes mellitus and NAFLD: A population –based study

Nuria Alonso[1,4,7], María Teresa Julián[1], Guillem Pera[2,3], Berta Soldevila[1,4], Llorenç Caballería[2,3], Josep Julve[5,6,7], Carlos Puig[1], Rosa Morillas[3,8], Pere Torán[2,3], Carmen Expósito[2,3], Manel Puig-Domingo[1,4,7], Esmeralda Castelblanco[5,7], Josep Franch-Nadal[7,9]Dídac Mauricio[5,7,10]

[1]Department of Endocrinology and Nutrition Department, Hospital Germans Trias I Pujol, Badalona, Barcelona; [2]Unitat de Suport a la Recerca Metropolitana Nord, Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Mataró; [3]CIBEREHD, Barcelona; [4]Department of Medicine, Autonomous University of Barcelona (UAB), Barcelona; [5]Hospital de la Santa Creu i Sant Pau, & Institut d'Investigació Biomèdica Sant Pau (IIB Sant Pau), Barcelona; [6]Departament de Bioquímica y Biología Molecular, Universitat Autònoma de Barcelona, Barcelona; [7]CIBERDEM; [8]Hepatology Department, Hospital Germans Trias I Pujol, Badalona, Barcelona; [9]Primary Health Care Center Raval Sud, Gerència d'Atenció Primaria, Institut Català de la Salut, Barcelona; [10]Department of Endocrinology and Nutrition, Hospital de la Santa Creu i Sant Pau; Institut d'Investigació Biomédica Sant Pau (IIB Sant Pau), Barcelona

19:11 RC9 Differential DNA Methylation Profile in Infants Born Small-for-Gestational-Age: Association with Markers of Adiposity and Insulin Resistance from Birth to Age 24 Months

Marta Díaz[1,2], Edurne Garde[1,2], Abel López-Bermejo[3], Francis de Zegher[4], Lourdes Ibáñez[1,2]

[1]Institut Pediàtric Hospital Sant Joan de Déu, University of Barcelona, Esplugues, Barcelona; [2]CIBERDEM; [3]Department of Pediatrics, Dr. Josep Trueta Hospital, Girona, and Girona Institute for Biomedical Research, Girona; [4]Department of Development & Regeneration, University of Leuven, Belgium

18:15-19:20 SESSION 2– RAPID COMUNICATIONS

ROOM 2

Chair: Marcelina Parrizas
IDIBAPS, Barcelona

Sonia Fernández-Veledo
Hospital Universitario de Tarragona Joan XXIII, Instituto de Investigación Sanitaria Pere Virgili, Tarragona

18:15 RC10 miR-155 influences diabetic kidney disease by regulating SOCS1

Ignacio Prieto[1], Luna Jiménez-Castilla[1], Iolanda Lázaro[2], Laura López-Sanz[1], Susana Bernal-Uribe[1], Mónica Flores-Muñoz[3], Óscar López-Franco[3], Jesús Egido[1], Carmen Gómez-Guerrero[1]

[1]Renal, Vascular and Diabetes Research Lab, Instituto de Investigaciones Sanitarias-Fundación Jiménez Díaz (IIS-FJD), Universidad Autónoma de Madrid (UAM) and CIBERDEM; [2] Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS) and CIBEROBN; [3] Instituto de Ciencias de la Salud, Universidad Veracruzana, Xalapa, Veracruz, México

18:22 RC12 mTOR activation in diabetic and hypertensive cardiomyopathy

Tianyu Hang, Sagrario Corrales, Mikel Azkargorta, Malu Martínez-Chantar M, Jairo Lumpuy-Castillo, Jesus Egido, Oscar Lorenzo

IIS-Fundación Jiménez Díaz, UAM, Madrid; CIC-BioGune

18:29 RC13 Vitamin D Receptor overexpression prevents high fat diet-induced body weight gain and ameliorates insulin resistance

Laia Vilà[1,3], Albert Ribera[1,2,3], Sylvie Franckhauser[1,3], Tura Ferré[1,3], Meritxell Morró[1,2,3], Ignasi Grass[1,2,3], Maria Luisa Jaen[1,2,3], Gemma Elias[1,2,3], Estefanía Casana[1,2,3], Fàtima Bosch[1,2,3], Alba Casellas[1,3]

[1]Center of Animal Biotechnology and Gene Therapy; [2]Department of Biochemistry and Molecular Biology, Universitat Autònoma de Barcelona, Bellaterra; [3]CIBERDEM

18:36 RC14 Extra virgin olive oil reduced weight gain and improved insulin sensitivity in high fat diet-induced obese LDLr-/-.Leiden mice but did not attenuate steatohepatitis

Leticia Álvarez-Amor[1,2], Amparo Luque Sierra[1], Antonio Cárdenas[1,2], Eloísa Andújar[1], Mónica Pérez-Alegre[1], Rocío Gallego-Durán[3,4], Alejandro Martin-Montalvo[1], Genoveva Berná[1,2], Anabel Rojas[1,2], Abdelkrim Hmadcha[1,2], Robert Kleemann[5], Manuel Romero-Gómez[3,4], Franz Martín[1,2]

[1]CABIMER-UPO, Seville; [2]CIBERDEM; [3]Hospital Universitario Virgen del Rocío-IBiS, Seville; [4]CIBEREHD; [5]Department of Metabolic Health Research, Netherlands Organisation for Applied Scientific Research-TNO, Leiden, Netherlands; [6]Department of Vascular Surgery, Leiden University Medical Centre, Leiden, Netherlands

18:43 RC15 Bace2 deficiency exacerbate body weight gain and hyperinsulinemia in mice fed a high fat diet

Daniela Díaz-Catalán[1], Gema Alcarraz-Vizán[1], Carlos Castaño[1], Mario Vallejo[2], Marcelina Párrizas[1], Joan Marc Servitja[1] and Anna Novials[1]

[1] Diabetes and Obesity Research Laboratory. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), CIBERDEM; [2]Instituto de Investigaciones Biomédicas Alberto Sols, Consejo Superior de Investigaciones Científicas/Universidad Autónoma de Madrid, CIBERDEM

18:50 RC16 The inhibition of ATP-citrate lyase protects from non-alcoholic fatty liver disease in a model of high fat diet feeding

Alejandro Sola-García[1], Manuel Aguilar-Diosdado[2], Maria Ángeles Cáliz-Molina[1], Vivian Capilla-González[1], Franz Martin[1,3,4], Benoit R. Gauthier[1,3], Alejandro Martín-Montalvo[1]

[1] Andalusian Center for Molecular Biology and Regenerative Medicine-CABIMER, Junta de Andalucia-University of Pablo de Olavide-University of Seville-CSIC, Seville; [2] Department of Endocrinology, Puerta del Mar Hospital Cádiz/ Department of Medicine, University of Cádiz; [3] CIBERDEM; [4] Department of Molecular Biology and Biochemistry Engineering, University Pablo de Olavide (UPO), Seville

18:57 RC17 Characterization and study of Goblet cells involved in mucus layer secretion in a rat model of metabolic syndrome associated to catch-up growth

Paula Martínez Oca[1,2]; Tamara Fernández Marcelo[1,2]; Alicia Sánchez Roncero[1,2]; María Ángeles Martín[2,3]; Fernando Escrivá[1,2]; Elisa Fernández Millán[1,2]; Carmen Álvarez Escolá[1,2]

[1] Department of Biochemistry and Molecular Biology, Faculty of Pharmacy, Complutense University of Madrid; [2] CIBERDEM; [3] Department of Metabolism and Nutrition, Institute of Food Science and Technology and Nutrition (ICTAN), Consejo Superior de Investigaciones Científicas (CSIC), Madrid

19:04 RC18 PTP1B deficiency protects male mice against insulin resistance but not thermogenic alterations upon Olanzapine intraperitoneal treatment

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

[1]IIBm Alberto Sols (CSIC-UAM), Madrid; [2]CIBERDEM

WEDNESDAY, NOVEMBER 4, 2020

14:45-15:45 SIMPOSIO SATÉLITE CIBERDEM/MSD 2020

Bienvenida Eduard Montanya
Servicio de Endocrinología y Nutrición, Hospital Universitario de Bellvitge, Barcelona
Director Científico CIBERDEM

Moderador Javier Escalada
Jefe de servicio de Endocrinología, Clínica Universitaria de Navarra (CUN), Pamplona

Incidencia y regresión del síndrome metabólico en una muestra representativa de la población española: resultados de la cohorte del estudio di@bet.es
Nuria García de la Torre
Servicio de Endocrinología y Nutrición, Hospital Clínico Universitario San Carlos, Madrid, CIBERDEM

16:00-18:00 SESSION 3

Chair: Deborah Burks
Centro de Investigación Príncipe Felipe, Valencia

Ivan Quesada
Instituto de Investigación, Desarrollo e Innovación en Biotecnología Sanitaria de Elche (IDiBE), Elche

16:00-16:30 STATE OF THE ART LECTURE

Circadian clocks and metabolic entrainment: Do the eyes talk to the liver?
Mario Vallejo
Instituto de Investigaciones Biomédicas Alberto Sols, CSIC, Madrid

16:30-17:45 ORAL PRESENTATIONS

16:30 OP6 Effects of aging on beta-cell mass and function
Eva Tudurí[1,2], Lucía Almagro[2], Sergi Soriano[2,3], Anabel García-Heredia[2], Ángel Nadal[1,2], Iván Quesada[1,2]
[1]CIBERDEM; [2]Instituto de Investigación, Desarrollo e Innovación en Biotecnología Sanitaria de Elche (IDiBE), Elche; [3]Departamento de Fisiología, Genética y Microbiología, Universidad de Alicante

16:45 OP7 Endoplasmic reticulum stress contributes to the loss of β-cell identity in human pancreatic islets treated with glibenclamide
Claudia Fernández[1,2,3], Noèlia Téllez[1,2,3], Víctor Gutiérrez[2], Kevin Rivera[2], Montserrat Nacher[1,2,4], Eduard Montanya[1,2,3,4]
[1]CIBERDEM; [2]Bellvitge Biomedical Research Institute, IDIBELL; [3]University of Barcelona; [4]Endocrine Unit, Hospital Universitari Bellvitge, Barcelona

17:00 OP8 LRH-1/NR5A2 Specifies BL001-Mediated β-cell Survival and Trans-Regeneration
Cobo-Vuilleumier, N[1], Martín-Vazquez, E[1], Lorenzo, PI[1], Irene Díaz-Contreras[1,2], Martín F[1,2], Gerdes, JM[3], Ferrer, J[4,2], Romero-Zerbo SY[5,2], García-Fernández M[6], Francisco Javier Bermúdez-Silva[5,2,] Gannon, M[7], Collombat, P[8], Benoit R Gauthier[1,2]
[1]Andalusian Center for Molecular Biology and Regenerative Medicine, Sevilla, [2]CIBERDEM; [3]Helmholtz Zentrum München, Neuherberg, Germany; [4]The Barcelona Institute of Science and Technology, Barcelona; [5]Instituto de Investigación Biomédica de Málaga-IBIMA, UGC Endocrinología y Nutrición. Hospital Regional Universitario de Málaga, Málaga; [6]Departamento de Fisiología, Facultad de Medicina, Universidad de Málaga, Málaga; [7]Vanderbilt University Medical Center, Nashville, TN, USA; [8]Nice Sophia Antipolis University, Nice, France

17:15 OP9 GPR40 mediated amplification of glucose-dependent insulin secretion requires expression of Alx3
Mercedes Mirasierra, Paula Nuevo-Gutierrez, Mario Vallejo
Instituto de Investigaciones Biomédicas Alberto Sols, CSIC/Universidad Autónoma de Madrid, CIBERDEM

17:30 OP10 Inhibition of insulin secretion by second-generation antipsychotics might mediate prediabetes development
Diana Grajales[1,2], Vázquez P[1,2], Ruíz-Rosario, M [3], Ferreira, V [1,2], Tudurí, E[2,4], Cigudosa, J[3], Quesada, I[2,4], Tirosh, B[5], Leibowitz, G[6], Valverde, ÁM[1,2]
[1]IIBm Alberto Sols (CSIC-UAM), Madrid; [2]CIBERDEM; [3]NIM Genetics, Madrid; [4]Instituto de Investigación, Desarrollo e Innovación en Biotecnología Sanitaria de Elche (IDiBE), Elche; [5]The Institute of Drug Research, School of Pharmacy, The Hebrew University of Jerusalem, Israel; [6]Endocrinology and Metabolism Service, Department of Medicine, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

18:00-19:05 SESSION 4 – RAPID COMUNICATIONS

ROOM 1

Chair: Patricia Rada
Instituto de Investigaciones Biomédicas Alberto Sols (CSIC-UAM), Madrid

Manuel Vázquez
University of Barcelona, Institute of Biomedicine of the University of Barcelona (IBUB), Research Institute-Hospital Sant Joan de Déu, Barcelona

18:00 RC19 Nuclear coactivator RAP250 modulates adiposity and the metabolic activity of brown adipose tissue

Manuela Sánchez-Feutrie[1,2,3]†, Sónia Rosa Veiga[1,2,3]†, Andrea Rodgers-Furones[1,2], Montserrat Romero[1,2,3], Alba Sabaté-Pérez[1,2,3], Luis Rodrigo Cataldo[1], Hans Burghardt[1,2,3], David Sebastián[1,2,3], Mònica Sabater-Masdeu[4,5], José María Moreno-Navarrete[4,5], Francisco Ortega[4,5], Wifredo Ricart[4,5], Natàlia Plana[1], Vanessa Hernández[1], Laura Isabel Alcaide[1], José Juan Marín [6], Manuel Palacín[1,2,7], Remy Burcelin[8], Joan Vendrell[9,10], José Manuel Fernández-Real[4,5], Per Antonson[11], Jan-Ake Gustafsson[11,12], Antonio Zorzano[1,2,3]

[1]Institute for Research in Biomedicine (IRB Barcelona), The Barcelona Institute of Science and Technology, Barcelona; [2] Departament de Bioquímica i Biomedicina Molecular, Facultat de Biologia, Universitat de Barcelona, [3] CIBERDEM; [4] CIBEROBN; [5] Department of Diabetes, Endocrinology and Nutrition, Institut d'Investigació Biomèdica de Girona (IdIBGi), Hospital of Girona 'Dr Josep Trueta', Girona; [6] Experimental Hepatology and Drug Targeting, CIBEREHD, IBSAL, University of Salamanca; [7] CIBERER; [8] UMR 5018 CNRS-UPS and IFR 31, Rangueil Hospital, L1 Bldg, BP 84225 Toulouse 31432 Cedex 4, France; [9] Department of Endocrinology, Hospital Joan XXIII, Rovira i Virgili University, Tarragona; [10] Institut d'Investigació Sanitaria Pere Virgili (IISPV), Tarragona; [11] Department of Biosciences and Nutrition, Karolinska Institutet, Novum, SE-141 83, Huddinge, Sweden; [12] Center for Nuclear Receptors and Cell Signaling, Department of Biology and Biochemistry, University of Houston, Houston, TX, USA; †MSF and SRV contributed equally

18:07 RC20 Role of Mfn-1 in brown adipose tissue during cold-challenge

Beatriz Jiménez, Gema García, Patricia Marqués, Jesús Burillo, Carlos González, Carlos Guillén, Manuel Benito

Diabetes and Obesity Group, Biochemistry and Molecular Biology Department; Pharmacy School, UCM, CIBERDEM

18:14 RC21 TP53INP2 regulates energy balance through brown adipose tissue thermogenesis

Alba Sabaté-Pérez[1,2,3], Montserrat Romero[1 2,3], Sam Virtue[4], Antonio Vidal-Puig[4,5], Xavier Testar[1,3], Antonio Zorzano[1,2,3]

[1]CIBERDEM, Barcelona; [2]Institute for Research in Biomedicine (IRB Barcelona), The Barcelona Institute of Science and Technology, Barcelona; [3]Departament of Biochemistry and Molecular Biomedicine, Faculty of Biology, University of Barcelona; [4]Metabolic Research Laboratories, Institute of Metabolic Science, Addenbrooke's Hospital, University of Cambridge, Cambridge, CB2 0QQ, UK; [5]Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, CB10 1SA, UK

18:21 RC22 Resveratrol enhanced cold-induced thermogenesis through a differential browning effect on the adipose organ in a mouse model showing atrophied interscapular adipose tissue: a therapeutic approach

Manuel Benito[1,2,3], Patricia Marqués[1], Helena Martínez[1], Beatriz Jiménez[1,2], Jesús Burillo[1,2,3], Carlos González[1], Gema García[1,2], Carlos Guillén[1,2,3]

[1]Department of Biochemistry and Molecular Biology, School of Pharmacy, Complutense University of Madrid; [2]CIBERDEM, [3]MOIR2: Mechanism of Insulin Resistance, General Direction of Universities and Investigation (CCMM), Madrid

18:28 RC23 Role of TP53INP2 in autophagy and apoptosis cross-talk

Saška Ivanova[1,2,3], Antonio Zorzano[1,2,3]

[1] Institute for Research in Biomedicine (IRB Barcelona), Barcelona Institute of Science and Technology (BIST), Barcelona; [2] CIBERDEM, Barcelona; [3] Departamento de Bioquimica i Biomedicina Molecular, Facultat de Biologia, Universitat de Barcelona

18:35 RC24 Mobilization of Arachidonic Acid and Adrenic Acid in Macrophages by Two Different Phospholipase A2s

Patricia Monge, Álvaro Garrido, María A. Balboa, Jesús Balsinde.

Instituto de Biología y Genética Molecular, Consejo Superior de Investigaciones Científicas (CSIC), Valladolid, CIBERDEM.

18:42 RC25 Role of the succinate/SUCNR1 axis in the physiopathology of NAFLD

Patricia Rada[1,2]*, Victoria Ceperuelo-Mallafré [2,3]*, Enrique Calvo [2,3], M. Mar Rodríguez [2,3], Catalina Núñez-Roa [2,3], Teresa Villanueva [2,3], Joan Vendrell [2,3], Ángela M. Valverde [1,2] and Sonia Fernández-Veledo [2,3]

[1] Instituto de Investigaciones Biomédicas "Alberto Sols" (CSIC-UAM), Madrid; [2] CIBERDEM; [3] Unitat de Recerca, Hospital Universitari de Tarragona Joan XXIII, Institut d´Investigació Sanitària Pere Virgili, Tarragona *Equal contributors

18:49 RC26 Inhibition of protein tyrosine phosphatase 1B protects against lipotoxicity in liver progenitor oval cells

Inés Barahona[1,2], M. Pilar Valdecantos[1,2], Patricia Rada[1,2], Alma Astudillo[2,3], Jesús Balsinde[2,3], Aránzazu Sánchez[4], Ángela M. Valverde[1,2]

[1]IIBm Alberto Sols (CSIC-UAM), Madrid, [2]CIBERDEM; [3]Instituto de Biología y Genética Molecular (CSIC-UVA), Valladolid; [4]Departamento de Bioquímica y Biología Molecular, UCM, Madrid

18:56 RC27 Effect of the hepatocyte-derived lipotoxic extracellular vesicles in liver inflammation in non-alcoholic fatty liver disease

Rosa Alén[1], Irma Garcia-Martinez[1], Laura Pereira[2], Jesús Balsinde[2], Manuel Izquierdo[1], Ángela M. Valverde[1].

[1]Instituto de Investigaciones Biomédicas Albero Sols, CSIC/UAM, Madrid; [2] Instituto de Biología y Genética Molecular, CSIC/UVa, Valladolid

18:00-19:05 SESSION 4 – RAPID COMUNICATIONS

ROOM 2

Chair: Sonia Gaztambide
Biocruces Bizkaia Health Research Institute, Cruces University Hospital, University of the Basque Country, Bizkaia

Oscar Lorenzo
IIS-Fundación Jiménez Díaz, UAM, Madrid; CIC-BioGune

18:00 RC28 Regular insulin added to total parenteral nutrition vs subcutaneous glargine in non-critically ill diabetic inpatients, a multicentre randomized clinical trial: INSUPAR trial

Cristina Maldonado-Araque[1,2,3], Jose Abuín[1,2], María J. Tapia[1], Rafael López[4], Sandra Herranz[5], Jose M. García-Almeida[6], Katherine García-Malpartida[7], Mercedes Ferrer[8], Emilia Cancer[9], Luis M. Luengo-Pérez[10], Julia Álvarez[11], Carmen Aragón[12], María J. Ocón[13], Álvaro García-Manzanares[14], Irene Bretón[15], Pilar Serrano-Aguayo[16], Natalia Pérez-Ferre[17], Juan J. López-Gómez[18], Josefina Olivares[19], Carmen Arraiza[20], Cristina Tejera[21], Jorge D. Martín[22], Sara García[23], Ángel L. Abad[24], María R. Alhambra[25], Ana Zugasti[26], Juan Parra[27], Sara Torrejón[28], María J. Tapia[1] Gabriel Olveira[1,2,3]

[1] Unidad de Gestión Clínica de Endocrinología y Nutrición, Hospital Regional Universitario de Málaga, Instituto de Investigación Biomédica de Málaga (IBIMA); [2] Universidad de Málaga; [3] CIBERDEM; [4] Servicio de Endocrinología y Nutrición, Hospital Universitario de Bellvitge, L'Hospitalet de Llobregat; [5] Servicio de Endocrinología y Nutrición, Hospital Universitario de Guadalajara; [6] Servicio de Endocrinología y Nutrición, Hospital Universitario Virgen de la Victoria, Málaga; [7] Servicio de Endocrinología y Nutrición, Hospital Universitario y Politécnico La Fe, Valencia; [8] Servicio de Endocrinología y Nutrición, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia; [9] Sección de Endocrinología y Nutrición, Hospital Universitario de Fuenlabrada; [10] Servicio de Endocrinología y Nutrición, Hospital Universitario de Badajoz; [11] Servicio de Endocrinología y Nutrición, Hospital Universitario Príncipe de Asturias, Madrid; [12] Servicio de Endocrinología y Nutrición, Hospital Universitario Fundación Jiménez Díaz, Madrid; [13] Servicio de Endocrinología y Nutrición, Hospital Universitario Lozano Blesa, Zaragoza; [14] Servicio de Endocrinología y Nutrición, Hospital General La Mancha Centro, Alcázar de San Juan; [15] Servicio de Endocrinología y Nutrición, Hospital Universitario Gregorio Marañón, Madrid; [16] Unidad de Endocrinología y Nutrición, Hospital Universitario Virgen del Rocío, Sevilla; [17] Servicio de Endocrinología y Nutrición, Hospital Clínico San Carlos, Madrid; [18] Servicio de Endocrinología y Nutrición, Hospital Clínico Universitario de Valladolid; [19] Servicio de Endocrinología y Nutrición, Hospital Universitario Son Llatzer, Illes Balears; [20] Servicio de Endocrinología y Nutrición, Complejo Hospitalario de Jaén; [21] Servicio de Endocrinología y Nutrición, Complejo Hospitalario Universitario de Ferrol, A Coruña; [22] Servicio de Endocrinología y Nutrición, Hospital Universitario Severo Ochoa, Leganés, Madrid; [23] Servicio de Endocrinología y Nutrición, Complejo Asistencial Universitario de León; [24] Unidad de Nutrición y Sección de Endocrinología, Hospital General Universitario de Alicante; [25] Servicio de Endocrinología y Nutrición, Hospital Universitario Reina Sofía, Córdoba; [26] Servicio de Endocrinología y Nutrición, Complejo Hospitalario de Navarra; [27] Servicio de Endocrinología y Nutrición, Hospital de Mérida, Badajoz; [28] Servicio de Endocrinología y Nutrición, Hospital de Sant Joan Despí Moisés Broggi, Barcelona.

