Societat Catalana de BIOLOGIA

4th MetNet International Annual Meeting

Organ crosstalk in the control of metabolism

Organitzadors: Joan-Marc Servitja, Rosa Gasa

Organitzada per la Secció de Senyalització de l'SCB

Coordinador: Marc Claret

PROGRAMA I RESUMS DE LES COMUNICACIONS

INSTITUT D´ESTUDIS CATALANS

Sala Pere i Joan Coromines, Institut d'Estudis Catalans
Carrer del Carme, 47. Barcelona

Carrer del Carme 47

Barcelona

4 de maig de 2018

Programa

8:30-9:00 Registration and documentation pickup

9:00-9:10 Welcome

Session I
Chair: Joan-Marc Servitja

9:10-9:50 Marc Donath (University of Basel, Switzerland)
Crosstalk between resident immune cells and endocrine cells in pancreatic islets

9:50-10:30 Maria Mittelbrunn (CBMSO, Madrid)
Immunometabolism in inflammatory diseases and aging

Short talks:

10:30-10:45 OP1 Carlos Castaño (CIBERDEM-IDIBAPS)
Obesity-associated exosomal miRNAs modulate glucose and lipid metabolism in mice

10:45-11:00 OP2 David Sebastian (IRB)
Regulation of mitochondrial plasticity by Mfn2 drives metabolic flexibility

11:00-11:30 Coffee Break

Session II
Chair: Laura Herrero

11:30-12:10 Paula Mera (Facultat de Farmàcia, UB, IBUB)
Bone endocrine regulation of energy metabolism

12:10-12:50 Manolo Tena-Sempere (IMIBIC, Córdoba)
Metabolism and reproductive function

Short talks:

12:50-13:05 OP3 Rebeca Fernández-Ruiz (CIBERDEM-IDIBAPS)
Identification of wisp-1 as a young blood-borne factor that promotes adult pancreatic β cell proliferation

13:05-13:20 OP4 Melisa Morcillo (Facultat de Farmàcia, UB, IBUB)
Activation of the Jun NH2-terminal (JNK) in pancreatic β cells protects against obesity-induced insulin resistance

13:30-15:00 Lunch

Session III
Chair: Rosa Gasa

15:00-15:40 Sylvia Boj (Foundation Hubrecht Organoid Technology, Utrecht, the Netherlands)
Organoids as model systems for the study of metabolism

15:40-16:20 Josep C. Jiménez-Chillarón (IRSJD, Barcelona)
Epigenome-wide association study in childhood obesity: Searching for new causal markers

16:20-17:00 Mariona Graupera (IDIBELL, Barcelona)
Role of the endothelium in the control of metabolism

Short talks:

17:00-17:15 OP5 Alicia G Gómez-Valadés (IDIBAPS)
Mitochondrial fusion protein Opa1 links mitochondrial dynamics in POMC neurons with fasting-induced adipose tissue lipolysis

17:15-17:30 OP6 Marion Peyrou (IBUB)
Kininogen is involved in the remodeling of fat tissue

17:30-17:40 Closing act

17:40-19:30 Drinks and networking

Resums

OP1

Obesity-associated exosomal miRNAs modulate glucose and lipid metabolism in mice

Carlos Castaño, Susana Kalko, Anna Novials, Marcelina Párrizas

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Maintenance of metabolic homeostasis relies on tissue cross-talk, which is disturbed by obesity. In addition to hormones and other soluble factors, cells communicate by releasing exosomes, small vesicles loaded with miRNAs that are detected circulating in blood and other biological fluids. The profile of exosomal miRNAs in blood depends on the physiological context. Hence, we focused on determining the changes induced by obesity in the profile of exosomal miRNAs in mice. In addition, we explored the role of these miRNAs in the establishment of glucose intolerance.

