Adipose tissue metabolism in obesity

MetNet annual meeting

Scientific Organizers:

Pablo García-Rovés

Laura Herrero

Sponsored by:

Societat Catalana de Biologia (SCB)

Facultat de Farmàcia, UB

Agilent Technologies

Institut de Biomedicina de la UB (IBUB)

May 27th, 2016

Institut d'Estudis Catalans

Barcelona

Adipose tissue metabolism in obesity

May 27th, 2016

Sala Prat de la Riba, Institut d'Estudis Catalans

C/ del Carme, 47, Barcelona

Obesity is a worldwide problem and is associated with important diseases such as type 2 diabetes, cardiovascular disease and some cancers. Adipose tissue has become a key player in the relationship between obesity and its metabolic disorders.

This meeting focuses on recent advances in adipose tissue metabolism and its pathogenesis and aims to foster translational collaborations between basic and clinic research in addition to systems biology.

We thank all the participants, sponsors, speakers and the SCB's assistants for their important contribution to a successful meeting.

Scientific Organizers:

Pablo García-Rovés

Laura Herrero

SPONSORED BY:

Societat Catalana de
BIOLOGIA

FACULTAT DE
FARMÀCIA

Agilent Technologies

Institut de Biomedicina de la Universitat de Barcelona

Thank you!!!

MetNet annual meeting

Adipose tissue metabolism in obesity

Barcelona, May 27th 2016

PROGRAM

Meeting location
Sala Prat de la Riba, IEC
C/ del Carme, 47, Barcelona
Registration
http://scb.iec.cat/
Meeting organizers
Pablo García-Rovés / Laura Herrero

9.00 - 9.10 **WELCOME**
Pablo M Garcia-Roves, Facultat de Medicina, UB-IDIBELL
Laura Herrero, Facultat de Farmàcia, CIBEROBN, IBUB

SESSION 1 **ADIPOSE TISSUE BIOLOGY**
Chair: Laura Herrero, Facultat de Farmàcia, CIBEROBN, IBUB

9.10 - 9.30 **Marta Giralt,** Facultat de Biologia, CIBEROBN, IBUB
"Adipose tissue biology: new insights from the study of adipose-related diseases"

9.35 – 9.55 **David Sánchez-Infantes,** Hospital German Trias i Pujol, Barcelona
"Oncostatin M impairs BAT thermogenic function and the browning of subcutaneous WAT"

10.00 - 10.20 **Ana Burgeiro,** University of Coimbra, Portugal
"Epicardial Adipose Tissue Metabolism - What do We Know?"

10.25 – 10.45 **Short presentations by MetNet young scientists**
10.45 - 11.15 **COFFEE BREAK**

SESSION 2 **SYSTEMS BIOLOGY**
Chair: Pablo García-Rovés, Facultat de Medicina, UB-IDIBELL

11.15 - 11.40 **PLENARY CONFERENCE 1**
Roger Guimera, Universitat Rovira I Virgili, Tarragona
"Systems biology to assess complex metabolic networks"

11.45 - 12.10 **Adil Mardinoglu,** KTH Royal Institute of Technology, Stockholm, Sweden
"The use of metabolic models in revealing the molecular mechanism of liver associated disorders"

12.15 - 13.00 **Uwe Sauer,** Institute for Molecular Systems Biology, ETH Zurich, Switzerland
"Real-time metabolome profiling of the metabolic switch between starvation and growth"

13.00 - 13.15 **Short presentations by MetNet young scientists**

13.15 - 15.00 **LUNCH**

SESSION 3 **PATHOPHYSIOLOGY OF INSULIN RESISTANCE**
Chair: Pep Villena, Hospital Universitari Vall d'Hebron

15.00 - 15.45 **PLENARY CONFERENCE 2**
Jan Eriksson, Dpt. of Medical sciences, Uppsala University, Sweden
"Adipose tissue mechanisms in human insulin resistance and T2D - translational studies"

15.50 - 16.10 **Brice Emanuelli,** University of Copenhagen, Denmark
"Novel elements of insulin signalling in adipose tissues"

16.15 - 16.35 **Ángela M. Valverde,** Instituto de Investigaciones Biomédicas Alberto Sols (CSIC-UAM), CIBERDEM, Madrid
"A novel GLP-1/Glucagon receptor dual agonist improves non-alcoholic steatohepatitis and liver regeneration in mice"

16.40 – 17.00 **Short presentations by MetNet young scientists**

PROGRAM

9.00 - 9.10 **WELCOME**

Pablo M Garcia-Roves, Facultat de Medicina, UB-IDIBELL

Laura Herrero, Facultat de Farmàcia, CIBEROBN, IBUB

SESSION 1 **ADIPOSE TISSUE BIOLOGY**

Chair: Laura Herrero, Facultat de Farmàcia, CIBEROBN, IBUB

9.10 - 9.30 **Marta Giralt,** Facultat de Biologia, CIBEROBN, IBUB

"Adipose tissue biology: new insights from the study of adipose-related diseases"

9.35 – 9.55 **David Sánchez-Infantes,** Hospital German Trias i Pujol, Barcelona

"Oncostatin M impairs brown adipose tissue thermogenic function and the browning of subcutaneous white adipose tissue"

10.00 - 10.20 **Ana Burgeiro,** University of Coimbra, Portugal

"Epicardial Adipose Tissue Metabolism - What do we Know?"

10.25 – 10.45 **Short presentations by MetNet young scientists**

María Calderon-Dominguez, Facultat de Farmàcia, CIBEROBN, IBUB

"Carnitine palmitoyltransferase 1 increases lipolysis, UCP1 protein expression and mitochondrial activity in brown adipocytes"

Rubén Cereijo, Facultat de Biologia, CIBEROBN, IBUB

"*A secretory role for brown adipose tissue: Identification of novel brown adipokines*"

10.45 - 11.15 **COFFEE BREAK**

SESSION 2 **SYSTEMS BIOLOGY**

Chair: Pablo García-Rovés, Facultat de Medicina, UB-IDIBELL

11.15 - 11.40 **PLENARY CONFERENCE 1**

Roger Guimera, Universitat Rovira I Virgili, Tarragona

"Systems biology to assess complex metabolic networks"

11.45 - 12.10 **Adil Mardinoglu,** KTH Royal Institute of Technology, Stockholm, Sweden

"The use of metabolic models in revealing the molecular mechanism of liver associated disorders"

12.15 - 13.00 **Uwe Sauer,** Institute for Molecular Systems Biology, ETH Zurich, Switzerland

"Real-time metabolome profiling of the metabolic switch between starvation and growth"

13.00 - 13.15 **Short presentations by MetNet young scientists**

Pau Gama-Perez, Facultat de Medicina, IDIBELL

"Systems biology approach for the assessment of metabolic plasticity after a lifestyle intervention in diet-induced obese mice"

Noelia Keiran, Hospital Universitari de Tarragona Joan XXIII, CIBERDEM

"Obesity and type 2 diabetes alters the immune properties of human adipose derived stem cells"

13.15 - 15.00 **LUNCH**

SESSION 3 **PATHOPHYSIOLOGY OF INSULIN RESISTANCE**

Chair: Pep Villena, Hospital Universitari Vall d'Hebron

15.00 - 15.45 **PLENARY CONFERENCE 2**

Jan Eriksson, Dpt. of Medical sciences, Uppsala University, Sweden

"Adipose tissue mechanisms in human insulin resistance and T2D - translational studies"

15.50 - 16.10 **Brice Emanuelli,** University of Copenhagen, Denmark

"Novel elements of insulin signalling in adipose tissues"

16.15 - 16.35 **Ángela M. Valverde,** Instituto de Investigaciones Biomédicas Alberto Sols (CSIC-UAM), CIBERDEM, Madrid

"A novel GLP-1/Glucagon receptor dual agonist improves non-alcoholic steatohepatitis and liver regeneration in mice"

16.40 – 17.00 **Short presentations by MetNet young scientists**

Alexandra Carrilho do Rosário, Facultat de Farmàcia, IBUB

"Regulation of PPARα target genes by Fsp27"

Gemma Sangüesa, Facultat de Farmàcia, CIBEROBN, IBUB

"Long term liquid fructose supplementation to female rats induces an atypical insulin resistance state in visceral adipose tissue"

17.00 - 18.00 **Social hour with lite bites**

SCB's assistants:

Mariàngels Gallego and Maite Sánchez

Societat Catalana de Biologia

C/ Maria Aurèlia Capmany, 14-16, 08001 Barcelona.