18:07 RC29 Lipid Biomarkers as Predictors of Diastolic Dysfunction in Diabetes with Poor Glycemic Control

[1]Jairo Lumpuy-Castillo, [2]Dina Khedr, [2]Noha Musa , [1,3]Óscar Lorenzo

[1]Laboratory of Diabetes Research, Instituto de Investigaciones Sanitarias-Fundación Jiménez Díaz, Universidad Autónoma, Madrid; [2]Pediatric Diabetes, Endocrine and Metabolism Unit, Children Hospital, Cairo University, Cairo, Egypt; [3]CIBERDEM

18:14 RC30 Lipidomic profile and subclinical carotid atherosclerosis in diabetes mellitus

Maria Barranco[1,8,9,10], Esmeralda Castelblanco[1,2], Paola Quifer[1,2], Oscar Yanes[2,3], Ralf Weber[4], Emilio Ortega[5,6], Nuria Alonso[2,7], Didac Mauricio[1,2]

[1]Sant Pau Biomedical Research Institute (IIB Sant Pau), Hospital de la Santa Creu i Sant Pau, Endocrinology and Nutrition, Barcelona; [2]CIBERDEM; [3]Institute of Health Research Pere Virgili (IISPV) & University Pere i Virgili, Metabolomics Platform, Reus; [4]Phenome Centre Birmingham and School of Biosciences, University of Birmingham, Bioinformatics, Birmingham, UK; [5]Institut d'Investigacions Biomèdiques August Pi i Suñer, Hospital Clinic, Endocrinology and Nutrition, Barcelona; [6]Center for Biomedical Research on Physiopathology of Obesity and Nutrition, CIBEROBN, Madrid; [7]Institute for Health Science Research Germans Trias i Pujol (IGTP), University Hospital and Health Research Institute Germans Trias i Pujol, Endocrinology and Nutrition, Badalona; [8]B2SLab, Departament d'Enginyeria de Sistemes, Automàtica i Informàtica Industrial, Universitat Politècnica de Catalunya, Barcelona; [9] CIBER-BBN, Madrid; [10]Institut de Recerca Pediàtrica Hospital Sant Joan de Déu, Esplugues de Llobregat, Barcelona

18:21 RC31 Relation between skin AGEs and the coronary artery calcium score: results of the PRECISED study

Alejandra Planas[1], Olga Simó-Servat[1], Jordi Bañeras[2], Cristina Hernández[1], Ignacio Ferreira[2] and Rafael Simó[1]

[1] Diabetes and Metabolism Research Unit, Endocrinology Department, Vall d'Hebron Research Unit, Vall d'Hebron Hospital, Autonomous University of Barcelona, Barcelona, CIBERDEM; [2] Cardiology Research Group, Cardiology Department, Vall d'Hebron Research Institute, Vall d'Hebron Hospital, Autonomous University of Barcelona

18:28 RC32 Addition of probiotics to anti-obesity therapy by percutaneous electrical stimulation of dermatome T6. A pilot study

[1]Jairo Lumpuy-Castillo, [1]Tianyu Hang, [1]Marta Crespo-Yanguas, [2,3]Jaime Ruiz-Tovar, [1,4]Óscar Lorenzo

[1]Laboratory of Diabetes and Vascular pathology. Instituto de Investigaciones Sanitarias-Fundación Jiménez Díaz. Universidad Autónoma, Madrid; [2]Obesity Unit. Clínica Garcilaso, Madrid, [3]Department of Health Sciences, Universidad Rey Juan Carlos, Madrid; [4]CIBERDEM

18:35 RC33 Incidence of diabetes mellitus in the Basque country and associated risk factors: reassessment of an adult population after seven years of follow-up

Inés Urrutia[1,2], Alicia Martín-Nieto[1,3], Rosa Martínez[1,2], J Oriol Casanovas-Marsal[1], Anibal Aguayo[1,2], Juan del Olmo[4], Eunate Arana[1], Elsa Fernandez-Rubio[1,3], Luis Castaño[1,2]*, Sonia Gaztambide[1,2,3]* on behalf of the Diabetes Epidemiology Group

[1]Biocruces Bizkaia Health Research Institute, Cruces University Hospital, University of the Basque Country UPV/EHU, Bizkaia; [2]CIBERDEM, CIBERER; [3]Endocrinology and Nutrition Department, Cruces University Hospital, Bizkaia; [4]Clinical Chemistry Laboratory, Cruces University Hospital, Bizkaia

18:42 RC34 After metformin: Analysis of the effectiveness of second oral glucose-lowering therapy in routine clinical practice from the Mediterranean area

Bogdan Vlacho[1], Manel Mata-Cases[1, 2], Joan Antoni Vallès-Callol[1], Jordi Real[1, 2], Xavier Mundet-Tudurí[1, 4], Kamlesh Khunti[5], Dídac Mauricio[1, 2,3], Josep Franch-Nadal[1, 2]

[1]DAP-Cat group, Unitat de Suport a la Recerca Barcelona, Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona; CIBERDEM); [3]Department of Endocrinology and Nutrition, Hospital Universitari de la Santa Creu i Sant Pau, Spain; [4] Departament of Medicine, Universitat Autònoma de Barcelona, Bellaterra; [5]Diabetes Research Centre, University of Leicester, Leicester, UK

18:49 RC35 Reduction in hypoglycemic frequency during and after short High Intensity Interval Training in type 1 diabetes individuals.

Serafín Murillo, Laura Brugnara, Anna Novials.
IDIBAPS, Barcelona; CIBERDEM

18:56 RC36 Serum copeptin is not associated with asymptomatic peripheral artery disease in patients with type 1 diabetes

Lía Nattero-Chávez[1,3], María Ángeles Martínez-García[3], Héctor F. Escobar-Morreale[1,3], Elena Fernández-Durán[3], Sandra Redondo López[2], Beatriz Dorado Avendaño[1], Manuel Luque-Ramírez[1,3]
[1]Department of Endocrinology and Nutrition; [2] Department of Vascular Surgery; [3] Diabetes, Obesity and Human Reproduction Research Group, Hospital Universitario Ramón y Cajal & Universidad de Alcalá, Madrid & Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS) & CIBERDEM

THURSDAY, NOVEMBER 5, 2020

14:45-15:45 SIMPOSIO SATÉLITE CIBERDEM/MSD 2020

Bienvenida Eduard Montanya
Servicio de Endocrinología y Nutrición, Hospital Universitario de Bellvitge, Barcelona
Director Científico CIBERDEM

Moderador Esteban Jodar
Jefe de servicio de Endocrinología y Nutrición, Hospitales Universitarios Quirón Salud Madrid

Los costes de la diabetes tipo 2: lecciones a partir de la base de datos poblacional SIDIAP en Catalunya
Manel Mata
Centro de Atención Primaria "La Mina", Sant Adrià de Besòs, Barcelona; Grupo DAP-Cat de la Unitat de Suport a la Recerca de Barcelona Ciutat (Institut Universitari IDIAP-Jordi Gol); CIBERDEM; RedGDPS

16:00-18:00 SESSION 5

Chair: Xavier Correig
Metabolomics Platform, Department of Electronic Engeniering (DEEEA), University Rovira i Virgili, Tarragona

Carlos Guillen
Universidad Complutense de Madrid

16:00-16:30 STATE OF THE ART LECTURE

Mitochondrial dynamics modulates phospholipid metabolism
Maribel Hernández
Instituto de Recerca Biomédica (IRB-Barcelona)

16:30-17:45 ORAL PRESENTATION

16:30 OP11 On-tissue metabolomics to describe the lipid composition of the atherosclerotic plaque in diabetic and non - diabetic patients
María García-Altares[1,2], Esmeralda Castelblanco[2,3], Lluc Sementé[1], Pere Ràfols[1], Óscar Yanes[1,2], Dídac Mauricio[2,3], Xavier Correig[1,2]
[1] Metabolomics Platform, Department of Electronic Engeniering (DEEEA), University Rovira i Virgili, Tarragona; [2] CIBERDEM; [3] Research Institute of "Santa Cruz y San Pablo" Hospital, Barcelona

16:45 O12 Neuregulin 4 is required to preserve insulin action in adipocytes
Francisco Díaz-Sáez[1,2], Marta Camps[1,2], Antonio Zorzano[1,3], Anna Gumà[1,2]
[1]Dept. Biochemistry and Molecular Biomedicine, Faculty of Biology, University of Barcelona; [2] Institute of Biomedicine of the University of Barcelona (IBUB), [3]Institute of Biomedical Research-Barcelona (IRB-Barcelona)

17:00 O13 Succinate-consuming bacteria from human gut microbiota as probiotic treatment for obesity
Enrique Calvo, Isabel Huber-Ruano, Catalina Núñez-Roa, María del Mar Rodríguez, Noelia Keiran, Joan Sabadell-Basallote, Jesús Seco, Joan Vendrell, Sonia Fernández-Veledo.
Servei d'Endocrinologia i Nutrició i Unitat de Recerca, Hospital Universitari de Tarragona Joan XXIII, Institut d'Investigació Sanitària Pere Virgili (IISPV)

17:15 OP14 Epicardial adipose tissue secretome from type 2 diabetic patients contains more ceramides and induce inflammation and cytotoxicity in cardiomyocytes.
José Luis Sánchez-Quesada, Nuria Puig, Ariadna Creus, Andrea Rivas-Urbina, Inka Miñambres, Pedro Gil, Francisco Blanco-Vaca, Antonio Pérez, Sonia Benítez.
Cardiovascular Biochemistry Group, Metabolic Basis of Cardiovascular Risk Group, and Endocrinology Department. Research Institute of the Hospital de Sant Pau, Barcelona

17:30 OP15 16:1-containing phosphatidylcholine reduces responses of macrophages to an inflammatory process
Miguel Ángel Bermúdez, María A. Balboa, Jesús Balsinde
Instituto de Biología y Genética Molecular (IBGM), Consejo Superior de Investigaciones Científicas (CSIC), Valladolid

18:00-19:00 SESSION 6– RAPID COMUNICATIONS

ROOM 1

Chair: Anabel Rojas
CABIMER-Universidad Pablo Olavide, Sevilla

Izortze Santin
University of the Basque Country and Biocruces Health Research Institute

18:00 RC37 Role of ERα, ERβ and GPER1 on INS-1E β-cell line apoptosis
Ignacio Babiloni-Chust[1], Laura Marroqui[1,2], Reinaldo S. Dos Santos[1,2], Medina-Galí R M[1, 2], Ángel Nadal[1, 2]
[1]Centre: Instituto de Investigación, Desarrollo e Innovación en Biotecnología Sanitaria de Elche (IDiBE), Universidad Miguel Hernández de Elche, Elche; [2]CIBERDEM

18:07 RC38 A T1D-associated lncRNA regulates the IRF7-driven inflammatory network (IDIN) in pancreatic beta cells.
Itziar González-Moro, Izortze Santin
University of the Basque Country and Biocruces Health Research Institute

18:14 RC39 Treatment of Type 1 diabetes in mice with a dual gene AAV vector encoding for insulin and glucokinase
Laia Vilà[1,3], Marisa Jaén[1,2,3], Verónica Jiménez[1,2,3], Miquel García[1,2,3], Ivet Elias[1,2,3], Jordi Rodó[1,2,3], Tura Ferré[1,3], Fàtima Bosch[1,2,3]
[1]Center of Animal Biotechnology and Gene Therapy, [2]Department of Biochemistry and Molecular Biology, Universitat Autònoma de Barcelona, 08193 Bellaterra; [3]CIBERDEM

18:21 RC40 Distribution of seven apoC-III glycoforms in plasma, VLDL, IDL, LDL and HDL of healthy subjects and association with insulin resistance and the lipid profile
Pere Rehues, Marina Rodríguez, Víctor Iranzo, Jorge Mora, Clara Balsells, Montse Guardiola, Josep Ribalta
Unitat de Recerca en Lípids i Arteriosclerosi, Facultat de Medicina, Universitat Rovira i Virgili, Hospital Universitari de Sant Joan de Reus, Institut d'Investigació Sanitària Pere Virgili, CIBERDEM.

18:28 RC41 Endocrine disruptors and type 2 diabetes: an integrated approach for hazard identification
Hilda Ferrero[1,2], Ruba Al-Abdulla[1], Paloma Alonso-Magdalena[1,2]
[1]Instituto de Investigación, Desarrollo e Innovación en Biotecnología Sanitaria de Elche (IDiBE), Universidad Miguel Hernández, Elche; [2]CIBERDEM

18:35 RC42 Role of exosomes in pancreatic β-cells survival and potential link between T2DM and neurodegeneration
Jesús Burillo, Carlos González-Blanco, Beatriz Jiménez, Patricia Marqués, Gema García, Carlos Guillén, Manuel Benito
Facultad de Farmacia, Universidad Complutense de Madrid

18:42 RC43 Link between type 2 diabetes and Alzheimer's disease in Irs2 deficient mice
Carlos Acosta, Deborah Burks
Centro de Investigación Príncipe Felipe; CIBERDEM

18:00-19:00 SESSION 6 – RAPID COMUNICATIONS

ROOM 2

Chair: Mª Angeles Balboa
Instituto de Biología y Genética Molecular, CSIC, Valladolid

Joan Guinovart
Institut de Recerca Biomèdica (IRB), Barcelona

18:00 RC 44 GDF15 mediates the metabolic effects of metformin
David Aguilar-Recarte, Emma Barroso, Javier Pizarro-Delgado, Lucía Peña, Xavier Palomer, Manuel Vázquez-Carrera
Department of Pharmacology, Toxicology and Therapeutic Chemistry, Faculty of Pharmacy and Food Sciences and Institute of Biomedicine of the University of Barcelona (IBUB), University of Barcelona; CIBERDEM; Pediatric Research Institute-Hospital Sant Joan de Déu, Esplugues de Llobregat, Barcelona

18:07 RC45 Regulation of mitochondrial plasticity by Mfn2 drives metabolic flexibility
David Sebastián and Antonio Zorzano
Institute for Research in Biomedicine (IRB Barcelona), The Barcelona Institute of Science and Technology, Barcelona; Departament de Bioquímica i Biomedicina Molecular, Facultat de Biologia, Universitat de Barcelona; CIBERDEM

18:14 RC46 Unraveling the role of the insulin-degrading enzyme (IDE) on hepatic insulin and glucagon signaling
Carlos M. González-Casimiro, Beatriz Merino, Jesús Balsinde, Irene Cózar-Castellano, Germán Perdomo
Instituto de Biología y Genética Molecular (CSIC-UVa), Valladolid

18:21 RC47 SIRT3 deficiency exacerbates fatty liver by attenuating the HIF1α-lipin 1 pathway and increasing CD36 through Nrf2
Emma Barroso[1,2,3], Rosalía Rodríguez-Rodríguez[1,2,3], Mohammad Zarei[1,2,3], Javier Pizarro-Degado[1,2,3], Anna Planavila[3,4,5], Xavier Palomer[1,2,3], Francesc Villarroya[3,4,5], Manuel Vázquez-Carrera[1,2,3]
[1]Department of Pharmacology, Toxicology and Therapeutic Chemistry, Faculty of Pharmacy and Food Sciences, University of Barcelona, Institute of Biomedicine of the University of Barcelona (IBUB), Barcelona; [2]CIBERDEM; [3]Research Institute-Hospital Sant Joan de Déu; [4]Department of Biochemistry and Molecular Biomedicine and IBUB, Faculty of Biology, University of Barcelona; [5] CIBEROBN.

18:28 RC48 Liver glycogen increases endurance capacity in mice
Iliana López-Soldado, Jordi Duran, Joan J. Guinovart
Institut de Recerca Biomèdica (IRB); CIBERDEM

18:35 RC49 Major genetic changes due to the disturbance of glycerolipid metabolism
Clara Meana, Javier Martínez-García, Jesus Balsinde, Mª Angeles Balboa
Instituto de Biología y Genética Molecular, Consejo Superior de Investigaciones Científicas (CSIC), Valladolid

18:42 RC50 Regulation of lipid levels by lipins and their impact on inflammatory processes
Álvaro Garrido, Patricia Monge, Jesús Balsinde, María A. Balboa
Instituto de Biología y Genética Molecular, CSIC, Valladolid, CIBERDEM

ABSTRACTS

ORAL PRESENTATIONS

OP1 Lack of beneficial effect of iron tissue depletion on metabolic outcomes in women with polycystic ovary syndrome or idiopathic hyperandrogenism on standard treatment with combined oral contraceptives. A randomized clinical trial

Andrés Eduardo Ortiz-Flores[1], Mª Angeles Martínez-García[1,2], Lia Nattero-Chávez[1,2,3], Elena Fernández-Durán[1,2], Quintero-Tobar, A.[1,2] Héctor F. Escobar-Morreale[1,2,3], Manuel Luque-Ramírez M[1,2,3]

[1] Diabetes, Obesity, and Human Reproduction Research Group, Instituto Ramón y Cajal de Investigación Sanitaria, CIBERDEM; [2] Department of Endocrinology and Nutrition, Hospital Universitario Ramón y Cajal, Madrid; [3] University of Alcalá, Alcalá de Henares, Madrid

Introduction We aimed to evaluate the effects of decreasing iron tissue depots by scheduled bloodletting on insulin sensitivity and carbohydrate metabolism of women with polycystic ovary syndrome (PCOS) or idiopathic hyperandrogenism taking combined oral contraceptives (COC).
Methods We conducted a randomized, parallel, clinical trial (NCT02460445). After a 3-month run-in period of treatment with Ethynil-estradiol 30 mcg/ Cyproterone acetate 2 mg, participants were randomized to scheduled bloodletting (3 times in 9 months) in the experimental arm versus only observation (control arm). The changes in insulin sensitivity and frequency of disorders of glucose tolerance were our primary outcomes. Secondary outcomes were the changes in circulating lipids and safety assessment of bloodletting.
Results Thirty-three patients out of 26 women ending the entire protocol were included in the intention-to-treat analysis. Circulating ferritin decreased during the follow-up in those women submitted to scheduled bloodletting, whereas there were no significant changes in the control arm. Fasting glucose, glucose 120 min-oGTT, area under the curve (AUC) insulin, HOMA-IR and insulin sensitivity index did not show significant changes in any arm of the study. In the experimental arm, women showed a significant increase in the AUC glucose [MD: 83 (12; 155) mmol/L*120 min; λ´s Wilks: 0.753; F:3.766; P=0.038; η2p:0.247]. No significant changes in the frequency of disorders of glucose tolerance were observed during the trial. ApoA1 concentrations increased in the whole group of participants with no significant interaction between the visit of the study and the arm of the follow-up. Regarding safety issues, women included in the experimental arm performed a mean of two phlebotomies during the study. No women had a plasma haemoglobin level < 110 g/L. Bloodletting was well-tolerated during the trial.
Conclusion Scheduled bloodletting does not appear to provide any advantage on the metabolic profile of women with PCOS or idiopathic hyperandrogenism taking COC.

OP2 Relationship between serum vascular endothelium growth factor b levels and the development of metabolic syndrome in the Di@bet.es study

Eva García-Escobar[1,2], Ana Lago-Sampedro[1,2], Sergio Valdés[1,2], Natalia Colomo[1,2], Cristina Maldonado[1,2], Luis Castaño [1], Javier Chaves[1], Alfonso Calle1, Josep Franch[1], Elías Delgado[1], Federico Soriguer[3], Gemma Rojo-Martínez[1,2], Sara García-Serrano[1,2]

[1]CIBERDEM; [2]Biomedical Research Institute of Malaga (IBIMA), Endocrinology and Nutrition Department, Regional University Hospital of Malaga, Malaga; [3]Science Academy of Malaga, Málaga

Background/aims. Despite vascular endothelial grown factor b (VEGFb) might have an impact in the onset of metabolic disturbances, there are not clinical evidences regarding development of metabolic syndrome (MS) in relation with serum VEGFb levels. The aim of our study was to evaluate the association between serum VEGFb levels and the development of MS and its components in the Spanish adult population after 7.5 years follow-up.
Materials and methods. Sample: 1428 adults from the Di@bet.es cohort study without MS at baseline with information about MS after 7.5 years follow-up.
Variables: Socio-demographic, habits, anthropometric and clinical data were recorder. An oral glucose tolerance test was performed. Fasting serum determinations of glucose, lipids, insulin (routine methods) and VEGFb (ELISA) were made. The presence of MS and its components were defined according to the ATPIII criteria. VEGFb levels were categorized according to variable tertiles (T1: VEGFb< 32.29µg/ml, T2: VEGFb=32.29-53.96µg/ml and T3: VEGFb>53.96µg/ml).
Association between VEGFb categories and the development of both MS and its components were tested by logistic regression models adjusted by confounding variables.
Results. Among the studied subjects, 227 individuals develop MS during the follow-up. VEGFb levels were different according to age (p<0.001) and gender of subjects (p=0.002). Subjects with highest VEGFb category shown a decreased likelihood to develop MS (0.62[0.40-0.97]) as well as low HDL-cholesterol levels (0.56[0.35-0.88]) regarding to the lowest category. When subjects were split according to baseline presence of abdominal obesity (AbOb) (Not_AbOb: N=943, AbOb: N=477), the previous association remained significant only in those subjects with baseline AbOb (MS: Not_AbOb: 0.77[0.42-1.42], AbOb: 0.48[0.25-0.93]; low HDL-cholesterol: Not_AbOb: 0.82[0.39-1.72], AbOb: 0.43[0.22-0.81]).
Conclusion. Our data show that increased VEGFb serum levels might be protecting from the MS development after 7.5 years in the Spanish adult population especially in subjects with AbOb.

OP3 Effects of Glucagon-like peptide-1 (GLP-1) in Diabetes-Induced Retinal Abnormalities: Involvement of Oxidative Stress

Hugo Ramos[1,2], Cristina Hernández C[1,2,3], Joel Sampedro [1], Jordi Huerta[1,2], Rafael Simó[1,2,3]* Patricia Bogdanov[1,2]*

[1]Diabetes and Metabolism Research Unit, Vall d'Hebron Research Institute, Barcelona; [2]CIBERDEM; [3]Department of Medicine, Universitat Autònoma de Barcelona

Introduction: Oxidative stress plays a key role in the development of diabetic retinopathy (DR). Diabetic patients present an imbalance between the production of free radicals and antioxidant defences in their retinas. Treatment with glucagon-like peptide-1 (GLP-1) has beneficial effects in experimental DR mainly due to its neuroprotective action. However, its role in DR-induced oxidative stress has not been evaluated.

Objective: To elucidate the effects of topical administration of GLP-1 on DR-induced oxidative stress using an experimental mouse model of DR.

Methods: At the age of 22 weeks, 15 db/db mice received a topical treatment of GLP-1 while other 15 db/db mice were treated with vehicle for 3 weeks. They were both compared to control mice (db/+). Retinal DNA/RNA and protein damage was evaluated through 8-hydroxyguanosine and nitrotyrosine protein levels respectively (Western Blot (WB) and Immunofluorescence (IF)). Superoxide dismutase, glutathione peroxidase, glutathione reductase and $Babam_2$ protein levels were investigated using WB and IF too. Finally, proliferative events were studied through Ki67 IF.

Results: Topical administration of GLP-1 significantly reduced the presence of 8-hydroxyguanosine and nitrotyrosine in db/db mice retinas at 24 weeks of age. In addition, GLP-1 prevented the decline of antioxidant enzymes, activated DNA repair mechanisms and triggered proliferative processes.

Conclusion: The amelioration of oxidative stress is one of the underlying mechanisms by which GLP-1 exerts is beneficial effects in experimental diabetes.

OP4 Subclinical macular edema and diabetic retinopathy: two entities evolving in parallel?