From a RT-PCR profiling of 378 miRNAs we observed increased levels of *miR-122*, *miR-192* and *miR-27a/b* in exosomes isolated by ultracentrifugation from the plasma of mice rendered obese by 15 weeks of high fat feeding. These data indicate that the development of glucose intolerance is associated with a modification of the population of circulating miRNAs. Surprisingly, the administration during 4 weeks of exosomes transfected with mimics of the aforementioned miRNAs induces glucose intolerance in control mice, which remain lean but show enhanced fat deposition in the epididymal depot. By bioinformatics analysis, we identified the transcription factor *ppara* as one of the main target genes of our miRNAs. Accordingly, in white adipose tissue of exosome-treated mice, the expression of *ppara* is decreased, and this is associated with a lower oxidative capacity, an increase in circulating free fatty acids and tissue inflammation. As a consequence, we observed increased expression of lipogenic genes in liver and hepatic steatosis. Liver damage is further reflected in an increase in plasma triglyceride levels.
Overall, our data suggest that obesity-associated exosomal miRNAs are novel mediators of tissue cross-talk and play an important role in the etiopathogeny of glucose intolerance and dyslipidemia.

OP2

Regulation of mitochondrial plasticity by Mfn2 drives metabolic flexibility

David Sebastián, Antonio Zorzano

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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 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. In addition, Mfn2 has been demonstrated to be crucial for a correct mitochondrial function and quality in muscle. Here we demonstrate that Mfn2 determines whole-body metabolic flexibility by controlling mitochondrial plasticity in skeletal muscle. Hence, Mfn2 protein expression is increased during fasting and it is necessary for metabolic switching from glucose to lipid oxidation in mouse skeletal muscle as well as in cultured muscle cells. These results strongly suggest that Mfn2 is an important factor in insulin resistance and type 2 diabetes by controlling metabolic flexibility in skeletal muscle.

OP3

Identification of Wisp-1 as a young blood-borne factor that promotes adult pancreatic β cell proliferation

Rebeca Fernández-Ruiz, Ainhoa García, Yaiza Esteban, Berta Serra-Navarro, Joan Mir-Coll, Elena G Ruano, Ramon Gomis , Rosa Gasa

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Restoring functional β-cell mass is a current therapeutic goal in diabetes. One of the proposed strategies is to promote replication of remaining β-cells. Under normal physiological conditions, adult β-cells have a limited capacity to proliferate. This decline in replication appears to occur around weaning by mechanisms that are still poorly understood. We hypothesize that blood borne factors present in early postnatal life but absent in adulthood have an important role in this age-related decay. Identification of these factors is important to uncover novel switchers of adult β-cell replication.

In order to test whether circulating factors are important to maintain β-cell replicative activity, we performed transplants of mouse adult islets into the anterior chamber of 16-days (young) and 20-weeks old (adult) mouse recipients. Our results show that adult β-cells exhibit a significantly higher proliferation rate when transplanted in young recipients. We next compared serum from young and adult mice by using commercially available antibody arrays, revealing Wisp-1/CCN4 as one of the circulating factors that are more abundant in young than in adult serum. We confirmed our results by a specific ELISA, and surveyed *Wisp1* gene expression in several tissues in young mice, showing highest expression in bone. To test whether Wisp-1 impacts β-cell proliferation, we performed both *in vitro* experiments incubating adult islets with Wisp-1 recombinant protein, and an *in vivo* approach increasing Wisp-1 levels in the circulation of adult mice using an adenovirus-overexpressing system. In both cases we obtained a significant induction of adult β-cell proliferation.

Our results provide evidence that Wisp-1 promotes proliferation of adult β-cells, hence supporting the idea that young blood borne factors may be a useful strategy to modulate the intrinsic ability of β-cells to proliferate later in life.