Tel. (+34) 933 248 584; email: scb@iec.cat

Organized by:

Pablo García-Rovés

Associate Professor

Dpt. Physiological Sciences

Faculty of Medicine and Health Sciences - University of Barcelona

4a planta Pavelló de Govern (Campus de Bellvitge) Feixa Llarga, s/n

08907 L'Hospitalet Llobregat, Barcelona

Tel. (+34) 934 024 295; email: pgarciaroves@ub.edu

Laura Herrero

Assistant professor

Dpt. Biochemistry and Physiology (IBUB, CIBEROBN)

School of Pharmacy, University of Barcelona

Av. Joan XXIII, 27-31, 08028 Barcelona

Tel. (+34) 934 024 522; email: lherrero@ub.edu

ORAL PRESENTATIONS

Carnitine palmitoyltransferase 1 increases lipolysis, UCP1 protein expression and mitochondrial activity in brown adipocytes

María Calderon-Dominguez[1,2], David Sebastián[3,4], Raquel Fucho[1,2], Minéia Weber[1,2], Joan F. Mir[1,2], Blanca Balanyà[1,2], Eduviges Bustos[1,2], Sandra Recalde[1,2], Mar Romero[1,2], Ester García-Casarrubios[5], María Jesús Obregón[5], Antonio Zorzano[3,4], Ángela M. Valverde[4,5], Dolors Serra[1,2], Laura Herrero[1,2]

[1]Department of Biochemistry and Physiology, Institut de Biomedicina de la Universitat de Barcelona (IBUB), Universitat de Barcelona, E-08028 Barcelona, Spain
[2]Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y la Nutrición (CIBEROBN), Instituto de Salud Carlos III, E-28029 Madrid, Spain
[3]Institute for Research in Biomedicine (IRB Barcelona) and Departament de Bioquímica i Biologia Molecular, Facultat de Biologia, Universitat de Barcelona, E-08028 Barcelona, Spain
[4]Centro de Investigación Biomédica en Red de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Instituto de Salud Carlos III, E-28029 Madrid, Spain
[5]Instituto de Investigaciones Biomédicas Alberto Sols (CSIC-UAM) and Instituto de Investigación Sanitaria La Paz, 28029 Madrid, Spain

The discovery of active brown adipose tissue (BAT) in adult humans and the fact that it is reduced in obese and diabetic patients have put a spotlight on this tissue as a key player in obesity-induced metabolic disorders. BAT regulates energy expenditure through thermogenesis; therefore, harnessing its thermogenic fat-burning power is an attractive therapeutic approach. We aimed to enhance BAT thermogenesis by increasing its fatty acid oxidation (FAO) rate. Thus, we expressed carnitine palmitoyltransferase 1AM (CPT1AM), a permanently active mutant form of CPT1A (the rate-limiting enzyme in FAO), in a rat brown adipocyte (rBA) cell line through adenoviral infection. We found that CPT1AM-expressing rBA have increased FAO, lipolysis, UCP1 protein levels and mitochondrial activity. Additionally, enhanced FAO reduced the palmitate-induced increase in triglyceride content and the expression of obese and inflammatory markers. Thus, CPT1AM-expressing rBA had enhanced fat-burning capacity and improved lipid-induced derangements. This indicates that CPT1AM-mediated increase in brown adipocytes FAO may be a new approach to the treatment of obesity-induced disorders.

A secretory role for brown adipose tissue: Identification of novel brown adipokines

Rubén Cereijo, Montserrat Cairó, Tania Quesada-López, Joan Villarroya, Teresa Mampel, Roser Iglesias, Marta Giralt, Francesc Villarroya
Department of Biochemistry and Molecular Biomedicine, Institute of Biomedicine, University of Barcelona, and CIBER Fisiopatología de la Obesidad y Nutrición, Barcelona, Catalonia, Spain

Background: White adipose tissue (WAT) and brown adipose tissue (BAT) exert opposing energy-storing and energy-dissipating functions. Although WAT communicates with distant organs by releasing adipokines, a potential analogous endocrine role for BAT has been scarcely explored. Here we identify CXCL14 as a brown adipokine involved in the adipose-immune cell crosstalk.

Methods: A dual data mining strategy was used to identify thermoregulated, BAT-enriched secreted proteins. The role of candidate protein CXCL14 was validated and further characterized using *in vitro* models (adipocytes and macrophages) and *in vivo* (loss- and gain-of-function murine models).

Results: Expression and release of CXCL14 was increased by pro-thermogenic stimuli in brown adipocytes *in vivo* and *in vitro*. Loss of function experiments revealed an impairment of BAT activation in CXCL14-knockout mice, concomitant with a lack of M2 macrophage infiltration. *In vitro* studies showed no autocrine effects on brown adipocytes, but demonstrated that brown adipocyte-derived CXCL14 promoted M2 macrophage polarization and migration. Likewise, M2 macrophage infiltration was enhanced in adipose tissues upon continuous administration of CXCL14 *in vivo*, resulting in local BAT activation and the browning of WAT depots.

Conclusions: CXCL14 is a novel brown adipocyte-derived adipokine which favors M2 macrophage recruitment to adipose tissues during adaptive thermogenesis.

Systems biology approach for the assessment of metabolic plasticity after a lifestyle intervention in diet-induced obese mice

Pau Gama-Perez [1], Alba Gonzalez-Franquesa [2], Giancarlo Castellano [3], Antoni Aguilar-Mogas[4], Sara Samino[5], Oscar Yanes[5], Laura Herrero[6], Jose Ignacio Martin-Subero[3], Marta Sales-Pardo[4], Roger Guimera[4], Pablo M Garcia-Roves[1].

1 Department of Physiological Science, Faculty of Medicine, University of Barcelona. Bellvitge Biomedical Research Institute (IDIBELL). Barcelona, Spain.
2 Research Division, Joslin Diabetes Center. Boston, MA, USA.
3 Department of Pathology, Pharmacology and Microbiology, University of Barcelona, August Pi i Sunyer Biomedical Research Institute (IDIBAPS). Barcelona, Spain.
4 Department of Chemical Engineering, University Rovira i Virgili. Tarragona, Spain.
5 Center for Omic Sciences, University Rovira i Virgili. Reus, Spain.
6 Department of Biochemistry and Physiology, School of Pharmacy, University of Barcelona. Barcelona, Spain.

Background: The progression to obesity-related type 2 diabetes (T2DM) is complex and requires holistic and integrative approaches to elucidate its underlying mechanisms. Thus, therapeutic strategies have to impact multiple organ systems and combat the pleiotropic effects of their root causes. Lifestyle intervention promoted by calorie restriction and exercise training has shown to be a successful approach to combat T2DM.

Aim: The experimental model was designed to study metabolic plasticity towards T2DM state, and assess the degree of reversibility that can be reached by undergoing a lifestyle intervention.

Methods: A system biology top-down approach from a phenotypic characterization at a systemic level to tissue-specific functional and metabolic read-outs was implemented.

Results: Lifestyle intervention was sufficient to reverse most of the phenotype disruptions observed in the pathological state, showing a high degree of reversibility. Tissue-specific metabolic alterations were also evaluated according to patterns of reversibility by different multivariate analysis, pointing out the high degree of irreversibility observed in epididymal white adipose tissue (eWAT).

Conclusions: The development and application of systems biology tools have allowed a comprehensive understanding of metabolic plasticity, and the identification of those metabolic pathways and tissues mostly altered in pathological states.

Obesity and type 2 diabetes alters the immune properties of human adipose derived stem cells

Noelia Keiran,[a,b] Carolina Serena,[a,b] Victoria Ceperuelo-Mallafre,[a,b] Miriam Ejarque,[a,b] Kelly Roche,[a,b] Catalina Nuñez-Roa,[a,b] Joan Vendrell,[a,b] and Sonia Férnandez-Veledo[a,b].

[a] Hospital Universitari de Tarragona Joan XXIII. Institut d´Investigació Sanitària Pere Virgili Universitat Rovira i Virgili, Tarragona, Spain
[b] CIBER de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Instituto de Salud Carlos III, Madrid, Spain

Background: Adipose tissue-derived stem cells (ASCs) are proposed as an alternative stem cell source to bone marrow-derived cells for immune cell therapy. However, microenvironmental factors may impact the functionality of this population in human adipose tissue (AT).

Aim: We evaluated whether the fat depot in addition to the donor phenotype controls the immunomodulatory capacity of ASCs. Focusing on obesity and type 2 diabetes (T2D) as metabolic disorders that might affect the immune response of ASCs.

Methods: We compared the inflammatory and functional response of ASCs from subcutaneous and visceral AT of age-matched donors (lean n=4, body mass index [BMI] 21.98$\pm$1.9; obese n=4 BMI 33.1$\pm$2.1 and T2D n=4 BMI 35.3$\pm$1.5).

Results: Obese and particularly T2D-derived ASCs showed increased expression of inflammatory markers, activation of NLRP3 inflammasome and higher migration, invasion and phagocytosis capacities than those derived from lean donors. Remarkably, ASCs derived from obese and T2D subjects exhibited a reduction in typical immunosuppressive activities attributed to stem cells.