Olga Simó-Servat[1], Efraín Cordero-Vázquez[1], Alejandra Planas[1], Marc Ribas[1], Eva Sanz[1], Helena Brossa[2], José García-Arumí[2], Cristina Hernández[1], Rafael Simó[1]

[1]Endocrinology Department, Vall d'Hebron Hospital; Diabetes and Metabolism Unit, Vall d'Hebron Research Institute (VHIR); [2]Ophtalmology Department, Vall d'Hebron Hospital

Clinically Significant Macular Edema (CSME) is the leading cause of vision loss in type 2 diabetes (T2D). Subclinical Macular Edema (SME) is an early stage of the disease and approximately 50% progresses to CSME. However, it is not well known if the development of SME runs in parallel with microvascular damage in the funduscopic examination.
Objective: To determine the prevalence of SME (abnormal retinal thickening) in T2D subjects and its association with the presence of microvascular abnormalities in the setting of DR.
Methods: T2D subjects without history of proliferative DR or photocoagulation were recruited from October 2017-November 2019. A fundus exam and an Optical Coherence Tomography (OCT) was performed, and clinical data was collected.
Results: A total of 197 subjects (65.2 ±7.2 years; diabetes duration: 15.4 ±8.5 years) were recruited, and the vast majority (73%) were under insulin treatment. We detected microvascular abnormalities (DR) in 158 of the 197 (80.2%) subjects. Among them the OCT examination revealed 56 with SME (34%), 32 with CSME (19%) and 70 did not present any abnormality in the OCT exam (42.4%). Clinical characteristics were compared between subjects with DR and normal OCT vs. patients with DR and SME/CSME and no significant differences were observed regarding age, sex, BMI, diabetes duration, presence of hypertension, dyslipidemia and use of insulin. We did not find any association with other diabetic complications. Glomerular filtration (GF) was significantly higher in those subjects with SME (p=0.006).
Conclusion: A significant percentage (42.4%) of the subjects with DR do not present SME. Therefore, the thickening of the retina is not always present when the vascular changes are apparent. These findings indicate the possible existence of two different phenotypes in early stages of DR. The relationship between SME and GF is intriguing and deserves further studies.

OP5 Seasonal Stochastic Local Modelling: a new framework for accuracy improvement of glucose prediction in type 1 diabetes

Eslam Montaser[1], José Luis Díez[1,2], Jorge Bondia[1,2]

[1]Universitat Politècnica de València, València; [2]CIBERDEM

Glucose prediction is at the core of diabetes technology for the treatment of type 1 diabetes, such as sensor-augmented pump, artificial pancreas and decision support systems. However, accurate prediction of glucose, especially for long prediction horizons, is challenging due to large intra-patient variability and complexity of glucose regulation.

Many techniques have been proposed in literature for glucose prediction, from standard linear empirical models to artificial intelligence techniques. However, prediction horizons still range between 30 to 60 minutes to keep accuracy. In this work, a new framework for prediction accuracy improvement allowing for longer prediction horizons is presented. It is based on the concept that observed glucose behaviors in past similar scenarios should help improving prediction at the present moment. This is mathematically formulated by means of seasonal stochastic models after a partition of historical continuous glucose monitoring data and a clustering step gathering together similar glucose responses to meal events and nocturnal periods, according to a given similarity measure. Seasonal models are then learned for each cluster providing local glucose predictions, which are weighted in real-time to produce, at each sampling time, a predicted glucose trajectory. Additionally, real-time indices indicating trust in the prediction and detecting patient abnormal states are provided.

Feasibility of the methodology was first analyzed in a retrospective study with clinical data from 18 60-h artificial pancreas controlled studies under meal and exercise challenges, achieving a mean absolute percentage error (MAPE) of 3.89%, 5.41%, 6.29% and 8.66% for 30-, 45-, 60-, and 90-min prediction horizons, respectively. Then, an in-silico study emulating free living conditions was conducted from 6-month data from the UVA/Padova simulator with extended intra-patient variability. High prediction accuracy was achieved for large prediction horizons, with MAPE values of 3.96%, 6.10%, 10.01%, 13.00%, and 13.65% for 30-, 60-, 120-, 180-, and 240-min prediction horizons, respectively.

OP6 Effects of aging on beta-cell mass and function

Eva Tudurí[1,2], Lucía Almagro[2], Sergi Soriano[2,3], Anabel García-Heredia[2], Ángel Nadal[1,2], Iván Quesada[1,2]

[1]CIBERDEM; [2]Instituto de Investigación, Desarrollo e Innovación en Biotecnología Sanitaria de Elche (IDiBE), Elche; [3]Departamento de Fisiología, Genética y Microbiología, Universidad de Alicante

Aging is associated with a progressive decline in the accurate management of glucose homeostasis, which may eventually lead to impaired glucose tolerance and type 2 diabetes. Insulin resistance has been reported in multiple aged models, and pancreatic islets must compensate undergoing morphological and functional adaptations in order to increase insulin secretion to maintain the normoglycemic state. In this study, we aimed to analyse those morpho-functional variations of pancreatic beta-cells in 3 and 20-month-old mice. Aged animals were categorized in two groups according to their quantitative insulin sensitivity check index (QUICKI): aged-HIS (high insulin sensitive) or aged-LIS (low insulin sensitive). Aged-LIS mice were hyperinsulinemic and glucose intolerant, and displayed impaired in vivo glucose-stimulated insulin secretion, whereas aged-HIS mice showed similar plasma insulin levels, glucose excursions and insulin secretion than control mice. The morphological analysis of pancreas sections revealed increased beta-cell mass with aging, an effect that was more pronounced in the aged-LIS group. By means of the patch-clamp technique, we observed similar Kv+ currents in beta-cells from control and aged animals, and increased Cav2+ currents in beta-cells from aged-LIS mice. Glucose-induced inhibition of KATP channel activity was reduced in beta-cells from aged-LIS mice. In addition, aged islets loaded with Fura-2 AM displayed increased intracellular Ca2+ signalling when exposed to high glucose concentration compared to the young ones. Altogether, our findings indicate that aging induces disruption of pancreatic endocrine cells at the level of mass, glucose-regulated hormonal secretion and signalling events. These effects are particularly exacerbated in the group of animals presenting insulin resistance.

OP7 Endoplasmic reticulum stress contributes to the loss of β-cell identity in human pancreatic islets treated with glibenclamide

Claudia Fernández[1,2,3], Noèlia Téllez[1,2,3], Víctor Gutiérrez[2], Kevin Rivera[2], Montserrat Nacher[1,2,4], Eduard Montanya[1,2,3,4]

[1]CIBERDEM; [2]Bellvitge Biomedical Research Institute, IDIBELL; [3]University of Barcelona; [4]Endocrine Unit, Hospital Universitari Bellvitge, Barcelona

Background and aims: Loss of pancreatic β-cell mass and β-cell dysfunction are central in the development of type 2 diabetes (T2DM). Reduced β-cell mass has been recently attributed to β-cell dedifferentiation. B-cell dedifferentiation has been described in response to chronic pathophysiological stress. Chronic closure of the K_{ATP} channel in rodent β-cells by exposure to the sulfonylurea glibenclamide, or by genetic manipulation results in impaired β-cell function, endoplasmic reticulum (ER) stress and loss of β-cell mass, that could account for the secondary failure to sulfonylurea treatment described in T2DM. We aimed to investigate whether chronic exposure of human islets to glibenclamide induces β-cell dedifferentiation, and the potential contribution of ER stress.

Materials and methods: Islets from human multi-organ donors (57.38±2.3 y.o.; BMI: 25.5±0.89) were cultured for one week at 5.5 mM glucose in the presence of Glibenclamide and the chemical chaperone 4-phenylbutyrate (PBA). B-cell function (GSIS), insulin content (ELISA) and β-cell apoptosis (TUNEL assay) were assessed. B-cell dedifferentiation and ER stress were determined by differential gene expression analyses of β-cell identity, disallowed, progenitor-related, and ER stress markers using qRT-PCR.

Results: Human islets exposed to glibenclamide showed β-cell dysfunction with increased basal insulin secretion and similar stimulated insulin secretion. Insulin content was similar between groups. Differential gene expression analyses showed downregulation of key β-cell transcription factors, as well as insulin ($p<0.05$). No differences were observed on disallowed or progenitor-related gene transcripts. Glibenclamide-cultured islets showed increased ER stress markers ($p<0.05$) and β-cell apoptosis was significantly increased. Addition of PBA prevented glibenclamide-induced changes in gene expression of ER stress markers and the downregulation of the β-cell identity markers.

Conclusion: Chronic exposure of human islets to glibenclamide resulted in ER stress and loss of β-cell identity. ER stress relief by addition of PBA partially prevented glibenclamide-induced loss of β-cell identity.

OP8 LRH-1/NR5A2 Specifies BL001-Mediated β-cell Survival and Trans-Regeneration

Cobo-Vuilleumier, N[1], Martín-Vazquez, E[1], Lorenzo, PI[1], Irene Díaz-Contreras[1,2], Martín F[1,2], Gerdes, JM[3], Ferrer, J[4,2], Romero-Zerbo SY[5,2], García-Fernández M[6], Francisco Javier Bermúdez-Silva[5,2,] Gannon, M[7], Collombat, P[8], Benoit R Gauthier[1,2]

[1]Andalusian Center for Molecular Biology and Regenerative Medicine, Sevilla, [2]CIBERDEM; [3]Helmholtz Zentrum München, Neuherberg, Germany; [4]The Barcelona Institute of Science and Technology, Barcelona; [5]Instituto de Investigación Biomédica de Málaga-IBIMA, UGC Endocrinología y Nutrición. Hospital Regional Universitario de Málaga, Málaga; [6]Departamento de Fisiología, Facultad de Medicina, Universidad de Málaga, Málaga; [7]Vanderbilt University Medical Center, Nashville, TN, USA; [8]Nice Sophia Antipolis University, Nice, France

We recently reported that the LRH-1/NR5A2 agonist, BL001 reverts autoimmune diabetes in mice through improving β-cell survival and stimulating regeneration potentially via α-to-β-cell conversion. Herein, we determined whether the anti-diabetic effect of BL001 is specifically via LRH-1 activation and whether it stimulates α-to-β-cell conversion. Two transgenic mouse lines were generated to: 1) Conditionally ablate LRH-1 in adult β-cells (PDX1-CreERT::LRH1$^{lox/lox}$::Rosa26-YFP denoted as βLRH1$^{lox/lox}$) upon tamoxifen (TAM) treatment and 2) Conditionally express YFP in α-cells (GlucrTTA::TetOCre::ROSA26-STOP-YFP denoted as AtoB/YFP) upon doxycycline (DOX) treatment. The βLRH1$^{lox/lox}$ mouse line was used to assess the direct contribution of LRH-1 to BL001 anti-diabetic properties while AtoB/YFP allowed α-cell lineage tracing. Both mouse models were treated with streptozotocin (STZ) and BL001 and glycemia monitored over several weeks. Pancreases of these mice were analyzed by immunofluorescence and flow cytometry. TAM treatment of βLRH1$^{lox/lox}$ mice induced YFP expression in 90% of β-cells with a concomitant 70% reduction in LRH-1 expression in islets but not in brain or liver. Alterations in glycemia, body weight and liver function were not observed upon TAM treatment in either gender. As previously reported for wild type mice, in the absence of TAM-treatment only 30-40% of βLRH1$^{lox/lox}$ mice developed hyperglycemia after BL001/STZ administration. In contrast, 85% of TAM-treated mice (LRH-1-βKO) developed hyperglycemia after BL001/STZ treatment. Hyperglycemic TAM/BL001/STZ-treated βLRH1$^{lox/lox}$ mice exhibited a near-total ablation of β-cells whereas normoglycemic vehicle/BL001/STZ-treated βLRH1$^{lox/lox}$ mice harbored normal islets. Separately, DOX treatment of AtoB/YFP mice induced YFP expression specifically in 85% of α-cells. In STZ-treated AtoB/YFP mice, BL001 reduced mortality by 50% while decreasing hyperglycemia and improving physical health. Eight-weeks post STZ administration, BL001-treated AtoB/YFP mice revealed a subpopulation of YFP^{+}/GLUT2^{+}/glucagon^{-} cells not detected in untreated mice. These results establish that the anti-apoptotic properties of BL001 are specifically conveyed by the LRH-1 signaling pathway and that BL001 favors α-to-β-cell conversion in STZ-treated mice.

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OP9 GPR40 mediated amplification of glucose-dependent insulin secretion requires expression of Alx3

Mercedes Mirasierra, Paula Nuevo-Gutierrez, Mario Vallejo

Instituto de Investigaciones Biomédicas Alberto Sols, CSIC/Universidad Autónoma de Madrid, CIBERDEM

The regulation and maintenance of glucose homeostasis requires the coordinated activity of insulin and glucagon. In previous studies we demonstrated that Alx3 participates in the regulation of insulin gene expression in β cells. In α cells, Alx3 contributes to the regulation of glucose-dependent glucagon gene expression via interactions with Pax6. The objective of the present study was to identify additional islets genes regulated by Alx3 to maintain glucose homeostasis. An initial screening using isolated islets from Alx3-deficient mice showed no significant changes in the expression of genes encoding proglucagon processing enzyme PC2, chaperone 7B2 or gastric inhibitory polypeptide receptor. In contrast, we found decreased levels of expression of the free fatty acid receptor G-protein coupled receptor 40 (GPR40) gene. GRP40, expressed in β and α cells, plays a major role in the regulation of insulin secretion by fatty acids. ChIP assays using MIN6 and αTC1 cells confirmed that Alx3 occupies the GPR40 promoter in both cell types, and EMSA indicated that Alx3 binds to P1 and P2 sites of the GPR40 promoter, which are also recognized by Pax6. Functional interactions between both transcription factors on the GPR40 promoter were demonstrated in transfected cells. GPR40 expression in cultured islets isolated from wild-type mice was increased in the presence of high concentration of glucose, but this response was significantly reduced when Alx3-deficient islets were used. Additionally, silencing Alx3 expression using siRNA resulted in a substantial decrease of GPR40 expression. Finally, we found that TAK 875, a specific GPR40 agonist, failed to potentiate glucose-stimulated insulin secretion from cultured isolated islets in the absence of Alx3. In conclusion, our data indicate that Alx3 is important for amplification of the glucose-induced insulin secretion response mediated by stimulation of GPR40.

OP10 Inhibition of insulin secretion by second-generation antipsychotics might mediate prediabetes development

Diana Grajales[1,2], Vázquez P[1,2], Ruíz-Rosario, M [3], Ferreira, V [1,2], Tudurí, E[2,4], Cigudosa, J[3], Quesada, I[2,4], Tirosh, B[5], Leibowitz, G[6], Valverde, ÁM[1,2]

[1]IIBm Alberto Sols (CSIC-UAM), Madrid; [2]CIBERDEM; [3]NIM Genetics, Madrid; [4]Instituto de Investigación, Desarrollo e Innovación en Biotecnología Sanitaria de Elche (IDiBE), Elche; [5]The Institute of Drug Research, School of Pharmacy, The Hebrew University of Jerusalem, Israel; [6]Endocrinology and Metabolism Service, Department of Medicine, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

Background: Second-Generation Antipsychotics (SGAs) have been associated with type 2 diabetes development in individuals with schizophrenia. We analysed possible effects of olanzapine, a commonly prescribed and highly diabetogenic SGA, or aripiprazole, a new antipsychotic with less metabolic side-effects, in beta-cell function.

Material and methods: Twelve-weeks-old wild-type female mice (C57/Bl6 x 129) were fed an olanzapine- or aripiprazole-supplemented diet (5.5-6 mg/kg/d) for 6 months. Control mice were fed a diet without medication. Metabolic tests (GTT, ITT and in vivo GSIS) were performed. Islets were isolated and analysed for static insulin secretion and RNA-sequencing. Whole pancreata were used for histology. For evaluating direct effects of antipsychotics in beta-cells, INS-1 cells and islets were used.

Results: mice fed an olanzapine diet had increased body weight (***$p<0.001$ vs control diet), developed glucose intolerance (**$p<0.01$), increased beta cell mass ($p=0.05$) and presented GSIS impairment (*$p<0.05$). Olanzapine activated unfolded protein response in INS-1 cells and islets. Mice receiving aripiprazole did not gain weight but developed glucose intolerance (**$p<0.01$ vs control diet), insulin resistance (**$p<0.01$), increased beta cell mass ($p=0.05$) and decreased GSIS (*$p<0.05$). Ex vivo analysis of GSIS in islets confirmed the reduction of insulin secretion by both SGAs (*$p<0.05$). Interestingly, aripiprazole increased phospho-S6 staining in islets from treated mice, suggesting hypertrophy as the mechanism behind increased beta-cell mass by this SGA. RNA-seq of islets from aripiprazole-treated mice showed up-regulation of mRNAs encoding serotonin-synthetizing enzymes (Tph1 and Tph2) and higher serotonin immunostaining was observed in islets from those mice ($p<0.05$).

Conclusion: our data shows differential effects of antipsychotics in beta-cells that could be critical for prediabetes development in individuals with schizophrenia. The effects mediated by olanzapine in islets seem to be dependent on an obesity-like phenotype, whereas those of aripiprazole point to a potential role of serotonin in beta-cell compensation driven by this antipsychotic.

OP11 On - tissue metabolomics to describe the lipid composition of the atherosclerotic plaque in diabetic and non - diabetic patients

María García-Altares[1,2], Esmeralda Castelblanco[2,3], Lluc Sementé[1], Pere Ràfols[1], Óscar Yanes[1,2], Dídac Mauricio[2,3], Xavier Correig[1,2]

[1] Metabolomics Platform, Department of Electronic Engeniering (DEEEA), University Rovira i Virgili, Tarragona; [2] CIBERDEM; [3] Research Institute of "Santa Cruz y San Pablo" Hospital, Barcelona

Diabetes increases the risk of suffering from cardiovascular diseases and accelerates the development of atherosclerosis that leads to the accumulation of lipoproteins on the arterial intima layer. The lipid composition of the plaques changes as the lesion develops and determines the stability of the arterial walls. Using Laser Desorption/Ionization Mass Spectrometry (LDI-MSI), we have analysed the lipid composition directly on-tissue in 21 samples of human atherosclerotic arteries extracted during coronary bypass surgery of diabetic and non-diabetic patients. The analyses show areas of the arteries rich in lipid species, including different profiles of diacylglycerols and cholesterol derivates located in the different layers of the blood vessels, that may explain the vulnerability, progression, and differential formation of the atherosclerotic plaque induced by diabetes.

OP12 Neuregulin 4 is required to preserve insulin action in adipocytes

Francisco Díaz-Sáez[1,2], Marta Camps[1,2], Antonio Zorzano[1,3], Anna Gumà[1,2]

[1]Dept. Biochemistry and Molecular Biomedicine, Faculty of Biology, University of Barcelona; [2] Institute of Biomedicine of the University of Barcelona (IBUB), [3]Institute of Biomedical Research-Barcelona (IRB-Barcelona)

Neuregulin 4 (Nrg4) is an adipokine that belongs to the epidermal growth factor (EGF) family. It binds to tyrosine kinase receptor ErbB4 which heterodimerize preferently with the orphan receptor ErbB2. Nrg4 is higher expressed in brown than white adipose tissue, and in minor levels in liver but no expression has been observed in skeletal muscle. Nrg4 has local effects in adipose tissue inducing angiogenesis and repressing the expression of proinflammatory cytokines, whereas has distal effects on liver protecting against non-alcoholic steatohepatitis (NASH). Moreover, adipose tissues have a reduced expression of Nrg4 in obesity, observed in rodent models and in humans. Here, we characterized the phenotype of 3T3-L1 adipocytes Nrg4 knockdown (Nrg4 KD) obtained by using lentiviruses that overexpress shRNA for Nrg4. Nrg4 KD preadipocytes fully differentiated according to the lipid droplets accumulation and the expression of adipocytes markers such as the Lipoprotein Lipase (LPL) or the transcription factor PPARgamma. However, the insulin action inducing glucose uptake was totally impaired. The protein levels of both, the insulin receptor and the insulin-sensitive GLUT4 glucose transporter were deeply reduced in Nrg4 KD adipocytes. Nrg4 deficiency induced the expression of proinflammatory cytokines in 3T3-L1 differentiated adipocytes and TNFalpha inversely correlated with the expression of Nrg4. Whereas the anti-inflammatory agent sodium salicylate allowed to recover the insulin receptor expression, the GLUT4 content remained diminished. Nrg4 KD adipocytes showed a higher activation of mTORc1, which is involved in the induction of autophagy. Nrg4 deficient adipocytes showed a higher autophagy flux and the presence of the lysosomal disruptor Bafilomycin allowed to recover the cell content in GLUT4 and TBC1D4, also known as AS160, a PKB-target protein responsible of the intracellular retention of GLUT4 storage vesicles (GSV). Nrg4 KD adipocytes showed a higher content in reactive oxygen species (ROS). As a whole, Nrg4 preserves insulin action in adipocytes.

OP13 Succinate-consuming bacteria from human gut microbiota as probiotic treatment for obesity

Enrique Calvo, Isabel Huber-Ruano, Catalina Núñez-Roa, María del Mar Rodríguez, Noelia Keiran, Joan Sabadell-Basallote, Jesús Seco, Joan Vendrell, Sonia Fernández-Veledo.

Servei d'Endocrinologia i Nutrició i Unitat de Recerca, Hospital Universitari de Tarragona Joan XXIII, Institut d'Investigació Sanitària Pere Virgili (IISPV)

Probiotics have emerged as a promising "pharmaco-nutritional" approach to reverse the metabolic alterations associated to obesity-driven dysbiosis, which is directly related to translocation of bacteria and their products into systemic circulation. In this context we recently reported a strong association between microbial gut flora and circulating succinate in humans, a signaling metabolite closely linked to inflammation which is increased in obesity and T2D. Specifically, we evidenced an intestinal bacterial signature – the ratio of succinate producers (Prevotellaceae + Veillonellaceae) versus consumers (Odoribacteraceae + Clostridaceae) – as a main determinant of plasma succinate. In the current study, we confirmed by using microbiota-depleted mice that gut microbiota strongly contributes to the higher circulating succinate levels detected in obesity context. Based on these findings, we screened for a set of non-pathogenic bacteria identified by an in silico approach as potentially consuming succinate strains in the human gut. Thus, we explored whether oral treatment in db/db and diet-induced obesity (DIO) mice with such bacteria could effectively decrease circulating succinate and improve the metabolic and inflammatory status. Our study shows that probiotic treatment with the selected bacteria, Odoribacter laneus, reduced the succinate circulating levels of obese mice, as well as improved glucose tolerance and decreased the expression of inflammatory markers in liver and intestine. These results confirm the potential of modulating intestinal microbiota with succinate-consuming bacterial species in order to mitigate obesity-related metabolic disturbances

OP14 Epicardial adipose tissue secretome from type 2 diabetic patients contains more ceramides and induce inflammation and cytotoxicity in cardiomyocytes

José Luis Sánchez-Quesada, Nuria Puig, Ariadna Creus, Andrea Rivas-Urbina, Inka Miñambres, Pedro Gil, Francisco Blanco-Vaca, Antonio Pérez, Sonia Benítez

Cardiovascular Biochemistry Group, Metabolic Basis of Cardiovascular Risk Group, and Endocrinology Department. Research Institute of the Hospital de Sant Pau, Barcelona

Epicardial adipose tissue (EAT) is a layer of fat located between the myocardium and the visceral pericardium that surrounds the heart. EAT is more than a simple fat storage depot; instead, EAT is an extremely active endocrine organ. EAT secretes adipokines, cytokines, chemokines and growth factors that could affect myocardial function. Besides proteins, EAT also secretes lipids, such as non-esterified fatty acids (NEFA) and ceramides, which could play a role in inflammation and apoptosis. However, the lipid content of the secretome of EAT from diabetic subjects has not been studied. Our aim was to determine the content of different species of ceramides and NEFA in the secretome of EAT from patients with or without diabetes, and to assess the putative inflammatory and apoptotic effects on cardiomyocytes. Explants of EAT from patients undergoing cardiac surgery were obtained and incubated for 24h with culture medium. Samples were classified according to the presence or absence of diabetes (12 samples in each group). Ten species of NEFA and 7 of ceramides were quantified by liquid chromatography mass spectrometry. The amount of NEFA species did not differ between diabetic and non-diabetic samples. Regarding ceramides, the concentration of total ceramides was similar between groups, but the ratio of ceramides 16:0 and 24:0, which has been related with increased cardiovascular risk, was higher in diabetic patients. Secretomes were added to human cardiomyocytes (AC16 cell line), and inflammation (cytokine release by ELISA) and apoptosis (annexin V by flow cytometry) were assessed. The ability of secretomes to induce inflammation and apoptosis was higher in samples from diabetic patients. Interestingly, the addition of HDL and apolipoprotein J partially prevented these inflammatory and cytotoxic effects. We conclude that an abnormal ceramide species ratio could be related with the deleterious effects of EAT from diabetic subjects on the myocardial function.