OP4

Activation of the Jun NH2-terminal kinase (JNK) in pancreatic β-cells protects against obesity-induced insulin resistance

Melisa Morcillo*, Jordi Lanuza-Masdeu*, Carles Bayod, Giuseppe Pulice, Cristina Vila, and Carme Caelles

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Obesity is epidemic worldwide and tightly associated to insulin resistance. Given that insulin resistance is an early trait in type 2 diabetes, obesity is a major risk factor for the development of this disease. It is well established that obesity-induced JNK activation inhibits insulin receptor signalling and, hence, promotes insulin resistance. Taking advantage of a genetically modified mouse model, MKK7D mice, we have previously shown that the activation of JNK in pancreatic β-cells interferes with the insulin paracrine action, thereby leading to a glucose intolerant phenotype due to impaired insulin release in response to hyperglycemia. Now, we show that MKK7D mice fed with a high fat diet develop obesity and glucose intolerance to a similar extend than control mice. In contrast, MKK7D mice are protected from the development of obesity-induced insulin resistance, as shown by insulin tolerant test and insulin-induced AKT activation in adipose tissue, as well as from hyperinsulinemia. Therefore, MKK7D mouse is one of the few examples in which obesity is dissociated from insulin resistance and hyperinsulinemia.

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OP5

Mitochondrial fusion protein Opa1 links mitochondrial dynamics in POMC neurons with fasting-induced adipose tissue lipolysis

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Hypothalamic neurons expressing pro-opiomelanocortin (POMC) are key players in energy homeostasis. Mitochondrial dynamics in POMC neurons represent a nutrient-sensing mechanism connecting energy status with systemic metabolic adjustments. Mice lacking Opa1 (an inner mitochondrial membrane GTPase critical for mitochondrial fusion and cristae maintenance) in POMC neurons (*POMCOpa1KO*) exhibit altered glucose metabolism and impaired lipolysis that precedes the onset of obesity. Fasting-induced rise in circulating FFA was reduced, along with HSL phosphorylation, perilipin levels and *Pnpla2* (coding for ATGL) gene expression in epididymal white adipose tissue (eWAT). Furthermore, catecholamine content was selectively reduced in eWAT, suggestive of a reduced SNS tone. Interestingly, acute ICV administration of either αMSH (whose presence in PVN projections is reduced) or Ru360, a specific inhibitor of the mitochondrial calcium uniporter (MCU) described to interact with Opa1, restored lipolysis. Importantly, Ru360 treatment was able to prevent body weight gain in a chronic treatment, by restoring lipolytic inputs. Our results highlight Opa1 in POMC neurons as a critical checkpoint for the connectivity between hypothalamic POMC neurons and adipose tissue, regulating lipolysis possibly through SNS.

OP6
Kininogen pathway is implicated in the remodeling of fat tissue

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Background: Brown adipose tissue (BAT) plays a beneficial role on metabolism through the induction of thermogenesis, while its inactivation is related to metabolism unbalance and favors obesity and type II diabetes. BAT might also have an endocrine function that could induce white adipose tissue (WAT) browning and affect other tissues leading to an improvement in the metabolic profile. The secreted products of the Kininogen (Kng) gene play a role in blood coagulation/pressure, pain and inflammation, but the role of these proteins in metabolism is poorly known. We observed that Kng is expressed by BAT and increased in case of BAT activation by cold exposure. Here, we aimed at unraveling the role of Kng in BAT activation and its potential role as a BAT endocrine factor.
Material and Methods: We performed *in vivo* experiments using Kng receptors knock-out (KO) mice exposed to cold or thermoneutrality, and measured various parameters using metabolic cages. We also cultured *in vitro* primary brown/white adipocytes and exposed them to Kng-derived products or β-adrenergic pathway inducers.
Results: When exposed to changes of temperature, mice deficient for Kng receptors showed an impaired brown- and beige-versus-white tissue remodeling and a lack of physiological adaptation. Indeed, KO mice under cold exposure consumed less oxygen and energy and had a reduced food intake compared to controls. They showed a dramatic impairment of induction of browning in WAT, while conversely, WAT lost the capacity of further “whitening” in response to thermoneutrality. Interestingly, Kng-derived proteins had no effect on brown and white adipocytes, indicating that the effect of Kng in mice is not cell-autonomous. However, markers of browning were increased in the KO, confirming the implication of Kng in browning.
Conclusions: All together, these data suggests that Kng is required for the plasticity of adipose tissues occurring in response to challenges in energy balance.