Conclusion: These data indicate that the donor metabolic phenotype compromises the immunomodulatory properties of ASCs. These results are relevant not only for understanding the physiology of ASCs in terms of cell-based therapies but also for their role as key regulators of the immune response.

Regulation of PPARα target genes by Fsp27

Alexandra Carrilho do Rosário, Albert Pérez Martí, Joana Relat, Pedro Marrero, Diego Haro

Facultat de Farmacia, Universitat de Barcelona

Background: FSP27 is a lipid-droplet associated protein expressed in liver and white and brown adipose tissues, which promotes intracellular lipid accumulation and prevents lipid utilization.
Previous work in our lab identified FSP27 as a key gene upregulated in the liver on the early response to fasting (Vilà-Brau et al. 2013), uncovering a link between its expression pattern and role in the unilocular lipid droplet formation, and the availability of PPARα ligands, the new fat, in fasting or feeding situations (Chakravarthy et al. 2005).

Aim: We hypothesized that liver activity of FSP27 promotes the intrahepatic accumulation of newly synthesized phospholipids during the early fasting state, which are then released into circulation, thus regulating the availability of endogenous ligands of PPARα.

Methods: To evaluate the effects of the loss of hepatic FSP27, its expression was silenced by using and adenovirus-mediated shRNA, in Ad Libitum conditions and at a 15hour fasting.

Results: The livers of fasted mice showed similar expression of PPARα target genes when compared to livers from control mice, but changes were found in PPARα target genes in brown adipose tissue.

Conclusion: These results suggest that lack of hepatic FSP27 activity would affect brown adipose tissue gene expression.

Long term liquid fructose supplementation to female rats induces an atypical insulin resistance state in visceral adipose tissue

Gemma Sangüesa,[1,2] José Carlos Montañés,[1] Mª del Mar Cascales,[1] Miguel Baena,[1,2] Núria Roglans,[1-3] Marta Alegret,[1-3] and Juan C Laguna[1-3]

[1] Department of Pharmacology and Therapeutic Chemistry, School of Pharmacy, University of Barcelona, Barcelona, SPAIN.
[2]IBUB (Institute of Biomedicine, University of Barcelona)
[3]CIBERobn (Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y Nutrición).

Background: Fructose consumption has been associated with the development of metabolic disorders. Our aim was to investigate the effect of long term liquid fructose supplementation on metabolic parameters and morphological and functional changes in visceral white adipose tissue (vWAT) in female rats.

Methods: Sprague-Dawley female rats were supplemented with 10% w/v fructose in drinking water for 28 weeks. Glucose tolerance test (GTT) was performed and organ weight, plasma analytes and gene/protein expression in WAT were measured.

Results: Fructose rats showed a significant increase in total body and vWAT weight and adipocyte size. Plasma triglycerides, NEFA, TBARS, AGEs and leptin were higher in fructose rats. Fructose caused hyperinsulinemia, an increase in the AUC of plasma insulin concentrations during the GTT, and impaired insulin signalling (Akt-p, IRS-2) in vWAT. Despite this, fructose reduced HSL-p (Ser660) and PPARɣ-p (Ser273) whereas PPARɣ protein expression was not modified.

Conclusions: Long term fructose supplementation causes hyperlipidemia, glucose intolerance, alters insulin signalling in WAT and produces adipocyte hypertrophy, suggesting WAT insulin resistance. However, it seems to be an atypical state of insulin resistance, as lipolysis is not increased and PPARɣ-p (Ser273), which is considered a diabetogenic marker, is decreased.

POSTER PRESENTATIONS

1) Alex3, a possible linker between energy homeostasis and cancer

Aleix Gavaldà-Navarro[1], Mariona Guitart-Mampel[1], Eduardo Soriano[2], Beatriz Minguez[3] and Francesc Villarroya[1]

[1]Department of Biochemistry and Molecular Biology, and Institute of Biomedicine, University of Barcelona, and CIBERobn, Barcelona, Spain. [2]Department of Cell Biology, University of Barcelona, and CIBERned, Barcelona, Spain. [3]Grupo de Investigación en Enfermedades Hepáticas. Vall d´Hebron Institut of Research. Servicio de Medicina Interna-Hepatología. Hospital Universitario Vall d´Hebron. UAB, and CIBERehd. Barcelona, Spain.

Background: Alex3 is a member of the Armcx family of proteins. Originally, the activity of this protein was established in the nervous system. Alex3 localizes to mitochondria, controls mitochondrial dynamics and trafficking, influences the Wnt/β-catenin intracellular pathway and has been proposed as a putative tumour suppressor.

Aim: To study the role of Alex3 in the relationship between energy metabolism and cancer.

Methods: Metabolic and gene expression characterization of Alex3-knockdown mice, obtained via embryonic siRNA injection.

Results: We found that Alex3 is expressed in peripheral tissues, such as liver, white (WAT) and brown (BAT) adipose tissues. Mice fed high-fat diet showed a rise in the hepatic expression of Alex3, whereas fasting repressed it, suggesting a strong regulation of Alex3 by nutritional factors. Alex3-knockdowned mice developed obesity spontaneously, showing hypertrophy of adipocytes in WAT depots. Accordingly, insulin levels were increased despite mild hyperglycemia, indicating insulin resistance. This was accompanied by impaired thermogenic activity of BAT, assessed by reduced heat production and lowered expression of thermogenic genes. Moreover, these mice developed hepatic steatosis and signs of hepatic lipotoxicity.

Conclusions: These data indicate that Alex3 may play a role in the control of energy metabolism and elicits disturbances leading to obesity and hepatic lipotoxicity.

2) Deciphering the role of mitochondrial fusion protein Opa1 in POMC neurons upon modulation whole-body energy balance

Alicia G Gómez-Valadés[1,3], Marc Schneeberger[1,2], Sara Ramírez[1], Antonio Zorzano[4,5], Ramon Gomis[1,2,3] and Marc Claret[1,3]

[1]Diabetes and Obesity Research Laboratory, IDIBAPS, Barcelona; [2]Department of Endocrinology and Nutrition, Hospital Clínic, University of Barcelona Barcelona; [3] Centro de Investigacion Biomedica en Red (CIBER) de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Barcelona; [4]Institute for Research in Biomedicine (IRBB) Barcelona. [5]Departament de Bioquímica i Biologia Molecular, Facultat de Biologia, UB, Barcelona.

Background and aims: A growing body of evidence indicates that hypothalamic neurons expressing pro-opiomelanocortin (POMC) are key players in the control of whole-body energy balance and glucose homeostasis. It has been proposed that impaired nutrient/energy sensing mechanisms in POMC neurons may underlie the development of obesity and glucose metabolism perturbations. On the other hand, recent findings strongly suggest that mitochondria sense energy/nutrient fluctuations and engage bioenergetic adaptions through dynamic remodeling of its architecture by fission and fusion events. A key mediator of mitochondrial fusion is Optic atrophy 1 (Opa1), an inner mitochondrial membrane dynamin-related GTPase.

Hypothesis: Herein we aim to uncover a potential role of Opa1 in POMC neurons sensing energetic/nutritional milieu and integrating specific physiological actions to maintain systemic energy balance.

Results: Mice lacking Opa1 in POMC neurons (POMCOpa1KO) exhibit glucose intolerance and insulin resistance irrespective of body weight. Furthermore, POMCOpa1KO mice present altered energy balance parameters which leads to an obesogenic phenotype. Analysis of second order neurotransmitters revealed a fasting-specific reduction in hypothalamic Crh and pituitary Pomc mRNA, concomitant with an impaired fasting-induced corticosterone release. Nevertheless, a possible pituitary-adrenal axis dysfunction can be discarded as an appropriate CRH-induced (CRH test) stress-induced (restrain test) ACTH and corticosterone release was observed.

Conclusions: Our results highlight Opa1 in POMC neurons as a critical mitochondrial dynamics actor particularly relevant for adequate hypothalamic energy balance regulatory function, possibly by modulating the hypothalamus-pituitary-adrenal axis. This is an unexplored area of research that may open new avenues to investigate in the field of metabolic control and diabetes therapy.

3) Cardiac dysfunction in obesity: effect of a high fat diet and involvement of Fgf21

Planavila A. [1], Rupérez C.[1], Lerin C.[2], Giralt M. [1], Villarroya F. [1]

[1] Departament de Bioquímica i Biologia Molecular. Institut de Biomedicina de la Universitat de Barcelona (IBUB), Universitat de Barcelona, 08028 Barcelona, Spain
[2] Endocrinology, Hospital Sant Joan de Deu, 08950 Barcelona, Spain

Background: High-fat diet (HFD)-induced obesity leads to development of cardiac dysfunction. Fibroblast growth factor-21 (Fgf21) is produced by the heart and prevents cardiac hypertrophy development.