OP15 16:1-containing phosphatidylcholine reduces responses of macrophages to an inflammatory process

Miguel Ángel Bermúdez, María A. Balboa, Jesús Balsinde

Instituto de Biología y Genética Molecular (IBGM), Consejo Superior de Investigaciones Científicas (CSIC), Valladolid

The role of 16:1 fatty acids has been described in mice as bioactive lipids that possess antidiabetic and anti-inflammatory properties. Although the molecular mechanism was uncertain, the finding that the major incorporation and storage of this fatty acid is produced in the phospholipid-class phosphatidylcholine (PC) in macrophages, specifically in the PC(16:0/16:1) molecule, gave a clue about the importance of this lipid on this effect. For this reason, we studied the biological activity of the different isomers of PC(16:0/16:1) synthetized in the laboratory, and their incorporation and distribution in RAW264.7 murine macrophages exposed to inflammatory process by mass spectrometric analyses. Our data reveal that the expression levels of the pro-inflammatory cytokines (IL-6 and TNF-α) and the nuclear NF-κB translocation are significantly decreased in cells previously incubated with the isomers of PC(16:0/16:1) and also after the exposure of LPS, compared to PCs with similar structure. A similar behaviour in the three double bound isomers tested (16:1n-7, 16:1n-9 and 16:1n-10) was observed. Interestingly, the effect of PC(16:0/16:1) is not limited to TLR4 ligands, since mRNA levels of abovementioned inflammatory molecules are also decreased after stimulation with opsonized zymosan (Fcγ and complement receptor ligands), PMA (PKC stimulus) and A23187 Ionophore (increasement effector cytosolic free Ca2+) when 16:1n-9-PC is pre-incubated. Regarding the 16:1n-9 profile in cellular lipids after incubation with PC(16:0/16:1n-9), a preferential enrichment in PC among other PL is observed. Strikingly, LPS stimulation shows a decrease in the levels of 16:1-PC and a remarkable increase in 16:1 contained in diacylglycerol (DAG), phosphatidic acid (PA) and phosphatidylinositol (PI) when the incorporation of this lipid is analysed by LC-MS and GS-MS. Collectively, our results show that 16:1 containing PC exerts a protective role in macrophages exposed to inflammatory stimuli and points to the 16:1-PI biosynthesized de novo as one of the possible contributors to these effects.

RAPID COMMUNICATIONS

RC1 Influence of obesity and sex hormones on surrogate markers of gut permeability after glucose, lipid and protein oral challenges

Mª Ángeles Martínez-García, María Insenser, Alejandra Quintero-Tobar, Elena-Fernández-Durán, Manuel Luque-Ramírez, Héctor F. Escobar-Morreale.

Diabetes, Obesity and Human Reproduction Research Group, Department of Endocrinology & Nutrition, Hospital Universitario Ramón y Cajal & Universidad de Alcalá & Instituto Ramón y Cajal de Investigación Sanitaria IRYCIS & CIBERDEM, Madrid

Gut microbiome dysbiosis, increased intestinal permeability (IP) and bacterial product translocation are important contributors to chronic systemic inflammation, characteristic of several metabolic diseases including type 2 diabetes mellitus (T2DM), obesity and polycystic ovary syndrome (PCOS). Interactions between dietary components and gut microbiota modulate IP and inflammation. Animal and human data have demonstrated the impact of high-fat, high-carbohydrate and high-energy diets on the onset of metabolic endotoxemia. Lipopolysaccharide (LPS) —derived from the outer membrane of gram-negative bacteria— is the classical marker of bacterial translocation.

We aimed to investigate the effect of single macronutrient loads, obesity and sex hormones on IP by measuring surrogate markers of gut barrier dysfunction and endotoxemia. Fifty-three young individuals including 17 women with PCOS, 17 non-hyperandrogenic control women and 19 control men, equally distributed in non-obese and obese subgroups, were submitted to isocaloric (300 Kcal) oral glucose, lipid and protein loads on alternate days.

Circulating levels of zonulin, glucagon-like peptide-2 (GLP-2), LPS-binding protein (LBP), soluble CD14 and succinate were determined at fasting and during the postprandial phase (60' after glucose and protein intake or 120' after the lipid challenge).

Zonulin is a physiological mediator that reversibly regulates IP by disassembling intestinal tight junctions, whereas GLP-2 is an intestinotrophic hormone that improves gut barrier function by restoring tight junction protein expression. LBP is an acute phase protein that plays a central role in the response to LPS. It transfers LPS to sCD14, which mediates the interaction of LPS with cells. Succinate is a metabolic signal released by LPS-activated proinflammatory macrophages. A relevant source of circulating succinate might also arise from gut bacteria, particularly in pathological conditions associated with increased IP such as obesity and T2DM.

Precise knowledge of the link between dietary macronutrients, gut microbiome and host metabolism may improve the study of metabolic diseases with implications on both underlying pathophysiology and potential treatments.

RC2 Acute-phase glycoprotein profile responses to different 1 oral macronutrient challenges: Influence of sex, functional hyperandrogenism and obesity.

Samuel Moncayo, María Insenser, M. Ángeles Martínez-García, Rocío Fuertes-Martín, Núria Amigó-Grau, Francisco Álvarez-Blasco, Manuel Luque-Ramírez, Xavier Correig-Blanchar, Héctor F. Escobar-Morreale

Diabetes, Obesity and Human Reproduction Research Group, Hospital Universitario Ramón y Cajal & Universidad de Alcalá & Instituto Ramón y Cajal de Investigación Sanitaria IRYCIS & CIBERDEM, Madrid. BiosferTeslab SL; Universitat Rovira i Virgili, IISPV; CIBERDEM, Reus. Metabolomics platform, DEEEA-Universitat Rovira i Virgili, IISPV; CIBERDEM, Tarragona.

Acute-phase glycoprotein 1H-NMR spectroscopy profiles serve as surrogate markers of chronic inflammation in metabolic disorders such as obesity, diabetes and polycystic ovary syndrome (PCOS). The latter is associated with increased height-to-width (H/W) ratios of GlycA and GlycB after fasting, but not to glycoprotein areas, regardless of obesity. We studied the responses to separate glucose, lipid and protein oral challenges of five glycoprotein variables (GlycA, GlycB, and GlycF areas and the GlycA and GlycB H/W ratios) in 17 women with PCOS, 17 control women, and healthy men. Glucose and protein ingestion resulted into decreases in all glycoprotein variables, whereas lipid ingestion increased GlycA, GlycF and induced minimal changes in GlycB and GlycB H/W. We found no effects of obesity or group of subjects on postprandial glycoprotein variables regardless of the macronutrient being ingested. However, a statistically significant interaction indicated that obesity blunted the decrease in some of these variables in control women and men, whereas obese women with PCOS showed larger changes when compared with their non-obese counterparts. In conclusion, acute-phase glycoprotein profiles indicate an anti-inflammatory response during postprandial phase that is less pronounced after lipid ingestion, and is counteracted by the chronic inflammatory background associated with obesity and PCOS

RC3 Gut Microbiota in Non-Obese Adolescent Girls with Polycystic Ovary Syndrome: Effects of Randomized Treatments

Cristina Garcia-Beltran[1,2], Rita Malpique[1,2], Belen Carbonetto[3], Pedro González-Torres[3], Desirée Henares[4,5], Pedro Brotons[4,5,6], Carmen Muñoz-Almagro[4,5,6], Abel López-Bermejo[7], Francis de Zegher[8], Lourdes Ibáñez[1,2]

[1] Endocrinology Department, Pediatric Research Institute Hospital Sant Joan de Déu, University of Barcelona, Esplugues, Barcelona; [2] CIBERDEM; [3] Microomics Systems S.L., Barcelona Biomedical Research Park (PRBB), Barcelona; [4] Molecular Microbiology Department, Pediatric Research Institute Hospital Sant Joan de Déu, Esplugues, Barcelona; [5] CIBERESP; [6] School of Medicine, Universitat Internacional de Catalunya, Barcelona; [7] Pediatric Endocrinology Research Group, Girona Institute for Biomedical Research (IDIBGI) and Dr. Josep Trueta Hospital, Girona, Spain; [8] Department of Development & Regeneration, University of Leuven, Leuven, Belgium

Introduction: Polycystic ovary syndrome (PCOS) in girls is usually accompanied by insulin resistance and hepato-visceral fat excess, even if non-obese. Treatment with a low-dose combination of one mixed anti-androgen/anti-mineralocorticoid (spironolactone) and two anti-diabetic medications (pioglitazone and metformin) (SPIOMET) results in more favourable endocrine-metabolic outcomes than treatment with an oral estro-progestagen contraceptive (OC). Women and obese adolescents with PCOS have altered gut microbiota. We studied the gut microbiota composition of non-obese girls with PCOS and the effects of a randomized treatment with OC or SPIOMET for 1 year.

Patients and Methods: 16S ribosomal subunit gene amplicon sequencing was performed in stool samples from 31 controls and 30 girls with PCOS, who were randomized to receive OC (N=15) or SPIOMET (N=15); samples from 23 of the latter 30 girls were available after 1 year on OC (N=12) or SPIOMET (N=11). Clinical and endocrine-metabolic variables were measured before and after intervention.

Results: Girls with PCOS had decreased diversity alpha, altered microbiota pattern and taxonomic profile with more abundance of Family XI (P= 0.002), and less abundance of family Prevotellaceae (P= 0.0006) and the genus Prevotella (P= 0.0001) and Senegalimassilia (P< 0.0001), as compared to controls. Family XI abundance related positively to hepato-visceral fat (R= 0.453; P= 0.0003). SPIOMET treatment, but not OC, normalized the abundance of Family XI. Prevotellaceae, Prevotella and Senegalimassilia abundance remained unchanged after either treatment.

Conclusion: SPIOMET's spectrum of normalizing effects in non-obese girls with PCOS is herewith broadened as to include Family XI abundance in gut microbiota.

RC4 Upregulation of CCL22 is related to insulin resistance in morbidly obese subjects

Luisa Hueso[1,3], Rebeca Ortega[1,3], Esther Benito[1,2,5], Marta Peiró [1,5] Joaquín Ortega[4], Miguel Civera[1,2], Maria-Jesus Sanz[1,3,5], José T Real[1,2,5], Laura Piqueras[1,3,5]

[1]Institute of Health Research-INCLIVA, Valencia; [2]Endocrinology and Nutrition Service, University Clinic Hospital of Valencia, Valencia; [3]Department of Pharmacology, Faculty of Medicine, University of Valencia, Valencia; [4]Surgery Service, University Clinic Hospital of Valencia, Valencia; Department of Surgery, University of Valencia, Valencia; [5]CIBERDEM

Background/Aims: subcutaneous and visceral white adipose tissue (AT) exhibit different intrinsic properties, which make visceral AT a more pathogenic depot associated with increased metabolic risk in obesity. However, the underlying mechanisms that regulate the heterogeneity between both human depots remains unknown. We investigated the role of the chemokine receptor CCR4/CCL22 axis in morbidly obese patients. Methods: Fifty morbidly obese patients (mean age: 44 years and body mass index: 45) undergoing bariatric surgery were studied. Insulin resistance was assessed by the homeostasis model assessment (HOMA index). Results: Circulating CCL22 levels were significantly higher in morbid obese patients than in controls ($p < 0.05$) and correlated positively with BMI ($p < 0.05$) and HOMA index ($p < 0.05$). Visceral AT showed increased CCR4 and CCL22 expression when compared with subcutaneous AT. CCR4 and CCL22 were mainly localized in CD3 and CD31 positive vessels in visceral fat. Conclusions: CCL22 may be a useful biomarker to assess insulin resistance among morbidly obese subjects.
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RC5 Up-regulation of nuclear retinoid-related orphan receptor RORα in adipose tissue from diabetic obese patients.

Rebeca Ortega[1,3], Luisa Hueso[1,3], Esther Benito[1,2,5], Marta Peiró [1,5] Joaquín Ortega[4], Miguel Civera[1,2], Maria-Jesus Sanz[1,3,5], *Laura* Piqueras[1,3,5], José T Real[1,2,5]

[1]Institute of Health Research-INCLIVA, Valencia; [2]Endocrinology and Nutrition Service, University Clinic Hospital of Valencia, Valencia; [3]Department of Pharmacology, Faculty of Medicine, University of Valencia, Valencia; [4]Surgery Service, University Clinic Hospital of Valencia, Valencia, Spain; Department of Surgery, University of Valencia, Valencia; [5]CIBERDEM

Background/Aims: Inflammation governs adipose tissue (AT) dysfunction in obesity. Retinoid-related orphan receptor-alpha (RORα) is associated with inflammation and insulin resistance in animal studies, but its role in human obesity remains elusive. We investigate the expression and function of RORα on inflammation in AT from obese patients with/without diabetes. Subjects/Methods: We assessed RORα expression in paired biopsies of subcutaneous and omental AT from 41 obese patients (body mass index [BMI] 43.3 ± 0.8 kg/m^2) during Roux-en-Y-gastric surgery and explored the functional consequences of pharmacological RORα blockade in AT *ex vivo*. Results: RORα expression was significantly higher in omental AT than in subcutaneous AT (p = 0.03) and was positively associated with BMI (r = 0.344, p = 0.027) and homeostasis model assessment of insulin resistance (r = 0.319, p = 0.041). In *ex vivo* assays, IL-8/CXCL8 and MCP-1/CCL2 chemokine release was significantly higher in omental fat explants from diabetic patients than from non-diabetics and was significantly diminished by RORα blockade (p < 0.05). Inhibition of RORα improved protein kinase B signaling and decreased NF-κB activity in omental AT from obese diabetic patients (p < 0.05). Conclusions: Overall, these results indicate that RORα blockade represents a potential therapy to prevent AT dysfunction and inflammation associated with insulin resistance in human obesity.

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RC6 Mediterranean Diet and healthy eating in subjects with prediabetes of the Mollerussa prospective cohort study, a semi-rural area

Mireia Falguera[1,2], Minerva Granado-Casas[3,5], Maria Belén Vilanova[2,4], Jordi Real[5,6], Neus Miró[7], Cristina Cebrian[8], Àngels Molló[9], Manel Mata-Cases[5,6,10], Josep Franch-Nadal[5,6,11], Esmeralda Castelblanco[6,12], Didac Mauricio[6,12,13]

[1]Primary Health Care Centre Cervera, Gerència d'Atenció Primaria, Institut Català de la Salut, Lleida; [2]Department of Medicine, University of Lleida & Biomedical Research Institute of Lleida (IRBLleida), Lleida; [3]Department of Endocrinology & Nutrition, University Hospital Germans Trias I Pujol & Health Sciences Research Institute, Badalona; [4]Primary Health Care Centre Igualada Nord, Gerència d'Atenció Primaria, Institut Català de la Salut, Lleida; [5]DAP-Cat Group, Unitat de Suport a la Recerca Barcelona, Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona; [6]CIBERDEM, Barcelona; [7]Primary Health Care Centre Tàrrega, Gerència d'Atenció Primaria, Institut Català de la Salut, Lleida; [8]Primary Health Care Centre Mollerussa, Gerència d'Atenció Primaria, Institut Català de la Salut, Lleida; [9]Primary Health Care Centre Guissona, Gerència d'Atenció Primaria, Institut Català de la Salut, Lleida; [10]Primary Health Care Centre La Mina, Gerència d'Atenció Primària Barcelona, Institut Català de la Salut, Barcelona; [11]Primary Health Care Centre Raval Sud, Gerència d'Atenció Primaria Barcelona, Institut Català de la Salut, Barcelona; [12]Department of Endocrinology & Nutrition, Hospital de la Santa Creu i Sant Pau & Institut d'Investigació Biomédica Sant Pau (IIB Sant Pau),Barcelona;[13] Faculty of Medicine, University of Vic (UVIC/UCC), Vic

Objectives: Our hypothesis was that subjects with prediabetes had an unhealthier dietary pattern in comparison with those with normal glucose tolerance. The aim was to assess differences in the dietary pattern (i.e. Mediterranean Diet and healthy eating indexes) between participants with prediabetes and a group with normal glucose tolerance. Secondarily, we analyzed the factors related to prediabetes and dietary pattern.

Methods: This was a cross-sectional study. From a sample of 594 participants recruited in the Mollerussa study cohort, a total of 535 participants (216 with prediabetes and 319 with normal glucose tolerance) were included. Inclusion criteria were age of 25 years or higher, normal glucose tolerance or prediabetes at baseline. Exclusion criteria were a diagnosis of diabetes mellitus and missing nutritional and glycemic data. A validated food frequency questionnaire was individually administered. Blood samples were collected, and clinical records were thoroughly revised. The alternate Mediterranean Diet score (aMED) and the alternate Healthy Eating Index (aHEI) were calculated. Bivariable and multivariable analysis were performed.

Results: Participants with prediabetes were older ($p<0.001$), showed poorer educational level ($p=0.001$), and higher body mass index (BMI) ($p<0.001$), waist ($p<0.001$), glycated hemoglobin ($p<0.001$), total cholesterol ($p=0.021$), frequency of hypertension ($p=0.009$) and dyslipidemia ($p<0.001$) compared with the normal glucose tolerance group. No differences were observed in daily food and nutrient intake (except for stearic acid, $p=0.011$). The multivariable analyses showed that female gender ($p=0.003$) and age ($p<0.001$) were positively associated with aMED and aHEI. Moreover, age ($p<0.001$), dyslipidemia ($p=0.016$) and BMI ($p<0.001$) were positively associated with prediabetes; however, educational level was negatively associated with this condition ($p=0.047$).

Conclusions: Subjects with prediabetes did not show a different dietary pattern compared with a normal glucose tolerance group. However, further research is needed on this issue.

RC7 Fatty Acid Binding Protein 4 is associated with Fatty Liver in metabolic patients

Ricardo Rodríguez-Calvo, Juan Moreno, Josefa Girona, Daiana Ibarretxe, Neus Martínez-Micaelo, Nuria Plana, Lluís Masana

Vascular Medicine and Metabolism Unit, Research Unit on Lipids and Atherosclerosis, "Sant Joan" University Hospital, Universitat Rovira i Virgili, Institut de Investigació Sanitaria Pere Virgili (IISPV), Reus; CIBERDEM

Background & Aims: Ectopic fat accumulation in liver is considered the onset of the non-alcoholic fatty liver disease (NAFLD). Nevertheless, non-invasive methods for its identification are currently lacking. Given the role of the Fatty acid binding protein (FABP4) as potential biomarker for the ectopic fat accumulation in non-adipose tissues, the aim of this study was to assess the relationship between this adipokine and the Fatty Liver Index (FLI) in metabolic patients and to evaluate its potential role as new-emerging biomarker for fatty liver.
Methods: The study enrolled 389 individuals, of whom 51.9% were obese, 67.9% had diabetes mellitus (DM) and 74.8% metabolic syndrome (MS). The Fatty liver index (FLI) was calculated in order to quantify the liver fat content. The serum FABP4 levels were assessed by using a sandwich enzyme-linked immunosorbent assay. The associations between serum FABP4 and FLI, as well as the potential role of FABP4 as a biomarker for liver steatosis were assessed by multiple regression models.
Results: Both, FLI and serum FABP4 levels were upregulated in metabolic patients. Serum FABP4 were robustly associated with FLI in metabolic patients in both linear and logistic regression analyses. Serum FABP4 levels were higher in individuals with liver steatosis (i.e. FLI ≥ 60), and it improved the discrimination of models based on clinical features to predict liver steatosis.
Conclusions: Our findings propose the serum FABP4 as a potential new-emerging biomarker for the diagnosis of liver steatosis.

RC8 Atherogenic dyslipidemia, but not hyperglycemia, is an independent risk factor for liver fibrosis in subjects with type 2 diabetes mellitus and NAFLD: A population –based study

Nuria Alonso[1,4,7], María Teresa Julián[1], Guillem Pera[2,3], Berta Soldevila[1,4], Llorenç Caballería[2,3], Josep Julve[5,6,7], Carlos Puig[1], Rosa Morillas[3,8], Pere Torán[2,3], Carmen Expósito[2,3], Manel Puig-Domingo[1,4,7], Esmeralda Castelblanco[5,7], Josep Franch-Nadal[7,9]Dídac Mauricio[5,7,10]

[1]Department of Endocrinology and Nutrition Department, Hospital Germans Trias I Pujol, Badalona, Barcelona; [2]Unitat de Suport a la Recerca Metropolitana Nord, Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Mataró; [3]CIBEREHD, Barcelona; [4]Department of Medicine, Autonomous University of Barcelona (UAB), Barcelona; [5]Hospital de la Santa Creu i Sant Pau, & Institut d'Investigació Biomèdica Sant Pau (IIB Sant Pau), Barcelona; [6]Departament de Bioquímica y Biología Molecular, Universitat Autònoma de Barcelona, Barcelona; [7]CIBERDEM; [8]Hepatology Department, Hospital Germans Trias I Pujol, Badalona, Barcelona; [9]Primary Health Care Center Raval Sud, Gerència d'Atenció Primaria, Institut Català de la Salut, Barcelona; [10]Department of Endocrinology and Nutrition, Hospital de la Santa Creu i Sant Pau; Institut d'Investigació Biomédica Sant Pau (IIB Sant Pau), Barcelona

Aims Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver conditions. Type 2 diabetes (T2D) is a well-known risk factor that worsens the prognosis of NAFLD. The aim of this study was to investigate the prevalence and risks factors associated with the presence of significant liver fibrosis in subjects with NAFLD and T2D.

Material and Methods This study was part of a population-based study conducted in the Barcelona metropolitan area among subjects aged 18 to 75 years old. Secondary causes of steatosis were excluded. Moderate-to-advanced liver fibrosis was defined as a liver stiffness measurement (LSM) ≥ 8.0 kPa assessed by transient elastography.

Results Prevalence estimates of increased LSM (≥ 8.0 kPa) in the general population was 5.5%. Among 930 subjects with NAFLD, the prevalence of moderate-to-advanced liver fibrosis in subjects with T2D was 30.8% compared to 8.7% in subjects without T2D. By multivariable analysis, one of the main factors independently associated with increased LSM in T2D with NAFLD was atherogenic dyslipidemia, followed by serum transaminase concentrations, body mass index (BMI) and age. In contrast, atherogenic dyslipidemia was not a risk factor for moderate-to-advanced liver fibrosis in non-diabetic subjects. The percentage of patients with moderate-to-advanced fibrosis was higher in subjects with T2D and atherogenic dyslipidemia than in subjects with T2D without atherogenic dyslipidemia, both for the cut-off point of LSM ≥8.0 kPa (45% vs 24%, p=0.002) and ≥13 kPa (13% vs 4%, p=0.020). No differences were observed in the prevalence of LSM ≥8.0 kPa regarding glycemic control among NAFLD-diabetic subjects.

RC9 Differential DNA Methylation Profile in Infants Born Small-for-Gestational-Age: Association with Markers of Adiposity and Insulin Resistance from Birth to Age 24 Months

Marta Díaz[1,2], Edurne Garde[1,2], Abel López-Bermejo[3], Francis de Zegher[4], Lourdes Ibáñez[1,2]

[1]Institut Pediàtric Hospital Sant Joan de Déu, University of Barcelona, Esplugues, Barcelona; [2]CIBERDEM; [3]Department of Pediatrics, Dr. Josep Trueta Hospital, Girona, and Girona Institute for Biomedical Research, Girona; [4]Department of Development & Regeneration, University of Leuven, Belgium

Introduction. Prenatal growth restraint followed by rapid postnatal weight gain increases lifelong diabetes risk. Epigenetic dysregulation in critical windows could exert long-term effects on metabolism and confer such risk.

Research Design and Methods. We conducted a genome-wide DNA methylation profiling in peripheral blood from infants born appropriate- (AGA, n=30) or small-for-gestational-age (SGA, n=21, with postnatal catch-up) at age 12 months, to identify new genes that may predispose to metabolic dysfunction. Candidate genes were validated by bisulphite pyrosequencing in the entire cohort. All infants were followed since birth; cord blood methylation profiling was previously reported. Endocrine-metabolic variables and body composition (Dual-energy X-ray absorptiometry) were assessed at birth and at 12 and 24 months.

Results. GPR120 (cg14582356, cg01272400, cg23654127, cg03629447), NKX6.1 (cg22598426, cg07688460, cg17444738, cg12076463, cg10457539), CPT1A (cg14073497, cg00941258, cg12778395) and IGFBP 4 (cg15471812) genes were hypermethylated (GPR120, NKX6.1 were also hypermethylated in cord blood), whereas CHGA (cg13332653, cg15480367, cg05700406), FABP5 (cg00696973, cg10563714, cg16128701),CTRP1(cg19231170, cg19472078, cg0164309, cg07162665, cg17758081, cg18996910, cg06709009), GAS6 (N/A), ONECUT1 (cg14217069, cg02061705, cg26158897, cg06657050, cg15446043) and SLC2A8 (cg20758474, cg19021975, cg11312566, cg12281690, cg04016166, cg03804985) genes were hypomethylated in SGA infants. These genes were related to β-cell development and function, inflammation, and glucose and lipid metabolism and associated to body mass index, body composition, and markers of insulin resistance at 12 and 24 months.

Conclusion. In conclusion, at 12 months, abnormal methylation of GPR120 and NKX6.1 persists, and new epigenetic marks further involved in adipogenesis and energy homeostasis arise in SGA infants. These abnormalities may contribute to metabolic dysfunction and diabetes risk later in life.

RC10 miR-155 influences diabetic kidney disease by regulating SOCS1

Ignacio Prieto[1], Luna Jiménez-Castilla[1], Iolanda Lázaro[2], Laura López-Sanz[1], Susana Bernal-Uribe[1], Mónica Flores-Muñoz[3], Óscar López-Franco[3], Jesús Egido[1], Carmen Gómez-Guerrero[1]

[1]Renal, Vascular and Diabetes Research Lab, Instituto de Investigaciones Sanitarias-Fundación Jiménez Díaz (IIS-FJD), Universidad Autónoma de Madrid (UAM) and CIBERDEM; [2] Institut d'Investigacions Biomèdiques August Pi Sunyer (IDIBAPS) and CIBEROBN; [3] Instituto de Ciencias de la Salud, Universidad Veracruzana, Xalapa, Veracruz, México

Diabetic nephropathy is the leading cause of chronic kidney disease worldwide. Hyperglycemia in concert with cytokines activate Janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathway and induce the expression of a large array of mediators involved in inflammatory and oxidative stress responses, which are critical events for the onset and progression of diabetic kidney damage. Suppressor of cytokine signalling 1 (SOCS1) is a STAT-inducible protein and a negative feedback regulator of cytokine signalling that inhibits JAK activity and STAT phosphorylation. Different microRNAs (miRs) are implicated in the epigenetic regulation of SOCS1 gene expression by direct interaction with mRNA, repressing translation and/or targeting mRNA for degradation. Our goal is to study the role of miR-155 in the regulation of JAK/STAT/SOCS1 axis in diabetic nephropathy.

In vivo, the induction of type 1 diabetes significantly upregulated miR-155 renal expression both in C57BL/6 and apolipoprotein E knockout mice (1.8- and 4.5-fold vs respective non-diabetic controls). The miR-155 levels directly correlated with parameters of renal damage (serum creatinine, albuminuria, kidney-to-body weight ratio and renal score) and the expression of chemokines and pro-oxidant enzymes (Ccl2, Ccl5, Nox2 and Nox4), but inversely with antioxidant genes (Sod1 and Cat). In vitro, the expression of miR-155 was increased in renal (mesangial and tubuloepithelial) cells and macrophages exposed to hyperglycaemia and/or inflammatory conditions. Overexpression of miR-155 reduced SOCS1 expression level, enhanced STAT1 and STAT3 activation and the expression of pro-inflammatory cytokines and chemokines (IL-6, TNFα, Ccl2 and Cxcl10). By contrast, miR-155 antagonism upregulated SOCS1 and had a protective effect on renal cells by decreasing STAT1 and STAT3 activation and pro-inflammatory gene expression.

In conclusion, our study indicates a pro-inflammatory role of miR-155 in renal cells by downregulating SOCS1. miR-155 inhibition may have a renoprotective effect in diabetic nephropathy through SOCS1-mediated feedback inhibition of JAK/STAT overactivation.

RC12 mTOR activation in diabetic and hypertensive cardiomyopathy

Tianyu Hang, Sagrario Corrales, Mikel Azkargorta, Malu Martínez-Chantar M, Jairo Lumpuy-Castillo, Jesus Egido, Oscar Lorenzo

IIS-Fundación Jiménez Díaz, UAM, Madrid; CIC-BioGune

Background: Type 2 Diabetes Mellitus (T2DM) and hypertension (HTN) can lead to cardiac dysfunction and eventually heart failure. Cardiac hypertrophy, apoptosis and fibrosis are common responses in these pathologies. However, the involved molecular mechanisms have not been depicted. Mitochondria physiology could play significant roles.
Materials: Cardiac biopsies from interventricular septum were isolated from patients with T2DM and/or HTN (n=7, each), who were intervened for acute myocardial infarction or unstable angina. Control biopsies were isolated from the patients with mitral regurgitation and atrial fibrillation (n=5). Then, proteomics was used to evaluate the differential expression of protein in each group, and cultured cardiomyocytes were used to study the relevant pathways under incubation with excess of glucose (HG), fatty acid (HF) or angiotensin-II (Ang-II).
Results: HTN patients showed an increase of 4 proteins and a decrease of 41 compared to control, while T2DM/HTN subjects exhibited an increase of 117 proteins and a decrease of 549. HTN induced an alteration of proteins related to muscle contraction and mitochondrial respiration (i.e., myosin-6, cytochrome-C oxidase, NADPH-dehydrogenase, mitofusin-2), whereas T2DM/HTN triggered changes in mitochondrial factors from glucose and fatty acid metabolism, biogenesis and respiration (i.e., insulin receptor, acyl CoA-oxidase, carnitine palmitoyl-transferase, nuclear respiratory factor-1, sirtuin-3). Moreover, in HF-stimulated cardiomyocytes, a reduction of p-Akt^{Ser473}/Akt and an increase of p-p70-S6K$^{Thr421/Ser424}$ /p70-S6K, as downstream mediators of mTORC2 and mTORC1, respectively, was noted. HG did not alter these ratios.
Conclusion: The addition of T2DM to hypertensive pathology could trigger further changes in the cardiac proteome. In particular, the excess of fatty acid may reduce metabolic, biogenetic and anti-oxidant factors in mitochondria by regulation of mTORC1/C2 complexes. Interestingly, Rictor may reflect a compensatory response to attenuate cardiac failure.

RC13 Vitamin D Receptor overexpression prevents high fat diet-induced body weight gain and ameliorates insulin resistance

Laia Vilà[1,3], Albert Ribera[1,2,3], Sylvie Franckhauser[1,3], Tura Ferré[1,3], Meritxell Morró[1,2,3], Ignasi Grass[1,2,3], Maria Luisa Jaen[1,2,3], Gemma Elias[1,2,3], Estefanía Casana[1,2,3], Fàtima Bosch[1,2,3], Alba Casellas[1,3]

[1]Center of Animal Biotechnology and Gene Therapy; [2]Department of Biochemistry and Molecular Biology, Universitat Autònoma de Barcelona, Bellaterra; [3]CIBERDEM

Vitamin D deficiency has been associated with increased incidence of diabetes, both in humans and animal models. Vitamin D mediates its action by interacting with its nuclear receptor (VDR), which is a member of the nuclear receptor superfamily of ligand-activated transcription factors. In addition, association between VDR gene polymorphisms and diabetes has also been described. However, the involvement of VDR in the development of diabetes, has not been elucidated yet. We recently reported that Vdr expression is modulated by glucose in healthy islets and decreased in islets from T1D, and that mice overexpressing VDR in β-cell (Tg-VDR) are protected against STZ-induced diabetes. This strongly suggests an essential role of Vitamin D/VDR axis in diabetes. Here we aimed to study the role of VDR in Type 2 diabetic context, in particular in well-established T2D mouse models such as Db/Db, Ob/Ob and diet-induced obese mice. The expression of VDR in pancreatic islets was decreased in T2D mouse models, as we previously observed in T1D mouse models. In addition, islet Vdr expression in mice fed with a high-fat diet (42% fat), which displayed a marked increase in body weight (about 40% of body weight gain), was reduced. In contrast, high-fat-fed Tg-VDR mice, in which islet VDR levels were maintained, were resistant to weight gain and maintained a normal body weight. Accordingly, Tg-VDR showed amelioration of insulin resistance, glycaemia and fat depots alterations. Moreover, Tg-VDR mice in high fat diet showed higher energy expenditure and were more active than their Wt littermates, which may have contributed to weight gain resistance. Altogether, these results suggest a role of the vitamin D/VDR axis in energy homeostasis in type 2 diabetes and that further studies are necessary to understand the molecular mechanisms underlying the regulation of Vdr gene expression during diabetes.

RC14 Extra virgin olive oil reduced weight gain and improved insulin sensitivity in high fat diet-induced obese LDLr-/-.Leiden mice but did not attenuate steatohepatitis

Leticia Álvarez-Amor[1,2], Amparo Luque Sierra[1], Antonio Cárdenas[1,2], Eloísa Andújar[1], Mónica Pérez-Alegre[1], Rocío Gallego-Durán[3,4], Alejandro Martin-Montalvo[1], Genoveva Berná[1,2], Anabel Rojas[1,2], Abdelkrim Hmadcha[1,2], Robert Kleemann[5], Manuel Romero-Gómez[3,4], Franz Martín[1,2]

[1]CABIMER-UPO, Seville; [2]CIBERDEM; [3]Hospital Universitario Virgen del Rocío-IBiS, Seville; [4]CIBEREHD; [5]Department of Metabolic Health Research, Netherlands Organisation for Applied Scientific Research-TNO, Leiden, Netherlands; [6]Department of Vascular Surgery, Leiden University Medical Centre, Leiden, Netherlands

Dietary fatty acids play a role in the pathogenesis of obesity-associated non-alcoholic fatty liver disease (NAFLD), which is tightly associated with insulin resistance (IR) and type 2 diabetes (DM2). Fatty acid composition appears to be critical for IR and subsequent NAFLD development. Extra-virgin olive oil (EVOO) is the main source of monounsaturated fatty acids in Mediterranean diets. This study examined whether EVOO-containing high fat diets may prevent diet-induced NAFLD and DM2 using Ldlr−/−. Leiden mice, which develop pronounced IR in conjunction with NAFLD. In female Ldlr-/-.Leiden mice, the effects of the following high fat diets (HFDs) were examined: a lard-based HFD (HFD-L); an EVOO-based HFD (HFD-EVOO); a phenolic compounds-rich EVOO HFD (HFD-OL). We studied changes in body weight (BW), lipid profile, transaminases, glucose homeostasis, liver pathology and transcriptome. Both olive oil diets reduced body weight (BW) and improved insulin sensitivity and glucose homeostasis. The EVOOs did not improve transaminase values and increased LDL-cholesterol. EVOOs and HFD-L groups had comparable liver steatosis. Both EVOOs increased liver collagen content. These profibrotic effects were substantiated by an up-regulation of gene transcripts related to glutathione metabolism, chemokine signaling and NF-kappa-B activation and down-regulation of genes relevant for fatty acid metabolism. In all, EVOO intake consistently improved weight gain and insulin sensitivity while worsening inflammation (mainly HFD-OL) and fibrosis (both EVOOs), which was supported by changes in hepatic genes expression.

RC15 Bace2 deficiency exacerbate body weight gain and hyperinsulinemia in mice fed a high fat diet

Daniela Díaz-Catalán[1], Gema Alcarraz-Vizán[1], Carlos Castaño[1], Mario Vallejo[2], Marcelina Párrizas[1], Joan Marc Servitja[1] and Anna Novials[1]

[1] Diabetes and Obesity Research Laboratory. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), CIBERDEM; [2]Instituto de Investigaciones Biomédicas Alberto Sols, Consejo Superior de Investigaciones Científicas/Universidad Autónoma de Madrid, CIBERDEM

Bace2 (β-site APP-cleaving enzyme 2) is a protease that may be involved in the development of Alzheimer's disease (AD). However, besides the brain, it has also been localized in the pancreas, where it plays a physiological role. Despite the potential link between AD and glucose homoeostasis deregulation in humans and rodents, the involvement of Bace2 in metabolic disturbances such as obesity has not been explored. Thus, the aim of the present study was to investigate the effect of Bace2 on whole-body metabolism.

Bace2-deficient (BACE2-KO) mice and their respective controls (WT) were used to analyse the phenotype after 2 and 16 weeks of chow or high-fat (HF) diet feeding. Glucose and insulin tolerance tests and indirect calorimetry were performed to evaluate metabolic phenotype. Plasma insulin, C-peptide and leptin levels were analysed by ELISA. mRNA expression of relevant genes from peripheral tissues were determined by quantitative PCR.

BACE2-KO mice fed HF diet for 16 weeks showed a higher food intake and body weight gain ($p<0.05$), with respect to their WT counterparts. Under HF diet, both BACE2-KO and WT animals showed glucose intolerance and decreased insulin sensitivity compared to chow diet groups. Nevertheless, both HF diet groups presented the same glucose intolerance despite the differences observed in body weight. This may be explained by increased glucose-induced insulin secretion in BACE2-KO mice compared with WT mice under HF diet. Similarly, plasma C-peptide levels were also increased in BACE2-KO mice. Interestingly, mice already presented increased food intake and hyperinsulinemia after 2 weeks of HF diet, indicating that acute metabolic events precede the increased body weight underlie the disturbances observed in these mice.

In summary, these results indicate that absence of Bace2 impacts glucose and energy metabolism. Thus, targeting Bace2 may induce metabolic side effects that should be considered in the clinical use of Bace2 inhibitors.

RC16 The inhibition of ATP-citrate lyase protects from non-alcoholic fatty liver disease in a model of high fat diet feeding

Alejandro Sola-García[1], Manuel Aguilar-Diosdado[2], Maria Ángeles Cáliz-Molina[1], Vivian Capilla-González[1], Franz Martin[1,3,4], Benoit R. Gauthier[1,3], Alejandro Martín-Montalvo[1]

[1] Andalusian Center for Molecular Biology and Regenerative Medicine-CABIMER, Junta de Andalucia-University of Pablo de Olavide-University of Seville-CSIC, Seville; [2] Department of Endocrinology, Puerta del Mar Hospital Cádiz/ Department of Medicine, University of Cádiz; [3] CIBERDEM; [4] Department of Molecular Biology and Biochemistry Engineering, University Pablo de Olavide (UPO), Seville

Aims: ATP-citrate lyase (ACLY) is a central enzyme involved in de novo fatty acid synthesis and cholesterogenesis, which are relevant pathways in the pathogenesis of non-alcoholic fatty liver disease (NAFLD). Herein, we explored whether the pharmacological inhibition of ACLY protects from the development of NAFLD in a model of High Fat diet feeding in mice.
Materials and methods: Wild type C57BL/6 mice were fed a diabetogenic high fat diet (HFD) TD06414 supplemented or not with the ACLY inhibitor SB-204990 for 15 weeks. Physiological determinations were monitored during the intervention. At the time of sacrifice, livers were harvested and histological, and multiomic analyses were performed.
Results: HFD-induced body weight gain was significantly reduced, with no significant differences in energy intake in mice treated with the SB-204990. Mice treated with SB exhibited enhanced glucose tolerance when compared to HFD fed mice, indicating improved glucose metabolism. Histological analysis of liver tissue indicated a marked reduction in lipid depositions in SB-204990-treated mice. Analyses in liver tissue indicated a significant induction of genes involved in the synthesis of cholesterol and a remarkable inhibition of genes involved in steroid synthesis. Proteomic data indicated that the modulation of lipid synthesis pathways might contribute to the phenotype of mice exposed to SB-204990. Untargeted metabolomics indicated that a robust alteration of hydrophilic metabolites is produced upon exposure to SB-204990.
Conclusions: Our data indicate that reduced activity of ACLY improves mechanisms involved in NAFLD in a model of high fat diet feeding in mice.

RC17 Characterization and study of Goblet cells involved in mucus layer secretion in a rat model of metabolic syndrome associated to catch-up growth

Paula Martínez Oca[1,2]; Tamara Fernández Marcelo[1,2]; Alicia Sánchez Roncero[1,2]; María Ángeles Martín[2,3]; Fernando Escrivá[1,2]; Elisa Fernández Millán[1,2]; Carmen Álvarez Escolá[1,2]

[1] Department of Biochemistry and Molecular Biology, Faculty of Pharmacy, Complutense University of Madrid; [2] CIBERDEM; [3] Department of Metabolism and Nutrition, Institute of Food Science and Technology and Nutrition (ICTAN), Consejo Superior de Investigaciones Científicas (CSIC), Madrid

Introduction: Accumulating evidence indicates that perinatal growth-restriction followed by catch-up growth increases the susceptibility to metabolic diseases in adulthood. We previously demonstrated that one possible mechanism of this association was the early endotoxemia development together with a marked dysbiosis. In the present study we focused on the colonic barrier integrity analysis, mainly on the mucin-producing Goblet cells physiology and replenishment.

Material and Methods: Offspring of Wistar rat dams fed ad libitum (control [C]) or 65% food-restricted during pregnancy and lactation (undernourished [U]) were weaned onto a high-fat (HF) diet (CHF and UHF) to drive catch-up growth. Akkermansia muciniphila and colonic Tff3, Muc2, IL6, IL1β, TNFα expression levels were analyzed by RT-qPCR. Colonic integrity was analyzed using Alcian blue-PAS staining and transmission electron microscopy (TEM). Insulin, glycemia, lipid profile and cytokines levels were determinated in serum. For CD68+ cell infiltrate identification we immunostained colonic tissue.

Results: U rats showed significant mucolytic-bacteria A.muiniphila expansion before and after the catch-up growth. This event was accompanied by colonic mucus thickness reduction, increased CD68+ macrophage abundance and expression of proinflammatory cytokines in UHF as compared to CHF animals. To determine whether altered mucin production might also be contributing to defective intestinal barrier, ultrastructural analysis was performed in Goblet cells. Reduced number of mucin-granules per cell was detected in the U and UHF colon rats because granules were merged. Moreover, food-restriction and HFD promoted ER-distension in Goblet cells from the colon. This fact might be attributable to an aberrant Goblet cell autophagy or immaturity, as we observed in the specific analysis with TEM and gene expression.

RC18 PTP1B deficiency protects male mice against insulin resistance but not thermogenic alterations upon Olanzapine intraperitoneal treatment

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

[1]IIBm Alberto Sols (CSIC-UAM), Madrid; [2]CIBERDEM

Background: Second generation antipsychotics (SGAs) are the first choice in schizophrenia's therapy. Patients under treatment develop several metabolic dysfunctions, including weight gain and insulin resistance, but the molecular mechanisms are poorly understood. Our aim was to decipher whether protein tyrosine phosphatase-1B (PTP1B) inhibition confers protection against metabolic abnormalities induced by olanzapine, a commonly prescribed SGA. Materials and Methods: Wild-type (WT) and PTP1B deficient (PTP1B-KO) mice were intraperitoneally injected 10 mg/kg/day olanzapine or vehicle for 8 weeks. Whole-body glucose homeostasis and energy balance were analysed. Tissue-specific insulin sensitivity and expression of key markers of lipid metabolism and brown/beige fat activation were determined. Results: Olanzapine-treated WT males presented insulin and pyruvate intolerance with reduced phosphorylations of insulin receptor and Akt in liver and skeletal muscle. Also, hepatic Fatty Acid Synthase (FAS) was increased correlating with hypothalamic JNK phosphorylation. PTP1B-KO males were protected against these alterations. UCP-1 levels were increased in brown adipose tissue (BAT) of both genotypes in parallel with decreased hypothalamic AMPK phosphorylation, resulting in enhanced whole-body energy expenditure and weight loss. However, olanzapine-treated females did not lose weight nor had alterations in energy expenditure, BAT UCP-1 levels, hepatic FAS expression or hypothalamic JNK/AMPK phosphorylations. Moreover, olanzapine treatment resulted in browning/beiging of subcutaneous white adipose tissue manifested by increased UCP-1 levels in males independently of the genotype and only in WT females. Olanzapine treatment of hepatocytes and brown adipocytes did not recapitulate the in vivo responses suggesting an inter-organ crosstalk responsible for the metabolic disturbances. Conclusions: Our results support the relevance of PTP1B inhibition in the protection against olanzapine-induced insulin resistance associated with the intraperitoneal treatment in male animals. Furthermore, this work arises the central effects of olanzapine as key events for the peripheral metabolic abnormalities, with sexual dimorphisms playing an important role in whole-body responses to this SGA.

RC19 Nuclear coactivator RAP250 modulates adiposity and the metabolic activity of brown adipose tissue

Manuela Sánchez-Feutrie[1,2,3]†, Sónia Rosa Veiga[1,2,3]†, Andrea Rodgers-Furones[1,2], Montserrat Romero[1,2,3], Alba Sabaté-Pérez[1,2,3], Luis Rodrigo Cataldo[1], Hans Burghardt[1,2,3], David Sebastián[1,2,3], Mònica Sabater-Masdeu[4,5], José María Moreno-Navarrete[4,5], Francisco Ortega[4,5], Wifredo Ricart[4,5], Natàlia Plana[1], Vanessa Hernández[1], Laura Isabel Alcaide[1], José Juan Marín [6], Manuel Palacín[1,2,7], Remy Burcelin[8], Joan Vendrell[9,10], José Manuel Fernández-Real[4,5], Per Antonson[11], Jan-Ake Gustafsson[11,12], Antonio Zorzano[1,2,3]

[1]Institute for Research in Biomedicine (IRB Barcelona), The Barcelona Institute of Science and Technology, Barcelona; [2] Departament de Bioquímica i Biomedicina Molecular, Facultat de Biologia, Universitat de Barcelona, [3] CIBERDEM; [4] CIBEROBN; [5] Department of Diabetes, Endocrinology and Nutrition, Institut d'Investigació Biomèdica de Girona (IdIBGi), Hospital of Girona 'Dr Josep Trueta', Girona; [6] Experimental Hepatology and Drug Targeting, CIBEREHD, IBSAL, University of Salamanca; [7] CIBERER; [8] UMR 5018 CNRS-UPS and IFR 31, Rangueil Hospital, L1 Bldg, BP 84225 Toulouse 31432 Cedex 4, France; [9] Department of Endocrinology, Hospital Joan XXIII, Rovira i Virgili University, Tarragona; [10] Institut d'Investigació Sanitaria Pere Virgili (IISPV), Tarragona; [11] Department of Biosciences and Nutrition, Karolinska Institutet, Novum, SE-141 83, Huddinge, Sweden; [12] Center for Nuclear Receptors and Cell Signaling, Department of Biology and Biochemistry, University of Houston, Houston, TX, 77204, USA; †MSF and SRV contributed equally to this manuscript

Here we report that common gene variants of the nuclear co-activator RAP250 in humans are associated with BMI, HOMA-IR, and plasma triglycerides. We also disclose that RAP250 exerts potent regulatory action over energy metabolism. RAP250+/- mice show enhancement of glucose tolerance, insulin sensitivity and energy expenditure, and they are resistant to high-fat diet-induced obesity. Local in vivo RAP250 silencing in BAT but not WAT of control mice reduced body weight and fat mass, and enhanced glucose oxidation, thereby indicating a role of RAP250 in the regulation of BAT metabolic activity. A role of BAT was also strongly suggested upon induction of thermoneutrality in RAP250+/- mice. In RAP250-deficient BAT, cyclic AMP-dependent protein kinase (PKA) activity was improved, which was explained by reduced expression of PKA regulatory subunits with low affinity for cAMP and by increased expression of ADORA2 adenosine receptors. Moreover, we uncovered the presence of negative circuitry linking RAP250 and PKA in BAT. While RAP250 deficiency enhances PKA activity in mice, an acute PKA-stimulating condition, such as cold exposure, represses RAP250. Overall, our data suggest that RAP250 plays a key role in maintaining energy metabolism and adiposity in humans and mice, mostly through PKA-induced modulation of the metabolic activity of BAT.