Aim: To determine the effects of Fgf21 on the cardiomyopathy associated to obesity development.

Methods: Wild-type (wt) and $Fgf21^{-/-}$ mice were fed a HFD for 16 weeks.

Results: HFD feeding increased the heart weight/tibia length (HW/TL) ratio in wt mice but not in $Fgf21^{-/-}$ mice. Ecocardiographic measurements (LVID, IVS, PWT and EDV) confirmed enhanced cardiac hypertrophy in $Fgf21^{-/-}$ mice. Fatty acid oxidation was induced in $Fgf21^{-/-}$ mice after HFD. The expression levels of genes involved in lipolysis were down-regulated in $Fgf21^{-/-}$ mice fed with a HFD and oil-red O staining revealed the presence of higher amounts of lipid droplets in these hearts.

Conclusions: Lack of Fgf21 confers more susceptibility to the cardiomyopathy induced by obesity.

4) β-enolase is decreased in muscle from sporadic inclusion body myositis patients

A. Justamante, M. Catalán-García, C. Morén, M. Guitart-Mampel, I. González-Casacuberta, D. Luz-Juárez, E. Tobias, P. Moreno, J. Milisenda, F. Cardellach, G. Garrabou, JM. Grau.

Muscle Research and Mitochondrial Function Laboratory, CELLEX-IDIBAPS, Faculty of Medicine-University of Barcelona, Internal Medicine Department- Hospital Clínic of Barcelona, CIBERER-U722 Barcelona, Spain.

Background: Sporadic inclusion body myositis (sIBM) is the most common myopathy in elderly and present three different pathogenic features: inflammation, mitochondrial abnormalities and muscle degeneration. However, its aetiology and treatment remain poorly understood and specific mechanisms responsible of muscle degeneration remain unknown.

Aim: To perform a high throughput evaluation of differentially expressed proteins in muscle from sIBM-patients compared to controls to search for a dysregulation of pathways underlying abnormal muscle regeneration.

Methods: A proteomic study was performed through mass spectrometry to evaluate proteic profile in 3 muscles from sIBM-patients and 3 controls. Afterwards results were confirmed by Western-blot technique in a larger cohort (15 muscles from sIBM-patients and 15 controls).

Results: Proteomic analysis revealed a significant decrease of β-enolase in muscle from sIBM patients with a fold change of 2.58 further confirmed through western blot with a fold change of 1.99.

Conclusions: β-enolase is involved in several pathways including glycolysis but also plasminogen activation, crucial for extracellular proteolysis, myogenesis and muscle regeneration. Abnormally low levels of β-enolase that have been found in muscle from sIBM-patients could play a role in the poor muscle regeneration characteristic of sIBM-patients.

5) Mrc1 integrates multiple stress signals to prevent genomic instability in s-phase

Canal-Torres B.*, Duch A.*, de Nadal E. & Posas F.

Cell Signaling Research Group. Departament de Ciències Experimentals i de la Salut (UPF). 08003 Barcelona, Spain.

Replication and transcription processes are coordinately regulated to prevent genomic instability. Specific DNA structures and proteins isolate replication and transcription processes in highly transcribed regions of the genome. General transcription, in the other hand, takes place all over the genome and is thought to be temporary separated from replication. However, cell adaptation to abrupt environmental changes requires fast and massive reprogramming of the gene expression pattern. This transcriptional activation also occurs during S-phase and poses risk of collision between replication and transcription machineries, requiring a precise coordination of the replication and transcription to prevent genomic instability. We described the existence of a dedicated checkpoint pathway to coordinate both machineries upon osmostress-induced transcriptional outbursts (Duch et al., 2013). In response to osmostress, the same protein that orchestrates the activation of hundreds of osmoresponsive genes, the Stress-Activated Protein Kinase (SAPK) Hog1, phosphorylates the replisome protein Mrc1 to block DNA replication in order to prevent genome stability. Mutation of the three Hog1 target sites in Mrc1 avoids S-phase arrest leading to Transcription-Associated Recombination (TAR) and the subsequent genomic instability upon osmostress. Interestingly, this mechanism operates independently of the known DNA damage checkpoint pathway, pointing out the necessity of a dedicated S-phase checkpoint to deal with the massive transcription upon osmostress. The aim of this project is to study if Mrc1 is also targeted upon other environmental stresses demonstrating the existence of a universal mechanism to protect genomic integrity upon stress-induced transcriptional outbursts.

6) Obese BAT has increased inflammation and ER stress

Eduviges Bustos[1], María Calderon-Dominguez[1,2], Joan F. Mir[1], Minéia Weber[1], Sandra Recalde[1], Blanca Balanyà[1], Núria Casals[2,3], Dolors Serra[1,2], Laura Herrero[1,2]

[1]Department of Biochemistry and Physiology, Institut de Biomedicina de la Universitat de Barcelona (IBUB), Universitat de Barcelona, E-08028 Barcelona, Spain. [2]Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y la Nutrición (CIBEROBN), Instituto de Salud Carlos III, E-28029 Madrid, Spain. [3]Basic Sciences Department, Faculty of Medicine and Health Sciences, Universitat Internacional de Catalunya, E-08195 Sant Cugat del Vallés, Barcelona, Spain.

Introduction: Obesity is spreading worldwide with a concomintant increase in its associated pathologies such as type 2 diabetes. Obesity is utimately an imbalance between energy intake and energy expenditure. Brown adipose tissue (BAT) controls energy expenditure through thermogenesis and has emerged as an important player in obesity-induced diabetes. However, its molecular changes under a high-fat diet (HFD) had not been fully characterized.

Objective: To study BAT inflammation, ER stress, mitochondrial dysfunction, thermogenesis and adipocyte morphology in obese and diabetic mice.

Methods: Eight-week-old C75Bl/6J male mice were fed with either chow (10% Kcal fat) or HFD (60% Kcal fat) for 20 weeks.

Results: Obese BAT showed increased mRNA levels of the proinflammatory markers TNFα, IL-β and MCP-1 and the ER stress markers Chop and Bip, compared with lean littermates. Bmp8b mRNA levels were reduced pointing to a decrease in thermogenesis. No changes were seen in mitochondrial function. Morphological studies showed the typical brown-to-white transformation of brown adipocytes under HFD.

Conclusion: Obese BAT showed increased inflammation and ER stress without changes in mitochondrial function.

7) Lack of Mitochondrial Transcription Termination Factor 4 in brown adipose tissue leads to impaired mitochondrial function and cold sensitivity

Inés Pedriza[1], Maria Vilà[1], Edgar Martín[1], Rosario Pardo[1], Yolanda Cámara[2] and Josep A. Villena[1]

[1]Laboratory of Metabolism and Obesity, Vall d'Hebron Research Institute
[2]Group of Neuromuscular and Mitochondrial Pathology, Vall d'Hebron Research Institute

Altered mitochondrial function is linked to numerous diseases. Biogenesis of functional mitochondria requires of the coordinated expression of genes encoded by both the nuclear and the mitochondrial genomes. Although several regulators that control the expression of nuclear-encoded mitochondrial genes have been identified, little is known about the mechanisms that control the expression of proteins encoded by the mtDNA. The members of the MTERF protein family have been implicated in the regulation of mtDNA transcription and translation. Among them, MTERF4 has been described as an essential factor for the assembly of mitochondrial ribosomes and protein translation. To study the role of MTERF4 in adipose tissues, we have generated an adipose-specific knockout mouse model devoid of MTERF4 in mature adipocytes (MTERF4-FAT-KO). MTERF4-FAT-KO mice show increased brown adipose tissue (BAT) mass and abnormal accumulation of triglycerides in brown adipocytes. Lack of MTERF4 in BAT results in reduced mitochondrial mass and decreased levels of mitochondrial proteins of the OxPhos system. The reduced mitochondrial protein content correlates with impaired respiratory capacity of isolated brown adipocytes in response to norepinephrine and the inability of MTERF4-FAT-KO mice to maintain body temperature when exposed to cold. Our results demonstrate that MTERF4 is essential to sustain BAT thermogenesis.

8) Altered endothelial mitochondrial dynamics cause metabolic disturbances

Iñigo Chivite[1], Alicia G Gómez-Valadés[1], Sara Ramírez[1], Mariona Graupera[2] and Marc Claret[1]

[1]Neuronal Control of Metabolism (NeuCoMe) Laboratory, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), 08036 Barcelona, Spain.
[2]Vascular Signalling Laboratory, Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), 08908 L'Hospitalet de Llobregat, Barcelona, Spain.

Blood vessels distribute nutrients and signalling molecules to every single cell in the body. Endothelial cells define the vessel wall and thus they are in a privileged location to crucially modulate nutrients and signalling molecules availability to tissues. Mitofusins (Mfn) are GTPase-like family of proteins implicated in external mitochondrial membrane fusion. A connection between mitochondrial fusion in the vasculature and endothelial dysfunction has been suggested. However, it is unknown whether primary vascular dysfunction impacts on systemic metabolism. Our hypothesis is that altered mitochondrial fusion in endothelial cells would lead to energy balance and metabolic disorders.
In order to address this question we have generated an inducible endothelial cell-specific Mfn2 knock-out mice, and perform metabolic profiling. The vasculature of those animal models will be fully characterized by a combination of imaging and functional techniques in retinas.
Upon adult-induced Mfn2 ablation in endothelial cells, mice progressively reduce body mass until reaching a weight loss circa 25% less than control counterparts when fed a chow diet. Consistently, mutant mice show resistance to HFD-induced weight gain. Concomitantly, they are more sensitive to insulin, exhibit improved glucose tolerance and reduced hepatic glucose production. Moreover, control and knock-out animals did not show differences in appetite or intestinal nutrient absorption, suggesting increased energy expenditure. The physiological underpinnings underlying this reduction in body weight are currently under investigation.
We can conclude that mitochondrial dynamics in endothelial cells are implicated in systemic energy homeostasis control in mice.

9) Decreased CD36 gene expression is concomitant to subcutaneous fat depot reduction in postoperatively morbid obese

Josep Julve 1, Eva Pardina 2, Karen A. Méndez-Lara 1, Roser Ferrer 2, Joana Rossell 2, Juan Antonio Baena-Fustagueras 3, José Manuel Fort 4, Albert Lecube 5, Julia Peinado-Onsurbe 2

1 Institut de Recerca de l'Hospital de la Santa Creu i Sant pau. Institut d'Investigacions Biomèdiques Sant Pau. Barcelona; CIBER de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), CIBER, Madrid.
2 Departament de Bioquímica I Biologia Molecular. Facultat de Biologia. Universitat de Barcelona. Barcelona.
3 Unitat de Cirurgia. Hospital Arnau de Vilanova. Lleida.
4 Departament de Bioquímica i Unitat de Cirurgia. Institut de Recerca de l'Hospital universitari de la Vall d'Hebron. Barcelona.
5 Unitat de Recerca en Diabetes i Metabolisme. Institut de Recerca de l'Hospital universitari de la Vall d'Hebron, Barcelona; CIBER de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), CIBER, Madrid.

Background: Few data are available on the impact of bariatric surgery on the expression of molecular determinants of metabolic syndrome in subcutaneous adipose tissue (SAT) in postoperatively morbid obese.

Objective: The aim of this study was to analyze the gene expression profile controlling SAT homeostasis in postoperatively morbid obese.

Materials and methods: Morbidly obese patients undergoing Roux-en-Y gastric bypass (RYGB) surgery were recruited from Hospital de la Vall d'Hebron in Barcelona. Sample specimens were assayed for chemical and gene expression analysis. The effects of weight loss on the different parameters were determined by comparing the baseline values with those obtained at 12 mo. after surgery using a non-parametric Wilcoxon test.

Results: A favorable metabolic status was observed in our postoperatively obese. At baseline, the expression of several genes (LEP, ADIPOQ, LIPE, LPL, CD36, PAI1, NOS2, SLC2A4, FABP4, UCP2, and PPARG) was predominant in SAT vs visceral fat. Compared with baseline, their downregulation was associated with a commensurate decrease in adiposity. Notably, the change in the gene expression of CD36 was concomitant to that observed in SAT (Spearman r=+0.77; P=0.007).

Conclusion: Our data show that subcutaneous fat depot reduction was directly associated with concomitant decrease in the gene expression of CD36.

10) Nicotinamide supplementation improves glucose metabolism and prevents weight gain in mice

Karen A. Méndez-Lara, Elisabeth Rodríguez-Millán, Núria Cabrerizo, Jesús María Martín-Campos, Joan Carles Escolà-Gil, Francisco Blanco-Vaca, Josep Julve

Institut d'Investigació Biomèdica de l'Hospital de la Santa Creu i Sant Pau (IIB-Sant Pau), Barcelona, Spain (KAM-L, ER-M, NC, JMM-C, JCE-G, FB-V, y JJ). CIBER de Diabetes y Enfermedades Metabólicas Asociadas, CIBERDEM, Barcelona, Spain (JMM-C, JCE-G, FB-V y JJ). Departament de Bioquímica i Biologia Molecular, Universitat Autònoma de Barcelona, Barcelona, Spain (KAM-L, JMM-C, JCE-G, FB-V y JJ).

Background: The impact of nicotinamide (NAM) on glucose metabolism and body weight is controversial.

Objectives: To evaluate the effect of NAM administration on the glucose metabolism and weight gain in mice.

Materials and methods: Male mice (C57BL/6J) on a standard diet were treated with three doses of NAM (0, 1, and 2 g/kg), respectively. Sample specimens were assayed for chemical and gene expression analysis. An oral glucose tolerance test was made to assess glucose metabolism. The effects of NAM on the different parameters were compared using a non-parametric Kruskal-Wallis or U Mann-Whitney test, as appropriate.

Results: Administration of NAM did not result in signs of hepatotoxicity or altered renal function. NAM improved (+28%; $P<0.05$) the responsiveness to glucose oral load in mice and it was associated with a weight gain prevention. The latter was in part attributed to a decreased feed efficiency (-40%; $P<0.05$) and increased NAD content (+50%; $P<0.05$) in adipose tissue from NAM-treated mice.

Conclusions: Mice administrated with NAM showed an amelioration in the bioavailability of glucose; the NAM-treated mice also displayed a significant reduction in the body weight gain which was mainly attributed to an increased feed efficiency.

11) Ghrelin reduces GABAergic output through carnitine palmitoyltransferase (CPT) 1A

Joan Francesc Mir[1], Matthieu P Lichtenstein[3], Judit García-Villoria[4], Minéia Weber[1], María Calderón-Domínguez[1], Blanca Balanyà[1], David Sebastián[5], Antonio Zorzano[5], Núria Casals[2,6], Antònia Ribes[4], Cristina Suñol[3], Laura Herrero[1,2] and Dolors Serra[1,2]

[1]Departament de Bioquímica i Fisiologia, Facultat de Farmàcia, Institut de Biomedicina de la Universitat de Barcelona; [2]Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Barcelona, Spain; [3]Institut d'Investigacions Biomèdiques de Barcelona, Centro de Investigación Biomédica en Red (CIBER) de Epidemiología y Salud Pública, Barcelona, Spain; [4]Sección de Errores Congénitos del Metabolismo – IBC, Servicio de Bioquímica y Genética Molecular, Hospital Clínic, IDIBAPS, Centro de Investigación Biomédica en Red (CIBER) de Enfermedades Raras, Barcelona, Spain; [5]Institute for Research in Medicine (IRB Barcelona), Barcelona, Spain; [6]Departament de Ciències Bàsiques, Facultat de Medicina i Ciències de la Salut, Universitat Internacional de Catalunya (UIC), Barcelona, Spain

Introduction: Ghrelin modulates neuropeptides in arcuate hypothalamus and it is essential for the control of feeding and glycaemia. Nonetheless, little is known about its effect on amino acid neurotransmitters. We assessed ghrelin effect on gamma-aminobutyric acid (GABA) metabolism and release and the involvement of carnitine palmitoyltransferase (CPT) 1A as a downstream effector in primary cortical neurons (CTX) and hypothalamic GT1-7 cell line. We used a pharmacological inhibition with etomoxir, a CPT1A-specific inhibitor, and genetic inhibition with Ad-shCPT1A and total ablation in CTX from CPT1A(loxP/loxP) mice.

Results: we observed that ghrelin reduces GABA release in cortical neurons under physiological glucose concentration similar to that of the cerebrospinal fluid. This effect is mediated by CPT1A, since its pharmacological inhibition with etomoxir or genetic ablation restores this reduction. Ghrelin also produces an increase in mRNA of cpt1a, gadx, vgat and GABA shunt genes. Moreover, we observed that ghrelin induces changes in the levels of TCA intermediates, as well as it modifies mitochondrial function by reducing oxygen consumption rate and the production of reactive oxygen species. These three effects are reversed by genetic inhibition of CPT1A.

Conclusion: all these observations indicate that ghrelin treatment of cortical/hypothalamic neurons might modulate GABA metabolism and release and highlight CPT1A as a key mediator of ghrelin's effect.