RC20 Role of Mfn-1 in brown adipose tissue during cold-challenge

Beatriz Jiménez, Gema García, Patricia Marqués, Jesús Burillo, Carlos González, Carlos Guillén, Manuel Benito

Diabetes and Obesity Group, Biochemistry and Molecular Biology Department; Pharmacy School, UCM, CIBERDEM

Brown adipose tissue (BAT), through the adaptive thermogenesis, plays an essential role in the energy balance and body weight regulation that could be related with obesity. Two essential components in the non-shivering thermogenesis (NST) are the level of UCP-1 expression and the mitochondrial dynamics. Mitochondrial dynamics is the balance between mitochondrial fusion and fission which is involved in the amplification or not in energy expenditure. Whereas BAT thermogenic activity remains active in rodents for its entire life, few human individuals maintain an active brown fat beyond the adulthood. Moreover, the different adipose tissues conforming the adipose organ constitute the major lipid storage. The appearance of beige cells through the browning effect constitutes a new player in NST field even when these adipocytes can either express UCP1 or not.

The aim of this work was to study the role of mitofusin-1 (MFN-1), which is a mitochondrial fusion protein, in the energy expenditure during cold exposure. Therefore, we have generated a mouse model which lacks this protein specifically in UCP1+ tissues such as the most important thermogenic tissue: interscapular BAT (iBAT). Preliminary results have shown a possible trend towards a higher glucose tolerance and a better thermogenic adaptation to cold in BATMFN1KO mice as compared to control mice. Moreover, MFN-2 expression in iBAT seemed to be higher in BATMFN1KO mice as a compensatory system to MFN-1 deficiency, while the protein expression related to mitophagy did not appear to be affected. In addition, when we studied lipid distribution in the liver of these mice, we have seen differences in the size of the lipid droplets. Control mice had a tendency to a reduced size of lipid droplet that it could be explained by a higher lipolysis rate. However, it will be necessary a larger sample size to complete this work.

RC21 TP53INP2 regulates energy balance through brown adipose tissue thermogenesis

Alba Sabaté-Pérez[1,2,3], Montserrat Romero[1 2,3], Sam Virtue[4], Antonio Vidal-Puig[4,5], Xavier Testar[1,3], Antonio Zorzano[1,2,3]

[1]CIBERDEM, Barcelona; [2]Institute for Research in Biomedicine (IRB Barcelona), The Barcelona Institute of Science and Technology, Barcelona; [3]Departament of Biochemistry and Molecular Biomedicine, Faculty of Biology, University of Barcelona; [4]Metabolic Research Laboratories, Institute of Metabolic Science, Addenbrooke's Hospital, University of Cambridge, Cambridge, CB2 0QQ, UK; [5]Wellcome Trust Sanger Institute, Wellcome Trust Genome Campus, Hinxton, Cambridge, CB10 1SA, UK

Overweight and obesity have increased dramatically during recent decades becoming a major health problem for which therapeutic options are limited. Brown adipose tissue (BAT) non-shivering thermogenesis contributes to energy dissipation and impacts on energy balance. Functional BAT depots have recently been detected in lean adult humans which can be activated by cold exposure. Of relevance, human BAT activity correlates with lower body mass index and improved glycaemia, indicating that strategies that could increase BAT mass and/or its activation could become promising targets to combat obesity and its metabolic complications. Tumour protein p53-inducible nuclear protein 2 (TP53INP2) is a nuclear cofactor that stimulates a variety of nuclear hormone receptors and that exits to the cytosol to promote autophagy. Moreover, TP53INP2 expression is downregulated in the skeletal muscle and white adipose tissue from obese subjects. Recently, TP53INP2 has been reported as a negative regulator of white adipogenesis, which ablation in mice causes augmented adiposity. The study of TP53INP2 expression showed that its mRNA levels in BAT are upregulated under conditions of stimulated thermogenesis, such as cold or high-fat diet exposure. In contrast, its expression in this tissue is decreased under thermoneutral environment. The genetic ablation of TP53INP2 in brown adipose cells in mice (TP53INP2 KOMyf5) increases BAT weight and lipid accumulation in brown adipocytes. Moreover, young TP53INP2 KOMyf5 mice display reduced energy expenditure and thermogenic capacity, which leads to an obese phenotype at older ages. Overall, our results support the view that TP53INP2 expression is crucial for BAT thermogenesis and for the maintenance of energy balance, which opens a new door for potentially targeting obesity.

RC22 Resveratrol enhanced cold-induced thermogenesis through a differential browning effect on the adipose organ in a mouse model showing atrophied interscapular adipose tissue: a therapeutic approach

Manuel Benito[1,2,3], Patricia Marqués[1], Helena Martínez[1], Beatriz Jiménez[1,2], Jesús Burillo[1,2,3], Carlos González[1], Gema García[1,2], Carlos Guillén[1,2,3]

[1]Department of Biochemistry and Molecular Biology, School of Pharmacy, Complutense University of Madrid; [2]CIBERDEM, [3]MOIR2: Mechanism of Insulin Resistance, General Direction of Universities and Investigation (CCMM), Madrid

Obesity is a worldwide disease that tripled its prevalence since 1975. To combat obesity, the natural occurring polyphenol resveratrol mimics caloric restriction through the activation of SIRT1 pathway. We have developed a mouse model showing a double knockout (IR/IGF1R) in brown adipose tissue that showed a severe interscapular brown fat atrophy, accompanied by an accumulation of uncrest mitochondria. As a result, DKO mice showed a severe hypothermia upon 2-3 hours of cold exposure. DKO mice treated with resveratrol showed a significant reversion in their impaired thermogenesis as observed in the DKO mice treated with the adjuvant. This improved thermogenic adaptation was correlated with an enhanced expression of different mitochondrial markers and mitochondrial fusion proteins in the remnant iBAT as well as a manifest improvement in its mitochondrial integrity. Immunohistochemistry of different white adipose tissue depots in those mice showed an increase in mitochondrial markers and also in the UCP1 content, which suggest a significant browning effect on the several depots of the adipose organ studied. The use of leupeptin demonstrated an accumulation of several markers that reveal the occurrence of an ongoing autophagic flux within the BAT and in the liver in control mice. This accumulation effect was not observed in the DKO mice likely due to an inhibition in the endogenous mitophagic process. DKO mice treated with resveratrol partially restored the enhanced mitophagic flux in response to leupeptin and the presence of mitophagosomes has been demonstrated in brown adipose tissue. DKO mice present an important damage in their mitochondrial structure with a constitutive failure in the intrinsic mitophagy in iBAT as well as in liver. In addition, resveratrol plays an important role increasing cold tolerance, mitochondrial biogenesis and thermogenesis in those animals. These data suggest a potential therapeutic use of resveratrol improving the content of healthy mitochondria.

RC23 Role of TP53INP2 in autophagy and apoptosis cross-talk

Saška Ivanova[1,2,3]*, Antonio Zorzano[1,2,3]

[1] Institute for Research in Biomedicine (IRB Barcelona), Barcelona Institute of Science and Technology (BIST), Barcelona; [2] CIBERDEM, Barcelona; [3] Departamento de Bioquimica i Biomedicina Molecular, Facultat de Biologia, Universitat de Barcelona

TP53INP2 is a nuclear protein that transactivates a number of nuclear hormone receptors and regulates myogenic and adipogenic differentiation. Upon cellular stress TP53INP2 rapidly shuttles from the nucleus to the cytoplasm into punctate structures named autophagosomes (1). TP53INP2 positively regulates autophagy by binding to Atg8 proteins through a consensus LIR motif, and over-expression of DOR in HeLa cells increased the number of autophagosomes under basal and stress-induced conditions, indicating that DOR is a positive regulator of autophagy (1). In addition, DOR mRNA and protein levels are down-regulated in muscle and adipose tissue in diabetic and obese mice and in human samples (2, 3).

Recently, we published a novel role of TP53INP2 in death-receptor signaling, where TP53INP2 binds caspase-8 and TRAF6, thereby promoting the ubiquitination and activation of caspase-8 by TRAF6. We found TRAF6 interacting motif (TIM) and ubiquitin interacting motif in TP53INP2 that enable it to function as a scaffold for already ubiquitinated caspase-8 and TRAF6 for further poly-ubiquitination of caspase-8. A screen of cancer cell lines showed that those with higher protein levels of TP53INP2 are more prone to TRAIL-induced apoptosis, indicating TP53INP2 as a potential predictive marker of the responsiveness of cancer cells to TRAIL treatment (4). Moreover, overexpression of TP53INP2 upregulates levels of p62 (2), another protein that plays a role in autophagy and apoptosis. Thus, different protein levels of TP53INP2 might lead to different outcomes (i.e. autophagy or apoptosis) depending on celular context and stimuli.

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RC24 Mobilization of Arachidonic Acid and Adrenic Acid in Macrophages by Two Different Phospholipase A2s

Patricia Monge, Álvaro Garrido, María A. Balboa, Jesús Balsinde.

Instituto de Biología y Genética Molecular, Consejo Superior de Investigaciones Científicas (CSIC), Valladolid, CIBERDEM.

Cardiovascular and metabolic diseases have been widely studied in recent years as they have a major impact on worldwide mortality. In the last decades it has been observed that the metabolism of n-6 polyunsaturated fatty acids of 20 carbon atoms (i.e. arachidonic acid and adrenic acid) is involved in the appearance and development of different metabolic diseases with cardiovascular impact such as diabetes, since its metabolites are important factors in the initiation and resolution of inflammation.

In our work we focus on the importance of different enzymes involved in the mobilization of both arachidonic acid and adrenic acid, as well as the mechanisms involved in the reacylation of these fatty acids. For this, we have used mouse peritoneal macrophages and a series of enzymatic inhibitors of cPLA2 (pyrrophenone) and iPLA2 (FKGK18, GK436 and BEL) by measuring phospholipid levels by liquid chromatography coupled to mass spectrometry. We observe that the mobilization of arachidonic acid is mediated by the enzyme cPLA2, whereas in the case of adrenic acid, both cPLA2 and iPLA2 are involved. On the other hand, under stimulating conditions, the release of arachidonic acid and adrenic acid is uneven in different phospholipids, which can limit the synthesis of eicosanoids. In the case of arachidonic acid, the release is produced in the PC and PI species, with no variations observed in PE, while in the case of adrenic acid, mobilization is only observed in the PC species.

Finally, we have observed that the supplementation of the cells with adrenic acid displaces certain phospholipid fatty acids such as oleic acid, linoleic acid and dihomo-γ-linolenic acid (gas chromatography coupled to mass spectrometry) but it does not influence the metabolism of the arachidonic acid nor in the production of eicosanoids, which provides us with information about the biological functions of these two polyunsaturated fatty acids. Our results identify separate mechanisms for regulating the utilization of adrenic and arachidonic acids and suggest that the two fatty acids may serve non-redundant functions in cells.

RC25 Role of the succinate/SUCNR1 axis in the physiopathology of NAFLD

Patricia Rada[1,2]*, Victoria Ceperuelo-Mallafré [2,3]*, Enrique Calvo [2,3], M. Mar Rodríguez [2,3], Catalina Núñez-Roa [2,3], Teresa Villanueva [2,3], Joan Vendrell [2,3], Ángela M. Valverde [1,2] and Sonia Fernández-Veledo [2,3]

[1] Instituto de Investigaciones Biomédicas "Alberto Sols" (CSIC-UAM), Madrid; [2] CIBERDEM; [3] Unitat de Recerca, Hospital Universitari de Tarragona Joan XXIII, Institut d´Investigació Sanitària Pere Virgili, Tarragona *Equal contributors

Background: Non-alcoholic fatty liver disease (NAFLD) is one of the main causes of liver failure worldwide. Recent findings revealed that NAFLD patients present increased circulating succinate. Succinate, an extracellular signaling metabolite acting through its cognate receptor SUCNR1, is an intermediate of the tricarboxylic acid cycle that is accumulated at intracellular level during inflammatory processes. A profibrogenic function of SUCNR1 in hepatic stellate cells has been reported in NAFLD, however the role of SUCNR1 in hepatocytes is unknown. Herein, our work is focused in studying the impact of Sucnr1 deficiency in diet-induced NAFLD. Moreover, the specific molecular events downstream SUCNR1 activation have been analysed in primary hepatocytes.

Methods: Male Sucnr1-/- and wild-type (WT) mice were fed a standard (NCD) or choline-deficient high fat diet (HFD-CD) for 16 weeks. Parameters that assess glucose homeostasis and NAFLD progression were analysed. To test cell-autonomous insulin sensitivity, primary hepatocytes were treated with succinate prior to insulin stimulation.

Results: Circulating succinate levels were significantly higher in Sucnr1-/- mice than WT mice. Glucose, insulin and pyruvate tolerance tests revealed that Sucnr1 deficiency in HFD-CD-fed mice led to an imbalance of glucose homeostasis. In addition, an increased hepatic triglyceride content, but less hepatic fibrosis, was observed in Sucnr1-/- mice. HFD-CD-fed Sucnr1-/- mice showed elevated gene expression of several inflammatory, and glucose and lipid metabolism-related genes compared to WT mice. Preliminary data in primary hepatocytes revealed that short-term succinate exposure resulted in an enhanced IR and AKT phosphorylation in response to insulin. However, long-term succinate treatment impaired insulin response by reducing pIR and pAKT protein levels.

Conclusions: Our preliminary results suggest that Sucnr1 deficiency impairs glucose homeostasis, enhances inflammation and reduces fibrosis. Also, in primary hepatocytes a dual effect on insulin action was observed after succinate exposure. Overall, our findings suggest a role for succinate-SUCNR1 axis in NAFLD progression.

RC26 Inhibition of protein tyrosine phosphatase 1B protects against lipotoxicity in liver progenitor oval cells

Inés Barahona[1,2], M. Pilar Valdecantos[1,2], Patricia Rada[1,2], Alma Astudillo[2,3], Jesús Balsinde[2,3], Aránzazu Sánchez[4], Ángela M. Valverde[1,2]

[1]IIBm Alberto Sols (CSIC-UAM), Madrid, [2]CIBERDEM; [3]Instituto de Biología y Genética Molecular (CSIC-UVA), Valladolid; [4]Departamento de Bioquímica y Biología Molecular, UCM, Madrid

Background and aims: Oval cells are progenitor cells with an emerging role in liver regenerative responses. However, the characterization of their susceptibility to lipotoxicity in during obesity-associated non-alcoholic fatty liver disease (NAFLD) is unknown. Inhibition of protein tyrosine phosphatase 1B (PTP1B) is a pharmacological strategy against insulin resistance/obesity. PTP1B deficiency also protects against acute/chronic hepatocyte damage. We analysed the susceptibility of oval cells with or without PTP1B to lipotoxicity and the molecular mechanisms involved. Materials and methods: Oval cells from PTP1B+/+ and PTP1B -/- mice were treated with palmitic acid (PA), after which unfolded protein response (UPR) and autophagy/apoptosis markers were analysed. A lipidomic study was conducted to characterize the accumulation of lipid species upon PA stimulation in both genotypes of oval cells. Results: Treatment of PTP1B+/+ oval cells with PA induced apoptotic cell death in parallel to a blockade of the autophagy flux. This lipotoxic effect was absent in PTP1B-/- cells that accumulated lipid droplets upon PA treatment and presented elevated levels of UPR-sensitive mediators, AMPK phosphorylation and Sirtuin 1. These effects were also found in PTP1B silenced wild-type oval cells. Moreover, PA-treated PTP1B-/- oval cells showed an enhanced antioxidant response including nuclear factor erythroid 2-related factor nuclear translocation. Elevation of stearoyl CoA desaturase 1 (Scd1) mRNA was found in PTP1B-/- oval cells treated with PA and lipidomics revealed higher unsaturated/saturated fatty acids either free or incorporated into triacylglicerides, diacylglicerides or phospholipids. Blockade of autophagy flux in PTP1B-/- oval cells inhibited lipid droplet formation and restored lipoapoptosis. Conclusion: Liver oval cells are susceptible to lipotoxicity, and PTP1B deficiency protects against lipotoxic cell death by mechanisms including enhanced antioxidant defences and capacity to generated unsaturated lipid species stored in lipid droplets, suggesting a potential benefit in cellular regenerative therapies against NAFLD. These effects are likely mediated by autophagy-derived energy suppliers.

RC27 Effect of the hepatocyte-derived lipotoxic extracellular vesicles in liver inflammation in non-alcoholic fatty liver disease

Rosa Alén[1], Irma Garcia-Martinez[1], Laura Pereira[2], Jesús Balsinde[2], Manuel Izquierdo[1], Ángela M. Valverde[1].

[1]Instituto de Investigaciones Biomédicas Albero Sols, CSIC/UAM, Madrid; [2] Instituto de Biología y Genética Molecular, CSIC/UVa, Valladolid

Background: Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide. Lipotoxicity is a key trigger of NAFLD progression due to accumulation of toxic lipids species in hepatocytes including saturated free fatty acids (SFAs), which activate pro-inflammatory pathways. Lipotoxic hepatocyte injury might affect the responses of surrounding liver cells through the release of extracellular vesicles (EVs). We analysed the impact of EVs secretion by hepatocytes under lipotoxic insult in liver inflammation. Methods: C57Bl6j male mice were fed chow (control) or high-fat diet (HFD) for 14 weeks. Exosome-enriched fraction (Exos) was isolated by differential ultracentrifugation from: 1) hepatocytes from chow-fed mice without (ExoCh) or with palmitic acid (PA) treatment (ExoPA), 2) hepatocytes from HFD-fed mice (ExoHFD), 3) plasma from chow- (Circ-ExoCh) or HFD-fed mice (Circ-ExoHFD). Exos were characterized by Western-blot, Transmission Electron Microscopy, Nanoparticle Tracking Analysis and lipidomics. Mouse macrophages were stimulated with Exos and pro-inflammatory responses were assessed by Western-blot, RT-qPCR, immunofluorescence, and lipidomics. Stained Exos were added to macrophages to monitor internalization and injected intravenously to mice to study biodistribution and effects in liver inflammation. Results: Release of ExoPA, ExoHFD and Circ-ExoHFD was increased compared to ExoCh and Circ- ExoCh. Exos were internalized by macrophages through the endosomal pathway and both ExoPA and ExoHFD triggered pro-inflammatory responses: IκBα degradation, nuclear NF-κB translocation and elevation in Il6 and Il1b mRNAs. Inhibition of TLR4 blocked the inflammatory pathway activation. ExoPA and ExoHFD fractions as well as macrophages treated with these Exos, were enriched in SFAs, such as palmitic acid (C16:0) and estearic acid (C18:0), both TLR4 activators. Exos injected in vivo targeted liver Kupffer cells. ExoPA and ExoHFD delivery increased stress kinases and NF-kB nuclear translocation. Conclusion: Data revealed a novel molecular mechanism by which SFAs loaded-exosomes released by hepatocytes under NAFLD conditions target macrophages and trigger TLR4-mediated inflammatory pathways.

RC28 Regular insulin added to total parenteral nutrition vs subcutaneous glargine in non-critically ill diabetic inpatients, a multicenter randomized clinical trial: INSUPAR trial

Cristina Maldonado-Araque[1,2,3], Jose Abuín[1,2], María J. Tapia[1], Rafael López[4], Sandra Herranz[5], Jose M. García-Almeida[6], Katherine García-Malpartida[7], Mercedes Ferrer[8], Emilia Cancer[9], Luis M. Luengo-Pérez[10], Julia Álvarez[11], Carmen Aragón[12], María J. Ocón[13], Álvaro García-Manzanares[14], Irene Bretón[15], Pilar Serrano-Aguayo[16], Natalia Pérez-Ferre[17], Juan J. López-Gómez[18], Josefina Olivares[19], Carmen Arraiza[20], Cristina Tejera[21], Jorge D. Martín[22], Sara García[23], Ángel L. Abad[24], María R. Alhambra[25], Ana Zugasti[26], Juan Parra[27], Sara Torrejón[28], María J. Tapia[1] Gabriel Olveira[1,2,3]

[1] Unidad de Gestión Clínica de Endocrinología y Nutrición, Hospital Regional Universitario de Málaga, Instituto de Investigación Biomédica de Málaga (IBIMA); [2] Universidad de Málaga; [3] CIBERDEM; [4] Servicio de Endocrinología y Nutrición, Hospital Universitario de Bellvitge, L'Hospitalet de Llobregat; [5] Servicio de Endocrinología y Nutrición, Hospital Universitario de Guadalajara; [6] Servicio de Endocrinología y Nutrición, Hospital Universitario Virgen de la Victoria, Málaga; [7] Servicio de Endocrinología y Nutrición, Hospital Universitario y Politécnico La Fe, Valencia; [8] Servicio de Endocrinología y Nutrición, Hospital Clínico Universitario Virgen de la Arrixaca, Murcia; [9] Sección de Endocrinología y Nutrición, Hospital Universitario de Fuenlabrada; [10] Servicio de Endocrinología y Nutrición, Hospital Universitario de Badajoz; [11] Servicio de Endocrinología y Nutrición, Hospital Universitario Príncipe de Asturias, Madrid; [12] Servicio de Endocrinología y Nutrición, Hospital Universitario Fundación Jiménez Díaz, Madrid; [13] Servicio de Endocrinología y Nutrición, Hospital Universitario Lozano Blesa, Zaragoza; [14] Servicio de Endocrinología y Nutrición, Hospital General La Mancha Centro, Alcázar de San Juan; [15] Servicio de Endocrinología y Nutrición, Hospital Universitario Gregorio Marañón, Madrid; [16] Unidad de Endocrinología y Nutrición, Hospital Universitario Virgen del Rocío, Sevilla; [17] Servicio de Endocrinología y Nutrición, Hospital Clínico San Carlos, Madrid; [18] Servicio de Endocrinología y Nutrición, Hospital Clínico Universitario de Valladolid; [19] Servicio de Endocrinología y Nutrición, Hospital Universitario Son Llatzer, Illes Balears; [20] Servicio de Endocrinología y Nutrición, Complejo Hospitalario de Jaén; [21] Servicio de Endocrinología y Nutrición, Complejo Hospitalario Universitario de Ferrol, A Coruña; [22] Servicio de Endocrinología y Nutrición, Hospital Universitario Severo Ochoa, Leganés, Madrid; [23] Servicio de Endocrinología y Nutrición, Complejo Asistencial Universitario de León; [24] Unidad de Nutrición y Sección de Endocrinología, Hospital General Universitario de Alicante; [25] Servicio de Endocrinología y Nutrición, Hospital Universitario Reina Sofía, Córdoba; [26] Servicio de Endocrinología y Nutrición, Complejo Hospitalario de Navarra; [27] Servicio de Endocrinología y Nutrición, Hospital de Mérida, Badajoz; [28] Servicio de Endocrinología y Nutrición, Hospital de Sant Joan Despí Moisés Broggi, Barcelona.

Background: There is no established insulin regimen in T2DM patients receiving parenteral nutrition.
Aims: To compare the effectiveness (metabolic control) and safety of two insulin regimens in patients with diabetes receiving total parenteral nutrition (TPN).
Design: Prospective, open-label, multicentre, clinical trial on adult inpatients with type 2 diabetes on a non-critical setting with indication for TPN. Patients were randomized on one of these two regimens: 100% of regular insulin (RI) on TPN or 50% of RI added to TPN bag and 50% subcutaneous Glargine Insulin (GI). Data were analysed according to intention-to-treat principle.
Results: 81 patients were on RI and 80 on GI. No differences were observed in neither average total daily dose of insulin, programmed or correction, nor in capillary mean blood glucose during TPN infusion (165.3 ± 35.4 in RI vs 172.5 ± 43.6 mg/dL in GI; p=0.25). Mean capillary glucose was significantly lower in the GI group within two days after TPN interruption (160.3 ± 45.1 in RI vs 141.7 ± 43.8 mg/dL in GI; p=0.024). The percentage of capillary glucose above 180 mg/dL was similar in both groups. The rate of capillary glucose £70 mg/dL, the number of hypoglycemic episodes per 100 days of TPN, and the percentage of patients with non-severe hypoglycemia were significantly higher on GI group. No severe hypoglycemia was detected. No differences were observed in length of stay, infectious complications, or hospital mortality.