12) Increased PI3K signalling in endothelial cells depletes lipids from white adipose cells

Erika Monelli & Mariona Graupera

Vascular Signalling Laboratory, Institut d´Investigació Biomèdica de Bellvitge (IDIBELL), Gran Via de l'Hospitalet 199-203, 08907 L´Hospitalet de Llobregat, Barcelona, Spain

PTEN is a dual lipid/protein phosphatase, and represents the major negative regulator of PI3K. Previous data from our laboratory place PTEN as a key enzyme regulating endothelial cell (ECs) proliferation during angiogenesis and suggest that loss of PTEN in ECs do not compromise mice viability, but it results in aberrant vasculature exclusively in white adipose tissue (WAT). Physiological WAT remodeling is coordinated with vessel growth and this is partially mediated by a not yet fully characterized crosstalk between adipocytes and ECs. To study this crosstalk we took advantage of our mouse model of PTEN deletion in ECs. We crossed Ptenflox/flox mice with PdgfbiCreERT2 transgenic mice that express a tamoxifen-activatable Cre recombinase in ECs; 4-hydroxytamoxifen was administered in vivo at postnatal day 1 (P1) and P2 to activate Cre expression. Loss of quiescence in ECs induced by PTEN loss resulted in: i) vascular hyperplasia in adult WAT, (ii) ECs metabolic switch from glycolisis to beta-oxidation, (iii) reduced body weight gain, (iii) decreased WAT mass and reduced adipocyte size. This phenotype points out that the metabolic switch of ECs, induced by loss of PTEN, increases lipid mobilization from WAT. Our data further suggest that normal ECs are secreting protective factors that inhibit lipolysis, which likely are down regulated in PTEN null cells; identifying those protective factors may help in develop a novel therapeutic approach against obesity.

13) A drug discovery strategy to target PEPCK-M: implications in cancer and diabetes treatments

Juan Moreno-Felici[a], Petra Hyroššová[a], Sònia Abás[b], Anna Vidal Alabró[a], Javier Luque[c], C. Escolano[b], Jose C. Perales[a].

[a] Department of Fisiological Sciences II, Faculty of Medicine, University of Barcelona.
[b] Department of Pharmacology and Medicinal Chemistry, Faculty of Pharmacy, and Institute of Biomedicine (IBUB), University of Barcelona, Spain.
[c] Departament de Fisicoquímica and Institut de Biomedicina (IBUB), Facultat de Farmàcia, Universitat de Barcelona, Campus de l'Alimentació, Spain.

In the liver, mitochondrial and cytosolic phosphoenolpyruvate carboxykinase (PEPCK-M and PEPCK-C) isoforms play an important role potentiating gluconeogenesis and TCA flux through the conversion of mitochondrial oxaloacetate to phosphoenolpyruvate. However, PEPCK-M is specifically present in non-gluconeogenic tissues; including pancreatic β-cells where it critically regulates insulin secretion by coupling TCA cycle coupled GTP recycling to GSIS. On the other hand, we showed that PCK2 has a critical role in the survival program initiated upon ER and AAR stress in tumor cells. Therefore, we are developing a drug discovery/validation programme targeting PEPCK-M in cancer and diabetes. Our initial attempts, produced novel potent inhibitors based on C-8 modifications of 3-alkyl-1,8-dibenzylxanthines derivatives proven to target PEPCK-C. In fact, in INS1 cells, we demonstrated complete ablation of GSIS when PEPCK-M was inhibited. Also, we saw a decrease in cell viability under nutritional stress in several breast and colon carcinoma cell lines. Our results indicate that these PEPCK-M inhibitors could be useful tools to inhibit tumor cells growth *in vivo* and limit insulin exhaustion at the terminal phase of compensatory insulin resistance in type 2 diabetes patients.

14) Orexin receptor-1 signaling characterization in white adipose tissue

Gemma Navarro[1,2], Josefa Mallol[1,2], Enric I. Canela[1,2], David Aguinaga[1,2], Edgar Angelats[1,2], Rafael Franco[1,2]

[1]Departament de Bioquímica i Biomedicina Molecular. Universitat de Barcelona, Barcelona. Spain.
[2]Centro de Investigación en Red, Enfermedades Neurodegenerativas. CIBERNED. Instituto de Salud Carlos III, Madrid. Spain.

Two orexin receptors, OX_1 and OX_2 (OX_1R and OX_2R), have been identified, with orexin-A being non-selective for both receptors and orexin-B having more affinity for OX_2R (de Lecea et al., 1998; Sakurai et al., 1998). Signaling via OX_1R expressed in brown adipose tissue (BAT) constitutes an important mechanism that participates in the control of temperature and body weight (Sellayah et al., 2012). On the one hand, orexinergic neurons in the lateral hypothalamus project from the CNS indirectly through multisynaptic pathways to liver and epididymal white fat (Stanley et al., 2010). On the other hand, orexin receptors are expressed in WAT and significant levels of orexin A are present in plasma. Moreover, plasma levels associate with physical activity in obese people (Hao et al., 2016). We here describe orexin A-induced OX_1R signaling pathway in WAT to understand better the system and to explore new paradigms in obesity-related research.

References

Hao YY et al., 2016. Sellayah et al., 2012. Stanley et al., 2010

15) Similar expression of amino acid metabolism enzymes in rat white and brown adipose tissues

Laia Oliva[1], Sofía Arriarán[1], Silvia Agnelli[1], Marià Alemany[1,2], José-Antonio Fernández-López[1,2], Xavier Remesar[1,2]
[1]Department of Biochemistry and Molecular Biomedicine, Faculty of Biology, University of Barcelona
[2]CIBER-OBN; Barcelona

Background: White (WAT) and brown (BAT) adipose tissue glucose and fatty acid metabolism may be highly active depending on energy availability. Their amino acid (AA) metabolism is similarly active albeit unknown. Here we analyzed whether BAT thermogenesis and WAT fat-storage roles and diet, modulate AA metabolism-related enzymes.

Methods: Male rats were fed 30 days with standard or cafeteria diets. Subcutaneous WAT and interescapular BAT samples were used for gene expression analysis of common AA enzymes; data were expressed as fmol/g protein to allow comparison.

Results: WAT and BAT expression levels were mostly in the 20-30 cycle range. Ratios for Glul/Gls, and Bcat1/Bcat2 ratios were uniform despite site and diet. In BAT, Glud1 expression and the ALAT1/ALAT2 expressions ratio were higher in BAT. Glycine cleavage system was expressed in all samples.

Conclusion: BAT and WAT showed a similar high AA catabolic potential regardless of function and diet (protein energy availability). To be adipose is a main defining factor for AA metabolism.

16) Analysis of inflammation and ER stress in different tissues of mice overexpressing CPT1AM in liver

Sandra Recalde[1,*], Minéia Weber[1,*], Joan F. Mir[1], María Calderon-Dominguez[1,2], Eduviges Bustos[1], Blanca Balanyà[1], Núria Casals[2,3], Laura Herrero[1,2], Dolors Serra[1,2]

[1]Department of Biochemistry and Physiology, Institut de Biomedicina de la Universitat de Barcelona (IBUB), Universitat de Barcelona, E-08028 Barcelona, Spain.[2]Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y la Nutrición (CIBEROBN), Instituto de Salud Carlos III, E-28029 Madrid, Spain.[3]Department of Basic Sciences, Faculty of Medicine and Health Sciences, Universitat Internacional de Catalunya.* Equally contributed.

Introduction: Previous studies from our group have shown that an enhanced fatty acid oxidation (FAO) in liver of high-fat diet (HFD) mice reduces hepatic steatosis and blood glucose and insulin levels. However, the effect of this liver-specific enhancement of FAO on other tissues is unknown.

Objective: To determine the effect of liver FAO enhancement on the inflammation and ER stress gene expression markers in different tissues of HFD mice.

Methods: FAO was increased by expressing a permanently active mutant form of carnitine palmitoyltransferase 1A (CPT1AM) specifically in liver of obese or control mice by AAV9-CPT1AM tail vein injection. AAV9-GFP was used as a control. Inflammation and ER stress gene expression were analysed by qRT-PCR.

Results: HFD CPT1AM-expressing mice showed a decrease in the hypothalamic mRNA levels of the TNFα inflammatory gene compared to HFD control mice. In contrast, mRNA levels of ER stress gene markers were not modified. In brown adipose tissue, HFD-induced increase in MCP1 mRNA levels was restored in CPT1AM-expressing mice. No changes were observed in epididymal white adipose tissue and muscle.

Conclusions: Results point to a reduction in hypothalamus and BAT inflammation by the enhancement of liver FAO in HFD fed mice.

17) Maternal carbohydrate intake provokes oxidative stress in liver but not in adipose tissue

Silvia Rodrigo, Lourdes Rodríguez, María I. Panadero, Juan J. Álvarez-Millán[2], Paola Otero and Carlos Bocos.
Facultad de Farmacia, Universidad San Pablo-CEU, Montepríncipe, Boadilla del Monte, Madrid, Spain. [(2)] CQS Lab, Madrid, Spain.

Background: Fructose consumption from added sugars correlates with the epidemic rise in obesity, metabolic syndrome and cardiovascular diseases. One feature of metabolic syndrome is an impairment of the redox status. Therefore, we have investigated whether liquid fructose modifies the redox status in pregnant rats.

Methods: Pregnant rats were separated into three groups: control, fructose- and glucose-fed. Carbohydrates were supplied as a 10% (wt/vol) solution in drinking water throughout gestation. Different markers of oxidative stress were measured in plasma, liver and adipose tissue.

Results and Conclusions: Maternal carbohydrate intake throughout gestation increased hepatic maternal oxidative stress. However, their plasma lipid peroxides levels were decreased. Curiously, adipose tissue showed a lower oxidative stress in carbohydrate-fed rats versus control animals. Late pregnancy is known to show an augmented lipolytic activity. Therefore, it is proposed that scarcely oxidized fatty acids were released from adipose tissue to the circulation, leading to low plasma lipid peroxidation.

18) Lack of brain-specific carnitine palmitoyltransferase 1C (CPT1C) impairs leptin- and diet-induced thermogenesis

Rosalía Rodríguez-Rodríguez[1,2], Macarena Pozo[1,2], María Calderón-Domínguez[2,3], Laura Herrero[2,3], Dolors Serra[2,3], Miquel Vellvehi[4], Xavier Perpiñá[4], Núria Casals[1,2]

[1]Basic Sciences Department, Faculty of Medicine and Health Sciences, Universitat Internacional de Catalunya, Sant Cugat del Valles, Spain
[2]CIBER Fisiopatología de la Obesidad y la Nutrición (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain
[3]Department of Biochemistry and Molecular Biology, Institut de Biomedicina de la Universitat de Barcelona (IBUB), Universitat de Barcelona, Barcelona, Spain
[4]Institut de Microelectronica de Barcelona, Centre Nacional de Microelectronica, IMB-CNM (CSIC), Campus UAB, Bellaterra, Spain

Brain-specific carnitine palmitoyltransferase-1C (CPT1C), despite its minimal CPT1 catalytic activity, is implicated in central regulation of food intake and energy homeostasis. CPT1C knock-out (KO) mice show an increased susceptibility to diet induced obesity and an impaired regulation of food intake in response to leptin or ghrelin. However, it is completely unknown whether CPT1C is involved in hypothalamic regulation of thermogenesis. Here we explore the role of CPT1C in leptin- and diet-induced thermogenesis in brown adipose tissue (BAT).
CPT1C KO and WT mice were fed a standard or high fat diet (HFD) for 7 or 14 days. In WT mice, HFD significantly increased interscapular BAT temperature and the expression of thermogenic markers, while CPT1C KO mice showed lower interscapular BAT temperature and thermogenic gene expression. They also showed higher body weight gain and adiposity. Moreover, acute HFD consumption increased ER stress markers and dysregulated p-STAT3 and SOCS3 mRNA levels in mediobasal hypothalamus (MBH) from CPT1C KO mice compared to WT mice. In addition, CPT1C KO mice showed hyperleptinemia after 7 days of HFD suggesting an earlier onset of leptin resistance compared to WT mice. In another set of experiments, leptin injection into the lateral ventricle of WT mice revealed a sustained increase of interscapular BAT temperature for 4h after injection and the upregulation of BAT thermogenic markers, whereas these responses were significantly attenuated in CPT1C KO mice.
Therefore, our results demonstrate that CPT1C could be crucial in hypothalamic regulation of BAT thermogenesis in response to acute HFD and central leptin administration. These evidences contribute to explain the reported protective role of CPT1C against fat feeding.

19) Stromal vascular cells contribute significantly to adipose tissue lactate production from glucose, as the adipocytes do

Rotondo F.[1], Romero M.M.[1,2], Ho-Palma A.C.[1], Fernández-López J.A.[1,2], Remesar X.[1,2], Alemany M.[1,2].

[1]Department of Biochemistry and Molecular Biomedicine, Faculty of Biology, Universitat de Barcelona, Barcelona.
[2]CIBEROBN, Barcelona

White adipose tissue (WAT) produces large amounts of lactate by glycolysis from glucose. Lactate production correlates with lactate dehydrogenase (activity and gene expression). Cultured 3T3L1-derived adipocytes mimic these effects. Although most of WAT volume corresponds to adipocytes, it also contains stromal vascular cells (SVC).
In this study, we analysed glucose conversion to lactate using adipocytes and SVC isolated from epididymal (EPI) WAT. Erythrocytes contribution to total WAT lactate synthesis was also checked.
Male Wistar rats were anaesthesized and killed; EPI cells were isolated using collagenase; they were incubated with 14 mM glucose under standard (normoxic) conditions for 48h.
The adipocytes in 1g EPI produced 62% of total lactate; SVC lactate production was 37% of total. Erythrocyte-derived lactate was almost negligible.
In conclusion, adipocytes produced lactate at high glycolytic (i.e. non-oxidative) rates, SVC also produced lactate at lower rates (their combined mass was smaller), decreasing the glucose levels at the expense of lipogenesis.

20) Immunoregulatory properties of human adipose derived stem cells (hASCs) in inflammatory diseases. Differences between Crohn´s disease and obesity

Serena C,[1,2] Keiran N,[2] Millan M,[1] Ejarque M,[1,2] Roche K,[1,2] Vendrell J,[1,2] Fernández-Veledo S[1,2]

[1]Hospital Universitari de Tarragona Joan XXIII. Institut d´Investigació Sanitària Pere Virgili. Universitat Rovira i Virgili, Tarragona, Spain
[2]CIBER de Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Instituto de Salud Carlos III, Madrid, Spain

Background: Cohn's disease (CD), obesity and type 2 diabetes (T2D) are inflammatory diseases. Visceral adipose tissue (VAT) plays a decisive role in the inflammatory environment observed in these pathologies. Specifically, in CD subjects there is frequently an increase of mesenteric fat-tissue which is called "creeping fat".

Methods: We isolated adipose dervied stem cells (ASC) from subcutaneous (SAT) and VAT of a well-characterized cohort including 4 groups: inactive CD (in remission), active CD, obese, and obese subjects with diabetes (T2D). ASCs were immunophenotyped by flow cytometry.

Results: ASCs obtained from CD subjects shown a significantly greater migratory invasive and phagocytic capacities than those derived from obese subjects, regardless of the presence of diabetes. This distinctive difference in phenotype between CD versus obese ASCs was observed in both active and inactive CD donors and in both depots SAT and VAT. Accordingly, AT inflammation markers (IL-6, TNFα, IL-1β, MCP-1) indicated that both active and inactive CD subjects present a higher proinflammatory environment compared to obese subjects. Remarkably, we demonstrate that CD produces a detrimental effect not only on mesenteric adipose tissue-resident stem cells, but also on the subcutaneous fat depots.

Conclusion: ASCs may have different immuno-modulatory capacities depending on the inflammatory event.

21) Role of FGF21 in brown and white adiposity *in vivo* and *in vitro*

Quesada T., Planavila A., Ribas F., Cairó M., Iglesias R., Giralt M., Villarroya F.
Department of Biochemistry and Molecular Biomedicine, and Institute of Biomedicine (IBUB).
University of Barcelona, and CIBERobn. Barcelona. Catalonia. Spain.

Background. FGF21 experimental treatments protect against diabetes and obesity in rodents. However, obese patients and rodent models of obesity show a paradoxical increase in blood FGF21.

Aim: Elucidate the role of FGF21 on adiposity through 'loss-of-function' approaches.

Methods: BAT, inguinal and epididymal WAT were collected from male FGF21-KO and wild-type mice. Cell precursors were isolated and differentiated to adipocytes in culture, and 14C-glucose oxidation was determined. Cell morphology, gene expression and hormone/cytokine protein levels were determined by optical microscopy, qRT-PCR, ELISA or Multiplex, respectively.

Results. FGF21-null mice showed increased glycemia and insulinemia, reduced adiponectinemia but unaltered weight of adipose depots. The expression of marker genes for carbohydrate and lipid metabolism, adipogenesis and "browning" was essentially unaltered whereas expression of inflammation and macrophage infiltration marker genes was increased in BAT but reduced in iWAT from FGF21-KO mice. Morphological differentiation in culture of brown and white adipocytes from FGF21-KO was unaltered, whereas glucose oxidation and the expression of marker genes of "browning" were reduced.

Conclusions. Absence of FGF21 causes minor effects in adipose tissues *in vivo,* except for increased local inflammation status. However, the impaired glucose oxidation found in FGF21-KO adipocytes points to an autocrine role of adipose FGF21 on glucose homeostasis.