Conclusion: Effectiveness of both regimens was similar. GI group achieved better metabolic control after TPN interruption, but non-severe hypoglycemia rate was higher in the GI group.

RC29 Lipid biomarkers as predictors of diastolic dysfunction in diabetes with poor glycemic control

[1]Jairo Lumpuy-Castillo, [2]Dina Khedr, [2]Noha Musa , [1,3]Óscar Lorenzo

[1]Laboratory of Diabetes Research, Instituto de Investigaciones Sanitarias-Fundación Jiménez Díaz, Universidad Autónoma, Madrid; [2]Pediatric Diabetes, Endocrine and Metabolism Unit, Children Hospital, Cairo University, Cairo, Egypt; [3]CIBERDEM

Uncontrolled type-1 diabetes (T1DM) can lead to dyslipidaemia and albuminuria, which may promote cardiovascular injuries. However, some lipidemic factors could be useful in predicting cardiac dysfunction. Seventy-eight adolescents under insulin treatment due to a 6-year history of T1DM and were retrospectively examined. Glycemia, lipidemia, and albuminuria were measured in addition to development of cardiovascular abnormalities Both girls and boys showed higher HbA1c and fasting blood glucose and 27.1% females and 33.3% males exhibited microalbuminuria though their plasma levels of total cholesterol (TC), triglycerides (TG), and low-density lipoproteins (LDL) and high-density lipoproteins (HDL lipoproteins were in the normal range. They exhibited a preserved systolic function, but 50% of females and 66.6% of males had developed diastolic failures. Interestingly, girls with diastolic dysfunction showed significantly lower concentrations of HDL and higher TC/HDL and TG/HDL ratios. In fact, low HDL levels (OR 0.93; 95% CI 0.88–0.99; p = 0.029) and high TC/HDL (OR 2.55; 95% CI 1.9–5.45; p = 0.016) and TG/HDL (OR 2.74; 95% CI 1.12–6.71; p = 0.028) ratios associated with the development of diastolic complications. The cut-off values for HDL, TC/HDL, and TG/HDL were 49 mg/dL, 3.0 and 1.85, respectively. HDL and TC/HDL and TG/HDL ratios may be useful for predicting diastolic dysfunction in girls with uncontrolled T1DM.

RC30 Lipidomic profile and subclinical carotid atherosclerosis in diabetes mellitus

Maria Barranco[1,8,9,10], Esmeralda Castelblanco[1,2], Paola Quifer[1,2], Oscar Yanes[2,3], Ralf Weber[4], Emilio Ortega[5,6], Nuria Alonso[2,7], Didac Mauricio[1,2]

[1]Sant Pau Biomedical Research Institute (IIB Sant Pau), Hospital de la Santa Creu i Sant Pau, Endocrinology and Nutrition, Barcelona; [2]CIBERDEM; [3]Institute of Health Research Pere Virgili (IISPV) & University Pere i Virgili, Metabolomics Platform, Reus; [4]Phenome Centre Birmingham and School of Biosciences, University of Birmingham, Bioinformatics, Birmingham, UK; [5]Institut d'Investigacions Biomèdiques August Pi i Suñer, Hospital Clinic, Endocrinology and Nutrition, Barcelona; [6]Center for Biomedical Research on Physiopathology of Obesity and Nutrition, CIBEROBN, Madrid; [7]Institute for Health Science Research Germans Trias i Pujol (IGTP), University Hospital and Health Research Institute Germans Trias i Pujol, Endocrinology and Nutrition, Badalona; [8]B2SLab, Departament d'Enginyeria de Sistemes, Automàtica i Informàtica Industrial, Universitat Politècnica de Catalunya, Barcelona; [9] CIBER-BBN, Madrid; [10]Institut de Recerca Pediàtrica Hospital Sant Joan de Déu, Esplugues de Llobregat, Barcelona

Lipid metabolism disruption and excess cardiovascular risk have been observed in diabetes subjects, but the associations between diabetes, serum lipidome, and subclinical carotid atherosclerosis (SCA) have not been fully characterized. Our aim was to evaluate serum lipidomic profiles and their associations with SCA in subjects with type 1 (T1D), type 2 (T2D) diabetes and control subjects without diabetes (CT).

A cross-sectional study of 536 subjects, 156 with T1D, 159 with T2D and 221 CT (with SCA in 48.7%, 50.3% and 47.1%, respectively). All subjects were free from cardiovascular and/or chronic kidney disease. All subjects underwent a comprehensive lipidomic analysis using ultra-high-performance liquid chromatography-electrospray ionization tandem mass spectrometry (UHPLC-ESI-MS), carotid ultrasound (mode B) to assess SCA and clinical assessment. PCA, PLSDA and multiple linear regression models were used to assess the association between each metabolite feature and the presence of SCA.

The lipidomic profile was not different between subjects with and without SCA in T2D and CT. However, T1D subjects with SCA had higher triglycerides (p=0.016). On the other hand, multiple linear regression models were applied considering the number of atherosclerotic plaques as a continuous variable and several lipidic species were found to be significantly associated. Sixteen lipid sub-classes had a corrected p-value lower than 0.05 (number of lipidic species): acyl-carnitine (1), lysophosphatidylethanolamine (1), phosphatidylethanolamine (16), ceramide (7), Lysophosphatidylcholine (3), diglyceride (2), cholesterol ester (1), phosphatidylcholine (13), methylphosphocholine (5), phosphatidylinositol (2), triglycerides (10), monosialodihexosylganglioside (1), lysophosphatidic acid (1), lysodimethyl phosphatidylethanolamine (1), monohexosylceramide (2) and ceramide-1-phosphate (2).

Although subjects with SCA do not show significantly different lipidomic profiles with respect to subjects without SCA, when considering the number of atherosclerotic plaques in each patient, several lipidic species appear to be statistically significant, this finding proves that the burden of SCA is associated with different lipidomic profile. This deserves further research.

RC31 Relation between skin AGEs and the coronary artery calcium score: results of the PRECISED study

Alejandra Planas[1], Olga Simó-Servat[1], Jordi Bañeras[2], Cristina Hernández[1], Ignacio Ferreira[2] and Rafael Simó[1]

[1] Diabetes and Metabolism Research Unit, Endocrinology Department, Vall d'Hebron Research Unit, Vall d'Hebron Hospital, Autonomous University of Barcelona, Barcelona, CIBERDEM; [2] Cardiology Research Group, Cardiology Department, Vall d'Hebron Research Institute, Vall d'Hebron Hospital, Autonomous University of Barcelona

Coronary artery disease (CAD) is a leading cause of mortality in subjects with type 2 diabetes (T2D). However, an early identification of diabetic patients at risk of developing CAD remains a challenge. Coronary artery calcium score (CACs) is considered the most sensitive risk stratification tool among asymptomatic persons with diabetes. Nevertheless, widespread screening cannot be recommended; consequently, the identification of a more targeted population is needed. The accumulation of advanced glycation end products (AGEs) plays an important role in the pathogenesis of CAD. In the recent years, a non-invasive method for AGEs assessment through skin autofluorescence (SAF) has been validated.

The aim of this study is to evaluate whether there is a relationship between SAF values and CACs in T2D patients.

Materials and methods**.** This is a case-control study, comprising 157 T2D subjects without known CAD, and 51 non-diabetic subjects matched by age and sex. We collected medical history and laboratory tests, fundus eye examination and SAF determination (AGE Reader™) were performed. A CT-scan was performed, and CACs was calculated. A value of CACs≥400 Agatston Units (AU) was considered as "high cardiovascular risk".

Results. T2D patients had higher value of SAF compared to controls (2.67±0.66 VS. 2.40±0.62; p=0.011). Within T2D subjects, 122 presented CACs<400 and 35 CACs ≥400 AU. A significant difference regarding gender, age, HDL cholesterol and homocysteine was observed between T2D patients with CAC≥400 AU vs. patients with CACs<400. SAF values were significantly higher among the group with CACs≥400AU (2.96±0.86 VS. 2.59±0.57; p=0.0035). The logistic regression analysis showed that age, cholesterol HDL and SAF values were independently related to CACs≥400AU.

Conclusion: SAF value is independently associated to high CACs values in subjects with T2D. This finding suggests that SAF could be useful to identify those diabetic patients in which a more invasive examination such as CACs should be prioritized.

RC32 Addition of probiotics to anti-obesity therapy by percutaneous electrical stimulation of dermatome T6. A pilot study

[1]Jairo Lumpuy-Castillo, [1]Tianyu Hang, [1]Marta Crespo-Yanguas, [2,3]Jaime Ruiz-Tovar, [1,4]Óscar Lorenzo

[1]Laboratory of Diabetes and Vascular pathology. Instituto de Investigaciones Sanitarias-Fundación Jiménez Díaz. Universidad Autónoma, Madrid; [2]Obesity Unit. Clínica Garcilaso, Madrid, [3]Department of Health Sciences, Universidad Rey Juan Carlos, Madrid; [4]CIBERDEM

Obesity is becoming a serious pathology in current societies. Percutaneous electrical stimulation (PENS) of dermatome T6 has demonstrated to reduce stomach motility, and appetite allowing a significantly greater weight loss than isolated hypocaloric diets. However, modulation of intestinal microbiota through increasing anti-obesogenic bacteria could improve this effect and control hyperglycemia and dyslipemia in patients.

Methodology: A pilot prospective and randomized study was performed in patients (n= 20) with body mass index (BMI) > 30 Kg/m2. Half of them underwent ten weeks of PENS in conjunction with an hypocaloric diet (PENS-Diet), and the other half was treated with the same strategy plus the administration of probiotics (L. plantarum LP115, B. brevis B3 and L. acidophilus LA14). Fecal samples were obtained before and after interventions. The weight loss and changes in blood pressure, glycemic and lipid profile, and in gut microbiota were investigated.

Results: The weight loss was significantly higher (16.2 vs. 11.1 Kg, p=0.022) and glycated haemoglobin and triglycerides were lower (-0.46 vs. -0.05%, p=0.032, and -47.0 vs. -8.5 mg/dL, p=0.002, respectively) in those patients receiving PENS-Diet and probiotics comparing with those with only PENS-Diet. Also, an enrichment of anti-obesogenic bacteria, including Bifidobacterium spp, Akkermansia spp. and Prevotella spp, and the attenuation of the Firmicutes/Bacteroidetes ratio were noted in fecal samples after probiotics administration.

Conclusion: In obese patients, the addition of specific probiotics to a PENS intervention under hypocaloric diet, further improved weight loss and glycemic and lipid profile in parallel to the amelioration of gut dysbiosis.

RC33 Incidence of diabetes mellitus in the Basque country and associated risk factors: reassessment of an adult population after seven years of follow-up

Inés Urrutia[1,2], Alicia Martín-Nieto[1,3], Rosa Martínez[1,2], J Oriol Casanovas-Marsal[1], Anibal Aguayo[1,2], Juan del Olmo[4], Eunate Arana[1], Elsa Fernandez-Rubio[1,3], Luis Castaño[1,2]*, Sonia Gaztambide[1,2,3]* on behalf of the Diabetes Epidemiology Group

[1]Biocruces Bizkaia Health Research Institute, Cruces University Hospital, University of the Basque Country UPV/EHU, Bizkaia; [2]CIBERDEM, CIBERER; [3]Endocrinology and Nutrition Department, Cruces University Hospital, Bizkaia; [4]Clinical Chemistry Laboratory, Cruces University Hospital, Bizkaia

Objective. To estimate the incidence of diabetes mellitus in the Basque Country and the risk factors involved in the progression of the disease by reassessing an adult population representative of the whole territory after 7 years of follow-up.
Methods. A total of 517 people who agreed to participate in the reassessment were required to answer a questionnaire on personal and family medical history and lifestyle, followed by a physical examination and a 75 g Oral Glucose Tolerant Test (OGTT).
Results. The cumulative incidence of diabetes was 4.64% in 7 years and the raw incidence rate was 6.56 cases/1000 person-year (95%CI: 2.93-6.94). Of the incident cases, 59% (13/22) were unknown diabetes. The most strongly associated markers with diabetes by univariate logistic regression analyses were age from 60 onwards, dyslipidaemia, prediabetes at baseline and insulin resistance. We also found a statistically significant association with hypertension, obesity, family history of diabetes and low education level. Multivariate analysis adjusted for age and sex showed that dyslipidaemia, abdominal obesity (measured as waist to hip ratio), together with family history of diabetes had a high predictive value for diabetes (AUC-ROC=0.900, 95%CI: 0.848-0.953, p=0.942).
Conclusions. The incidence rate of diabetes in the Basque Country remains stable over time and lower than those reported for other Spanish regions probably due to the lower percentage of obesity. A set of risk factors assessed together such as dyslipidaemia, abdominal obesity and family history of diabetes, has great predictive value for diabetes and suggests the need for early intervention before the onset of prediabetes to prevent the diseases.

RC34 After metformin: Analysis of the effectiveness of second oral glucose-lowering therapy in routine clinical practice from the Mediterranean area

Bogdan Vlacho[1], Manel Mata-Cases[1, 2], Joan Antoni Vallès-Callol[1], Jordi Real[1, 2], Xavier Mundet-Tudurí[1, 4], Kamlesh Khunti[5], Dídac Mauricio[1, 2,3], Josep Franch-Nadal[1, 2]

[1]DAP-Cat group, Unitat de Suport a la Recerca Barcelona, Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol), Barcelona; CIBERDEM); [3]Department of Endocrinology and Nutrition, Hospital Universitari de la Santa Creu i Sant Pau, Spain; [4] Departament of Medicine, Universitat Autònoma de Barcelona, Bellaterra; [5]Diabetes Research Centre, University of Leicester, Leicester, UK

Background: In clinical practice there is often a need for the addition of second-line therapies to improve glycaemic control and to reduce risks from cardiovascular and renal diseases. Three classes of oral antidiabetics, namely dipeptidyl peptidase-4 inhibitors (DPP-4i), sodium-glucose co-transporter 2 inhibitors (SGLT-2i) and sulfonylureas (SU) are the most widely prescribed second-line options as add-on therapy to metformin.
Aim: To compare the efficacy data after the addition of a DPP-4i, SGLT-2i, or sulfonylureas (SU) to metformin in real-world condition.
Materials and methods: A retrospective cohort study. The included subjects were matched by propensity score according to baseline age, sex, HbA1c, weight, inclusion date, diabetes duration, and kidney function. We used the primary care SIDIAP database, containing electronic medical records. The observational period was until December 31st, 2017.
Results: After matching, 6,310 subjects were compared, 2124 for DPP-4i, 2124 for SGLT-2i and 2062 for SU. The proportion of patients who achieved combined target HbA1c (≥0.5%) and weight (≥3%) reductions after the addition of DPP-4i, SGLT-2i or SU, was: 23.3%, 40.2%, and 14.7%, respectively. Mean absolute HbA1c reduction was: 1.28 % for DPP4i, 1.29 % for SGLT2i and 1.26 % for SU. Mean weight reduction was: 1.21 kg for DPP4i, 3.47 kg for SGLT2i and 0.04 kg for SU. Small differences in systolic blood pressure reduction (1.07, 3.10 and 0.96 mmHg, respectively) were observed in favour of SGLT-2i. Concerning the lipids, we observed small differences, with an HDL-cholesterol increase with SGLT-2i. Users in the SU cohort had the greatest average reductions in total cholesterol, triglycerides, and LDL cholesterol.
Conclusion: Our real-world data show similar hypoglycaemic effectiveness after the addition to metformin of DPP-4i, SGLT-2i or SU. Greater reduction in weight and blood pressure was observed among SGLT-2i subjects.

RC35 Reduction in hypoglycemic frequency during and after short High Intensity Interval Training in type 1 diabetes individuals.

Serafín Murillo, Laura Brugnara, Anna Novials.

IDIBAPS, Barcelona, CIBERDEM

The aim of this study was to investigate the effect on fitness capacity and glycemic control of High Intensity Interval Training (HIIT) compared to traditional moderate Intensity Continuous Training (MICT). 30 sedentary individuals with type 1 diabetes (T1D) (age=35.5±6.4 yr., BMI= 24.7±3.8kg/m2, VO2max= 23.8±5.4ml·kg-1·min-1, HbA1c= 7.2±0.8%) volunteered to participate in the study. Participants were assigned to a HIIT (n=17) or MICT (n=13) training, including 3 weekly sessions of 30 minutes duration. Fitness status was assessed by VO2max before and after exercise, as well as blood glucose levels by flash glucose monitoring system throughout the study period, comparing differences in blood glucose levels and hypoglycemic episodes between rest and training days.

After the 3-week training period, there were no significant changes in nutritional parameters or body composition. However, both groups improved aerobic performance measured as aerobic work capacity, from 2.2 ± 0.26 to 2.4 ± 0.28 W/kg (p=0.008) in HIIT group and from 2.1 ± 0.78 to 2.3 ± 0.88 W/kg (p=0.004) in MICT group.

During workouts, blood glucose levels remained stable in HIIT exercise (from 148±18mg/dl before to 145±25mg/dl after the exercise), while they decreased in MICT (from 153±14mg/dl before to 126±13mg/dl; p<0.001 after the exercise). In addition, HIIT volunteers needed to take carbohydrate supplements to avoid hypoglycemia by only 6.2% of sessions, compared to 20% in MICT exercise (p=0.04).

In the analysis of blood glucose levels between rest and training days (24h-period), changes in mean glucose, glycemic variability and time in range (70-180mg/dl) were similar in both groups, but the MICT exercise results in an increase in the frequency of hypoglycemic episodes, from 1.1 ± 0.7 episodes in rest day to 1.0 ± 0.7 episodes in training day (p=0.34) in HIIT group and from 1± 0.5 episodes in rest day to 1.3 ± 0.7 episodes in training day (p=0.03) in MICT group.

In conclusion, HIIT training results in greater glycemic stability than MICT training, producing the same effects on fitness capacity.

RC36 Serum copeptin is not associated with asymptomatic peripheral artery disease in patients with type 1 diabetes

Lía Nattero-Chávez[1,3], María Ángeles Martínez-García[3], Héctor F. Escobar-Morreale[1,3], Elena Fernández-Durán[3], Sandra Redondo López[2], Beatriz Dorado Avendaño[1], Manuel Luque-Ramírez[1,3]

[1]Department of Endocrinology and Nutrition; [2] Department of Vascular Surgery; [3] Diabetes, Obesity and Human Reproduction Research Group, Hospital Universitario Ramón y Cajal & Universidad de Alcalá, Madrid & Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS) & CIBERDEM

Objective: Copeptin, a surrogate marker of vasopressin, is associated with cumulative incidence of lower-extremity amputations in people with type 1 diabetes (DM1). We aimed to address the putative association between copeptin concentrations and asymptomatic peripheral arterial disease (aPAD) in patients with DM1.

Design and methods: We conducted an observational cross-sectional study including 112 patients with DM1 from a larger cohort (clinicaltrials.gov NCT02910271). aPAD was evaluated using the toe-brachial index and peripheral doppler ultrasound. Thirty-seven patients had aPAD, 52 showed normal ankle-brachial index (ABI), and 23 presented with a normal vascular exploration despite an abnormal ABI. Both groups –those with and without aPAD– had similar mean age, sex distribution and duration of DM1. Copeptin concentration was measured in fasting serum samples by a highly sensitive ELISA assay, and its association with ABI, presence of aPAD, and other clinical and biochemical variables was evaluated.

Results: The study population´s age was 42±8 yrs, the duration of DM1 27±7 yrs, and mean HBA1c of 7.7±1.1%. We did not find differences in copeptin among patients with or without aPAD (68.3±43.6 vs 69.4±59.3, respectively, P = 0.462). Considering all patients as a whole, copeptin levels correlated with office systolic blood pressure (BP) (r = -0.209, P = 0.027), eGFR (r = -0.271, P = 0.004) and serum sodium (r = -0.208, P = 0.027), but not with ABI (r = -0.068, P = 0.476). We conducted a multiple lineal regression analysis introducing as independent variables: sex, age, duration of DM1, systolic and diastolic BP, eGFR and serum sodium. The stepwise model (R2: 0.059; P = 0.035) retained only systolic BP [β: -0.219 (95%CI -1.391; -0.089)] as the significant predictor of variability in fasting copeptin.

Conclusions: Serum copeptin concentrations do not appear to be associated with aPAD in patients with DM1. Further studies are needed to elucidate its potential role on the sub-clinical vascular disease in this population.

RC37 Role of ERα, ERβ and GPER1 on INS-1E β-cell line apoptosis

Ignacio Babiloni-Chust[1], Laura Marroqui[1,2], Reinaldo S. Dos Santos[1,2], Medina-Galí R M[1, 2], Ángel Nadal[1, 2]

[1]Centre: Instituto de Investigación, Desarrollo e Innovación en Biotecnología Sanitaria de Elche (IDiBE), Universidad Miguel Hernández de Elche, Elche; [2]CIBERDEM

Aims/hypothesis: Bisphenol A (BPA), one of the most common endocrine-disrupting chemicals used by the plastic industry, has been associated with type 2 diabetes development. Some of BPA effects on pancreatic β-cells are mediated via activation of oestrogen receptors (ERs), such as ERα, ERβ, and GPR30. Contrary to the natural ligand 17β-oestradiol, it was reported that BPA induces β-cell death. Considering that BPA can bind to and activate ERs, here we investigated which ERs might be involved in BPA-induced β-cell apoptosis.
Methods: Rat insulinoma INS-1E cell line was treated with BPA or different ER agonists, namely PPT (ERα), DPN (ERβ), and G1 (GPR30), for 24 h. G15, a GPR30 antagonist, was also used. Cell viability was determined after staining with the DNA-binding dyes Hoechst 33342 and propidium iodide.
Results: BPA induced a 6-fold of increase in apoptosis when compared to vehicle or ER agonists PPT and DPN. GPR30 agonist G1 increased β-cell apoptosis at 3 times. Combination of DPN + G1 or PPT + G1 induced apoptosis to a similar extent as G1 alone, whereas treatment with PPT + DPN increased apoptosis by 2-fold. Interestingly, combination of all three agonists induced as much apoptosis as BPA treatment. Finally, GPR30 antagonist G15 partially prevented BPA-induced apoptosis.
Conclusions/interpretation: These results suggest that BPA might induce β-cell apoptosis via activation of ERα, ERβ, and GPR30.
Conclusion: We suggest that both, an increase in mucin-degrading bacteria and Goblet cells modifications, seem to cause an unhealthy mucosa in U individuals, triggering inflammatory responses that might play a key role in the long-term health consequences of catch-up growth.

RC38 A T1D-associated lncRNA regulates the IRF7-driven inflammatory network (IDIN) in pancreatic beta cells.

Itziar González-Moro, Izortze Santin

University of the Basque Country and Biocruces Health Research Institute

The IRF7-driven inflammatory network (iDIN) is an antiviral expression pathway enriched for type 1 diabetes (T1D)-associated genes. The risk allele of a T1D-associated intergenic SNP located closed to EBI2 gene (rs9585056) was shown to correlate with lower EBI2 expression, and on average, increased expression levels of iDIN genes, suggesting that EBI2 might be a candidate trans-regulating locus of the human iDIN. However, recent analyses by our group have revealed that the T1D-associated rs9585056 is not intergenic, as it lies in an exon of a long non-coding RNA (lncRNA) that we have named Lnc10.

Against this background, the main objective of the present work was to analyze the potential role of Lnc10 in the regulation of the T1D-associated iDIN and virus-induced pancreatic beta cell inflammation.

Our results showed that Lnc10 is expressed in human pancreatic beta cells and its expression is upregulated by intracellular exposure to polyinosinic:polycytidylic acid (PIC), a synthetic viral dsRNA that mimics a viral infection. Lnc10 is preferentially located in the nucleus of pancreatic beta cells, especially after intracellular PIC exposure, suggesting a role in the regulation of PIC-induced gene expression. Indeed, upregulation of Lnc10 in pancreatic beta cells using an overexpression vector induced an increase in several iDIN genes, including ISG15, IFITM1, IFIT1, STAT1, STAT2 and IRF7.