Acknowledgements: Supported by MINECO-ISCIII-FEDER (Grants SAF2014/55725R and PI14/00063) and FP7-Health (BetaBat project). T.Q. is recipient of an international PhD scholarship by CONACyT. México.

22) PGC-1-dependent mitochondrial biogenesis in adipose tissue is not required for the effects of calorie restriction on glucose homeostasis

Luis Cervela[1], Marina de Marco[1], Rosario Pardo[1], Lucia Statuto[1], Pau Gama[2], Pablo García-Rovés[2], Josep A. Villena[1].

[1]Laboratory of Metabolism and Obesity, Vall d'Hebron-Research Institute, Barcelona, Spain.

[2]Department of Physiological Sciences II, University of Barcelona, Barcelona, Spain.

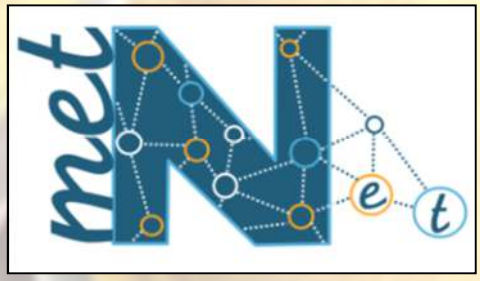
Calorie restriction (CR) exerts multiple effects on health, preventing and ameliorating numerous pathologies, including insulin resistance and type 2 diabetes. Besides the dramatic effects that CR has on adipose mass, little is known about the processes regulated by CR in WAT. Gene expression profiling analysis in WAT from mice subjected to 40% CR revealed mitochondrial biogenesis as the most up-regulated process in WAT in response to CR. CR dramatically increased mitochondrial gene expression concomitantly with a raise in the expression of PGC-1a and PGC-1b co-activators. To determine to which extent CR-induced mitochondrial biogenesis was dependent on PGC-1s, we generated a tissue-specific double knockout mouse model in which the expression of PGC-1a and PGC-1b was simultaneously ablated in adipocytes (PGC1a/b-FAT-DKO mice). WAT of PGC1a/b-FAT-DKO mice exhibited reduced expression of mitochondrial genes, decreased mitochondrial protein levels and impaired mitochondrial respiration. Moreover, mice lacking PGC-1s failed to increase mitochondrial biogenesis in response to CR. However, PGC1a/b-FAT-KO mice normally responded to CR by improving glucose tolerance and insulin sensitivity. Our results demonstrate that PGC-1 co-activators are the principal mediators of CR-induced mitochondrial biogenesis in WAT and that full oxidative function in WAT is not required for the beneficial effects of CR on glucose homeostasis.

MEETING PARTICIPANT LIST

Nom	Cognoms	Institucio
Marta	Alegret i Jordà	UB
Hugo	Alves Figueiredo	IDIBAPS
Núria	Amigó	Biosfer Teslab
Guillermina	Asins	Facultat de Farmàcia
Miguel	Baena Muñoz	UB
Emma	Barroso	UB
Marta	Bosch	IDIBAPS
Eduviges	Bustos	UB
Montserrat	Cairó	UB
María	Calderón Domínguez	UB
Enrique	Calvo Manso	IISPV
Laura	Campderrós Traver	UB
Alexandra	Carrilho Do Rosário	UB
Núria	Casals	UIC
Estefania	Casaña Lorente	CBATEG, UAB
Alba	Casellas Comallonga	CBATEG, UAB
Marc	Catalan	FUNDACIO CLINIC
Victòria	Ceperuelo Mallafré	IISPV
Rubén	Cereijo	UB
Iñigo	Chivite	IDIBAPS
Carles	Ciudad	UB
Marc	Claret Carles	IDIBAPS
Ivet	Elias	CBATEG, UAB
Brice	Emanuelli	University of Copenhagen
Jan	Eriksson	Uppsala University
Xavier	Escoté Miró	UNIVERSIDAD DE NAVARRA
Rebeca	Fernández Ruiz	REBECA
Sonia	Fernandez Veledo	Hospital Universitari de Tarragona Joan XXIII
Gemma	Ferrer Curriu	UB
Sylvie	Franckhauser	UAB
Rocio	Fuertes	Universitat Rovira i Virgili
Pau	Gama Perez	UB
Alicia	Garcia	IDIBAPS
Pablo	García-rovés González	UB
Aleix	Gavaldà Navarro	UB
Miríam	Gil	Universitat Rovira i Virgili
Marta	Giralt Oms	UB
Mariona	Graupera Garcia-milà	IDIBELL

Roger	Guimerà	URV
Anna	Gumà	UB
Roberta	Haddad Tovolli	IDIBAPS
Mercè	Hereu	IQAC-CSIC
Laura	Herrero	IBUB
Ana Cecilia	Ho Palma	UB
Petra	Hyrossova	UB
Claudia	Jambrina Pallarés	CBATEG
Josep	Jiménez-chillarón	Hospital Sant Joan de Déu
Josep	Julve Gil	Hospital de Sant Pau
Angela	Justamente Rodriguez	FUNDACIO CLINIC
Noelia	Keiran	CIBERDEM
Juan Carlos	Laguna Egea	UB
Iliana	Lopez-soldado	IRB BARCELONA
Janira	López Martínez	alumne Nuria Matias
Esmail	Lutfi Royo	UB
Àngela	M.valverde	CIBERDEM
Ana	Madeira	IISPV
Anna	Manzano Cuesta	UB
Oriol	Mañé Benach	
Anna	Marco Ramell	UB
Adil	Mardinoglu	KTH Royal Institute
Elsa	Maymó Masip	CIBERDEM
Karen Alejandra	Méndez Lara	Hospital de Sant Pau
Joan Francesc	Mir	UB
Erika	Monelli	IDIBELL
José Carlos	Montañés Domínguez	UB
Jaume	Morales	Agilent
Juan	Moreno Felici	UB
Sonia	Moreno Gómez	UB
Samantha	Morón Ros	UB
Sergio Antonio	Muñoz	CBATEG, UAB
Gemma	Navarro Brugal	UB
Cati	Nuñez	
Laia	Oliva Lorenzo	UB
Oscar	Osorio Conles	Fundació Sant Joan de Déu
Magalí	Palau Rodríguez	UB
Eva	Pardina	UB
Rosalia	Pardo	Vall d'Hebron Research Institute
Inés	Pedriza	Vall d'Hebron Research Institute
Jose Carlos	Perales Losa	UB
Carolina	Pimenta Costa	UB
Irene	Piquer García	Institut de Investigació Germans Trias i Pujol
Ana	Planavila	UB
Macarena	Pozo Ariza	UIC

Tania Paloma	Quesada López	UB
Sara	Ramirez Flores	IDIBAPS, CEK
Sara	Ramos	IQAC-CSIC
Sandra	Recalde Luna	UB
Ibon	Redondo Angulo	UB
Joana	Relat Pardo	UB
Carles	Rentero	UB
Sílvia	Ribó	FSJD
Natàlia	Riera	UB
Maria Àngels	Rigola Tor	UAB
Jordi	Rodó	UAB
Silvia	Rodrigo Duran	Universidad San Pablo CEU
Mª Del Mar	Rodríguez	IISPV
Matilde	Rodriguez Chacon	INST,INV.SANITARIA PERE VIRGILI
Maria Angels Rodriguez	Rodríguez García	Fundació Sant Joan de Déu
Rosalía	Rodríguez Rodríguez	UIC
Nuria	Roglans Ribas	UB
Mar	Romero	UB
Joana	Rossell	UB
Floriana	Rotondo	UB
Pim	Rullens	UB
Celia Helena	Rupérez Gonzalo	UB
Víctor	Sacristán Fraile	CBATEG
David	Sanchez-infantes	Hospital GermansTrias i Pujol
Gemma	Sangüesa	UB
Uwe	Sauer	Institute for Molecular Systems Biology
David	Sebastián	IRB Barcelona
Carolina	Serena	INST,INV.SANITARIA PERE VIRGILI
Dolors	Serra	UB
Alba	Serra Navarro	Fundació Clínic per la Recerca Biomèdica
Hagit	Shapiro	Israel
Maria Trinidad	Soria Florido	UB
Mònica	Suelves Esteban	IMPPC
Àlex	Teruel Molina	alumne Nuria Matias
Josep Lluís	Torres	IQAC-CSIC
Anna	Vidal	UB
Andrés	Vidal Itriago	IDIBAPS
Laia	Vilà Prats	CBATEG, UAB
Maria	Vilà Rovira	Institut de Recerca Vall d'Hebron (VHIR)
Joan	Villarroya	UB
Josep	Villena Delgado	Institut de Recerca Vall d'Hebron (VHIR)
Francesc	Viñals	IDIBELL
Marina	Viñas Vidal	alumne Nuria Matias
Òscar	Yanes	Universitat Rovira i Virgili


met
Net