In summary, our preliminary results suggest a role of Lnc10 in the regulation of iDIN expression at the pancreatic beta cell level. Further studies are required to establish the molecular mechanisms by which Lnc10 regulate this inflammatory gene network and to characterize its potential contribution to pancreatic beta cell inflammation and T1D development.

RC39 Treatment of Type 1 diabetes in mice with a dual gene AAV vector encoding for insulin and glucokinase

Laia Vilà[1,3], Marisa Jaén[1,2,3], Verónica Jiménez[1,2,3], Miquel García[1,2,3], Ivet Elias[1,2,3], Jordi Rodó[1,2,3], Tura Ferré[1,3], Fàtima Bosch[1,2,3]

[1]Center of Animal Biotechnology and Gene Therapy, [2]Department of Biochemistry and Molecular Biology, Universitat Autònoma de Barcelona, 08193 Bellaterra; [3]CIBERDEM

Regular and intensive insulin replacement therapy is currently the first-line therapeutic option for treating type 1 diabetes (T1D). Type 1 diabetic patients develop severe secondary complications because insulin treatment does not guarantee normoglycemia. Nevertheless, achievement of normoglycemia with exogenous insulin requires the use of high doses of hormone, which increases the risk of life-threatening hypoglycemic episodes. Therefore, new approaches are needed for safe T1D treatment. Our group has demonstrated long-term control of hyperglycemia and prevention of secondary complications in diabetic mice and dogs by engineering a glucose sensor in the skeletal muscle. This was achieved by adeno-associated viral (AAV) vector-mediated expression of insulin (Ins) and glucokinase (Gck) genes. Two AAV vectors encoding either Ins or Gck were intramuscularly (IM) administered to these animal models. Here, to improve gene transfer efficiency we have now developed a new approach focused in the generation of dual gene AAV vectors encoding both Ins and Gck genes. This will also allow the use of lower vector doses, minimizing potential toxicity and reducing AAV vector manufacturing costs. Compared with non-treated diabetic mice, long-term IM treatment by AAV-dual Ins+Gck vectors of STZ-induced diabetic mice normalized fasting serum glucose and ketone body levels, increased glucose tolerance and reduced hepatic gluconeogenesis. Moreover, treatment of diabetic mice with AAV-dual Ins+Gck vectors prevented the body and skeletal muscle weight loss associated to diabetes progression, and increased lifespan compared with non-treated diabetic mice. These results demonstrate that AAV-dual Ins+Gck vectors are very efficient to counteract diabetic alterations and that can be considered as new gene therapy products to treat type 1 diabetes.

RC40 Distribution of seven apoC-III glycoforms in plasma, VLDL, IDL, LDL and HDL of healthy subjects and association with insulin resistance and the lipid profile

Pere Rehues, Marina Rodríguez, Víctor Iranzo, Jorge Mora, Clara Balsells, Montse Guardiola, Josep Ribalta

Unitat de Recerca en Lípids i Arteriosclerosi, Facultat de Medicina, Universitat Rovira i Virgili, Hospital Universitari de Sant Joan de Reus, Institut d'Investigació Sanitària Pere Virgili, CIBERDEM.

Diabetes Mellitus patients have higher risk of developing cardiovascular disease, being the leading cause of death among this population. Both type I and type II diabetes are influenced by Apolipoprotein C-III, a known risk factor for CVD, which promotes beta cell dysfunction and apoptosis. Moreover, ApoC-III inhibits the uptake of triglyceride-rich lipoproteins and LPL activity and is associated with increased circulating TG, fasting plasma glucose and diabetes risk. Glycosylation of ApoC-III modulates its function on TG metabolism with some variants being associated with a protective or a pro-atherogenic lipid profile, but little is known about ApoC-III glycoform-specific functions on diabetes. These associations have been studied on whole plasma ApoC-III proteoforms but the amount of ApoC-III proteoforms in individual lipoprotein fractions is rarely evaluated. In the present study we aim to measure the relative content of ApoC-III proteoforms in each lipoprotein fraction (VLDL, IDL, LDL and HDL) in a group of healthy subjects as a potential biomarker for diabetes risk by means of the lipid profile. Lipoprotein fractions were separated by differential ultracentrifugation of plasma samples, the relative concentration of seven ApoC-III variants was measured by MSIA and the complete lipoprotein profile was determined by NMR, which was used to calculate the lipoprotein-insulin resistance score. The results show high inter-individual variability in the distribution of ApoC-III proteoforms across the study population but a uniform proportion in lipoprotein fractions. ApoC-III0b was inversely correlated with the lipoprotein-insulin resistance score. ApoC-III0b and ApoC-III1d negatively correlated with plasma and VLDL triglycerides irrespectively of VLDL size and were associated with increased LDL size when transported in LDL particles. Therefore, ApoC-III variants can be reliably measured in lipoprotein fractions and it is suggested that ApoC-III0b and 1d proteoforms may have a protective role on insulin resistance and TG metabolism in healthy individuals.

RC41 Endocrine disruptors and type 2 diabetes: an integrated approach for hazard identification

Hilda Ferrero[1,2], Ruba Al-Abdulla[1], Paloma Alonso-Magdalena[1,2]

[1]Instituto de Investigación, Desarrollo e Innovación en Biotecnología Sanitaria de Elche (IDiBE), Universidad Miguel Hernández, Elche; [2]CIBERDEM

Endocrine disrupting chemicals (EDCs) are chemicals, or mixtures of chemicals, that interfere with any aspect of hormone action. EDCs comprise an extensive class of molecules such as pesticides, herbicides, and industrial chemicals, such as plastics and plasticizers, flame retardants or fuels, with widespread occurrence in the environment. Over the last decade, the potential impact of EDCs on human health has been widely acknowledged. Metabolic diseases including diabetes, obesity, metabolic syndrome, etc. are among the most prominent health outcomes of EDCs. Despite this, today there is still no definitive and standardized in vitro tools to support risk metabolic assessment of existing and emerging EDCs for regulatory purposes. Our study is focused on the development of robust in vitro screening methods for the assessment of putative EDCs potentially leading to type 2 diabetes. Here, we have evaluated the capacity of 6 model EDCs (BPA, BPS, PFOS, DEHP, CdCl2 and DDE) to disrupt relevant metabolic endpoints in pancreatic β and α-cell models. First experiments have been performed in the murine pancreatic β-cell model Min6 and α-cell model α-TC1.9. Further experiments will be performed in the human pancreatic β-cell line EndoC BH1. Cells were incubated with the compounds for 24, 48, and 72 h at concentrations of 100 pM, 1 nM, 10 nM, 100 nM, 1 µM, or 10 µM. Cell viability was measured by means of three independent cytotoxicity assays (resazurin, CFDA-AM and neutral red). The effects of the selected chemicals on insulin and glucagon secretion and content were analysed, as well as changes on the expression of essential genes involved in β and α-cell entity and glucose homeostasis. Omics analysis (transcriptomics, metabolomics) will be next carried out for mapping of signaling and metabolic pathways deregulated by EDCs in pancreatic cells. Such integrative approach will help in better identification of metabolic effects of EDCs.

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RC42 Role of exosomes in pancreatic β-cells survival and potential link between T2DM and neurodegeneration

Jesús Burillo, Carlos González-Blanco, Beatriz Jiménez, Patricia Marqués, Gema García, Carlos Guillén, Manuel Benito

Facultad de Farmacia, Universidad Complutense de Madrid.

Type 2 Diabetes Mellitus (T2DM) is a metabolic illness which has been described as a "Misfolded Protein Disease", such as Alzheimer or Parkinson, due to accumulation of amylin (islet amyloid polypeptide, IAPP) during the transition from prediabetic stage to manifest T2DM. Pancreatic β-cells are essential in the maintenance of glucose homeostasis during the progression to T2DM, generating a compensatory hyperinsulinemia to counteract insulin resistance. It is well known that throughout this process there is an increased mTORC1 signaling pathway, with an impairment in different quality control systems including ubiquitin-proteasome system and autophagy. In addition, under this situation, pancreatic β-cells start to accumulate IAPP in aggregates, and this accumulation contributes to the failure of autophagy, damaging different organelles such as plasma membrane, endoplasmic reticulum, mitochondria, and others.
Here, we uncover a new mechanism by which, IAPP can be incorporated into multivesicular bodies (MVB) and secreted into exosomes, which is responsible for the exportation of these toxic aggregates to other territories and it may contribute to the alteration observed in extra-pancreatic tissues including the brain in T2DM. In addition, we have demonstrated that exosomes obtained from a pancreatic β-cell overexpressing hIAPP are able to induce a hyperactivation of mTORC1, a failure in the protein quality control as well as a pro-fission status of mitochondria in a mouse hippocampal cell line. In summary, our results indicate that the alterations observed in pancreatic β-cells, caused by the accumulation of hIAPP, could be exported to other tissues, including brain, facilitating neuronal failure and a possible explanation to the link between T2DM and other neurodegenerative diseases.

RC43 Link between type 2 diabetes and Alzheimer's disease in Irs2 deficient mice

[1,2]Carlos Acosta, [1,2]Deborah Burks

[1]Centro de Investigación Príncipe Felipe, [2]CIBERDEM

There have been many studies in recent years suggesting a close relationship between type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD); however, the molecular mechanisms underlying this association have not been fully understood. It has been reported that Insulin/insulin-like-growth-factor (IGF) signaling plays a crucial role in the regulation of different central nervous system (CNS). Insulin may also play a role in regulating the amyloid precursor protein and its derivative beta amyloid (Abeta), which is associated with senile plaques, a neuropathological hallmark of Alzheimer's disease. For this study we have we used Irs2-deficient mice. Loss of Irs2 produces diabetes leading to insulin resistance and beta cell failure. Irs2-deficiency also produces defects in brain development and functionality that resembles some neurodegenerative diseases. Additionally, some stress markers are altered in the brain of these animals suggesting an association between insulin resistance and brain degeneration.

RC44 GDF15 mediates the metabolic effects of metformin

David Aguilar-Recarte, Emma Barroso, Javier Pizarro-Delgado, Lucía Peña, Xavier Palomer, Manuel Vázquez-Carrera

Department of Pharmacology, Toxicology and Therapeutic Chemistry, Faculty of Pharmacy and Food Sciences and Institute of Biomedicine of the University of Barcelona (IBUB), University of Barcelona; CIBERDEM; Pediatric Research Institute-Hospital Sant Joan de Déu, Esplugues de Llobregat

BACKGROUND AND AIMS. One of the main mechanisms of action of metformin in the treatment of insulin resistance and type 2 diabetes is the activation of AMPK through its phosphorylation. Growth differentiation factor 15 (GDF15) is a stress-response cytokine that is implicated in fatty acid oxidation, glucose tolerance and insulin sensitivity. Given that metformin-treated patients show increased GDF15 serum levels, the objective of this study was to examine whether the beneficial effects of metformin on lipid-induced endoplasmic reticulum (ER) stress, inflammation and insulin resistance were dependent on GDF15.

METHODS. Wild-type C57BL/6J and GDF15 knockout (KO) mice were divided into different groups and fed a standard or a high-fat diet (HFD) (45% kcal from fat) for 21 days. The different groups received either an oral daily administration of vehicle (control groups) or metformin at a dose of 100 mg/kg/day and were used to evaluate glucose tolerance, and the levels of genes and proteins involved in fatty acid metabolism, ER stress, inflammation and the insulin signalling pathway in skeletal muscle and liver. In addition, C2C12 myotubes were used to examine the mechanisms by which metformin regulates GDF15 levels.

RESULTS. Wild-type mice fed an HFD diet and treated with metformin showed a reduction in the levels of genes and proteins involved in inflammation, ER stress, and insulin signalling pathways compared with the HFD group that received the vehicle. Metformin treatment also improved glucose tolerance and caused a reduction in total weight. By contrast, metformin effects were abolished or partially reduced in GDF15-KO mice receiving the same treatment, where glucose tolerance and total weight were not improved, demonstrating the involvement of GDF15 in metformin actions on insulin resistance. The potential mechanisms involved in the upregulation of GDF15 by metformin was evaluated in C2C12 myotubes.

CONCLUSIONS. Overall, the findings of the present study show that the increase in GDF15 levels contributes to the reduction of ER stress, inflammation and insulin resistance caused by metformin.

RC45 Regulation of mitochondrial plasticity by Mfn2 drives metabolic flexibility

David Sebastián and Antonio Zorzano

Institute for Research in Biomedicine (IRB Barcelona), The Barcelona Institute of Science and Technology, Barcelona; Departament de Bioquímica i Biomedicina Molecular, Facultat de Biologia, Universitat de Barcelona; CIBERDEM

Metabolic flexibility describes the ability of an organism to respond or adapt according to changes in metabolic or energy demands. Skeletal muscle plays a crucial role in energy metabolism, and therefore, has a deep impact in metabolic flexibility. In skeletal muscle, metabolic flexibility implies a good fuel selection either in the transition from fed to fasting state, switching from carbohydrate to lipid oxidation, or the transition from fasting to insulin stimulation, switching from lipid to carbohydrate oxidation. In this regard, several studies have shown that metabolic inflexibility in skeletal muscle is a key feature of insulin resistance and type 2 diabetes. Mitochondria are key organelles involved in metabolism and metabolic adaptation and therefore, they may have a prominent role in metabolic flexibility. Mitofusin 2 (Mfn2), a mitochondrial dynamics protein, is decreased in skeletal muscle of obese and type 2 diabetic subjects and is essential for normal glucose homeostasis and healthy aging in mice by controlling mitochondrial function and quality in muscle. By using in vitro and in vivo approaches, we demonstrate that Mfn2 is required for metabolic adaptation to fasting and determines whole-body metabolic flexibility by controlling mitochondrial plasticity in skeletal muscle. These results strongly suggest that Mfn2 is an important factor in insulin resistance and type 2 diabetes by controlling metabolic flexibility in skeletal muscle.

RC46 Unraveling the role of the insulin-degrading enzyme (IDE) on hepatic insulin and glucagon signaling

Carlos M. González-Casimiro, Beatriz Merino, Jesús Balsinde, Irene Cózar-Castellano, Germán Perdomo

Instituto de Biología y Genética Molecular (CSIC-UVa), Valladolid

IDE is a protease that degrades insulin and glucagon. Genetic Ide polymorphisms are linked to increased risk of developing T2DM. Reduced IDE levels associates with lower insulin clearance in T2DM patients. However, molecular mechanisms linking IDE with the pathophysiology of T2DM are poorly defined.

To investigate the role of IDE on T2DM, we fed mice with a standard diet (SD) or high-fat diet (HFD) and examined the impact of loss- versus -gain of IDE function on insulin and glucagon action in hepatocytes.

L-IDE-KO mice fed a SD exhibited insulin resistance and glucose intolerance with no change in hepatic insulin clearance. Insulin resistance was associated with increased FoxO1 activation, reduced insulin receptor (IR) protein levels, and reduced phosphorylation of CEACAM1, which promotes receptor-mediated insulin uptake to be degraded.

L-IDE-KO mice exacerbates hyperinsulinemia and insulin resistance in the setting of HFD-induced obesity, in parallel to an increase in pancreatic beta-cell function without altering insulin clearance. Insulin resistance was associated with increased FoxO1 activation and ~2-fold increase of GLUT2 protein levels. Conversely, gain of IDE function (adenoviral delivery) improves glucose tolerance and insulin sensitivity, in parallel to a reciprocal ~2-fold reduction in hepatic GLUT2 protein levels. Furthermore, in response to insulin, IDE co-immunoprecipitates with the IR.

On the other hand, hepatic IDE depletion did not alter circulating glucagon levels in mice fed SD or HFD. Interestingly, L-IDE-KO mice showed reduced CREB protein levels. Likewise, depletion of Ide in AML12 cells significantly reduced CREB protein levels, in parallel with increased glycogen synthase protein levels.

In conclusion, loss of IDE function aggravates insulin resistance and glucose intolerance, whereas gain of IDE function exerts beneficial effects on glucose tolerance and insulin sensitivity in the setting of obesity, providing a strong rationale for developing pharmacological compounds targeting IDE activation for T2DM treatment.

RC47 SIRT3 deficiency exacerbates fatty liver by attenuating the HIF1α-lipin 1 pathway and increasing CD36 through Nrf2

Emma Barroso[1,2,3], Rosalía Rodríguez-Rodríguez[1,2,3], Mohammad Zarei[1,2,3], Javier Pizarro-Degado[1,2,3], Anna Planavila[3,4,5], Xavier Palomer[1,2,3], Francesc Villarroya[3,4,5] and Manuel Vázquez-Carrera[1,2,3]

[1]Department of Pharmacology, Toxicology and Therapeutic Chemistry, Faculty of Pharmacy and Food Sciences, University of Barcelona, Institute of Biomedicine of the University of Barcelona (IBUB), Barcelona; [2]CIBERDEM; [3]Research Institute-Hospital Sant Joan de Déu; [4]Department of Biochemistry and Molecular Biomedicine and IBUB, Faculty of Biology, University of Barcelona; [5] CIBEROBN.

Sirtuin 3 (SIRT3) is a NAD+-dependent deacetylase protein that plays a key role in the regulation of mitochondrial function, in the prevention of oxidative stress and in the regulation in lipid homeostasis. It has been shown that SIRT3 deficiency contributes to the development of hepatic steatosis. For this reason, the aim of this study was to investigate which additional mechanisms may play a role in aggravating hepatic steatosis in Sirt3-deficient mice fed a high-fat diet (HFD). Wild-type and transgenic mice with reduced expression of SIRT3 were fed with normal chow or with a high fat diet (55% Kcal from fat) ad libitum for a period of 6 weeks. In addition, SIRT3-knockdown assays were performed in human Huh-7 hepatoma cell line.

Sirt3-/- mice fed an HFD presented exacerbated hepatic steatosis that was accompanied by decreased expression and DNA-binding activity of peroxisome proliferator-activated receptor (PPAR)α and of several of its target genes involved in fatty acid oxidation, compared to WT mice fed the HFD. Interestingly, Sirt3 deficiency in liver and its knockdown in Huh-7 cells resulted in upregulation of the nuclear levels of LIPIN1, a PPARα co-activator, and of the protein that controls its levels and localization, hypoxia-inducible factor 1α (HIF-1α). These changes were prevented by lipid exposure through a mechanism that might involve a decrease in succinate levels. Finally, Sirt3-/- mice fed the HFD showed increased levels of some proteins involved in lipid uptake, such as CD36 and the VLDL receptor. The upregulation in CD36 was confirmed in Huh-7 cells treated with a SIRT3 inhibitor or transfected with SIRT3 siRNA and incubated with palmitate, an effect that was prevented by the Nrf2 inhibitor ML385.

These findings demonstrate new mechanisms by which Sirt3 deficiency contributes to hepatic steatosis.

RC48 Liver glycogen increases endurance capacity in mice

Iliana López-Soldado, Jordi Duran, Joan J. Guinovart

Institut de Recerca Biomèdica (IRB); CIBERDEM

The main reason why fatigue occurs during exercise is not clear, and many mechanisms may be involved. It has been proposed that glycogen depletion leads to fatigue. In mice, muscle glycogen is not essential for exercise and rodents may be more dependent on liver glycogen stores for exercise. In this regard, we centered our attention on the role of liver glycogen in sustaining exercise. We hypothesised that mice that accumulate more glycogen in the liver (liver specific PTG KIn mice) would show enhanced exercise capacity compared to control counterparts. Upon exercise, control mice showed a decrease in liver glycogen; however, PTG KIn animals retained significant hepatic glycogen stores. Our data indicate that 18-20-week-old PTG KIn mice showed increased exercise capacity, as determined by the distance covered distance compared to age-matched wild type under low intensity endurance training. Moreover, fasted control mice ran less than fed counterparts. However, PTG KIn mice under fasting conditions showed a nearly 2-fold increase in exercise capacity. These results identify liver glycogen as a key regulator of endurance capacity in mice.

RC49 Major genetic changes due to the disturbance of glycerolipid metabolism

Clara Meana, Javier Martínez-García, Jesús Balsinde, Mª Balboa

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

Lipin-1, the most active isoform of the mammalian Mg2+ dependent phosphatidic acid phosphatases, is crucial for the glycerolipid homeostasis based on its diacylglycerol production. Its absence entails hypertriglyceridemia and fatty liver during neonatal development, as well as insulin resistance in adulthood, which compromises the body effectiveness to convert blood sugar into cell energy. This metabolic homeostasis disruption has fatal consequences on human health, increasing the risk of suffering from several conditions including osteoporosis, atherosclerosis or anaemia of inflammation. Previous work conducted in our laboratory has demonstrated the pro inflammatory role of lipin-1 in macrophages, cells highly involved in the progression of the above cited illnesses thanks to its ability to phenotypically differentiate to osteoclasts, foam cells or iron-retaining cells respectively. However, only expression of a few genes related to immune system was explored. Taking advantage of the gene microarray technology, a whole mouse genome analysis of microarray datasets obtained by single-colour hybridization has been done to study the effects that lipin-1 deficiency produces on mRNA expression both in unstimulated and classically activated peritoneal macrophages. Those genes whose expression has changed more than 2-fold were taken under consideration and grouped according to their cellular function role. Important changes have been detected in genes related to amino acid, lipid and carbohydrate metabolism as well as autophagy, membrane trafficking, phagocytosis, ferroptosis, cell cycle and cell migration. According to previous results in which arachidonic acid metabolism were disturbed due to lipin-1 deficiency, changes in genes regarding transcellular eicosanoid metabolism were also observed. Interestingly, although members of the lipin family are involved in cholesterol metabolism, no major differences were obtained at gene level, raising the possibility of a post-transcriptional regulation. Collectively, these findings open new perspectives into the study of macrophage lipin-1 and its weight in human pathologies dependent on the glycerolipid metabolism.

RC50 Regulation of lipid levels by lipins and their impact on inflammatory processes

Álvaro Garrido, Patricia Monge, Jesús Balsinde, María A. Balboa

Instituto de Biología y Genética Molecular, CSIC, Valladolid, CIBERDEM

The family of lipins (lipin-1, lipin-2, lipin-3) is a group of enzymes of key importance in de novo lipid synthesis. These enzymes possess phosphatidic acid phosphatase activity, that is, they catalyse the transformation of phosphatidic acid (PA) into diacylglycerol (DAG). This DAG is subsequently used for the biosynthesis of triacylglycerol (TAG) and phospholipids such as phosphatidylcholine (PC), phosphatidylethanolamine (PE). In addition, they act as transcriptional coactivators that regulate the expression of a variety of genes. The deficiency of these enzymes is related to diseases of a metabolic and inflammatory nature such as hypertriglyceridemia or Majeed syndrome. On the other hand, several studies have shown that polymorphisms in the human LPIN1 and LPIN2 genes are associated with characteristics of metabolic disease such as insulin resistance or diabetes. In this work we have studied the levels of the different lipid classes involved in the activity of these enzymes, paying special attention to lipids that contain bioactive fatty acids such as cis-7-hexadecenoic acid (16:1n-9) or arachidonic acid (20:4n-6). The different lipid species were isolated by thin layer chromatography and they were analysed by mass spectrometry. Different cell types were used, such as the RAW 264.7 cell line or the mouse embryonic fibroblasts (MEFs) lacking lipin-1 or lipin-2. In the case of the RAW 264.7 cell line, the expression of the lpin2 gene was silenced using siRNA technology. We have observed that in fibroblasts without lipin-1 or lipin-2, the levels of triacylglycerol and cholesterol esters (CE) are slightly decreased compared to wild type fibroblasts, which suggests that the synthesis of these lipids is affected by the lack of these enzymes. In the case of phospholipids, there seems to be a slight accumulation of phosphatidic acid in fibroblasts without lipin-1 or lipin-2, which suggests that they are not transforming it correctly to diacylglycerol. From these data we can deduce which classes of lipids are affected by the lack of these enzymes and understand better their mechanism of action in vivo.