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Role of p38MAPK in palmitate-induced inflammation in C2C12 muscle cells

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Track1: From genes to cells

Session 1: Adipose inflammation and remodelling

T1:S1:01
Immune Cell Cross-talk In Adipose Tissue

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Adipose tissue (AT) is constituted by adipocytes and distinct cell types, the so called stroma-vascular fraction (SVF), that define the adipocyte microenvironment. SVF contains progenitor cells, vascular cells and immune cells, mainly lymphocytes and macrophages. Flow cytometry analyses performed on SVF showed that the adipocyte microenvironment is dependent on both fat depot location (subcutaneous and visceral AT) and adiposity degree. Phenotypes, numbers and cell subsets of macrophages and lymphocytes are strongly modulated in a depot-specific manner by obesity, weight loss as well as nutritional conditions. To note, differences must be taken into account depending on species (human versus murine models).
The causes of AT immune cell remodeling are certainly plural. Alterations in oxygen tension and lipid metabolism, but also aging- and microflora-dependent mechanisms may be contributing events in AT immune cell infiltration, resident cell proliferation and/or shift in immune cell phenotypes. The consequences of such changes will impact on AT endocrine and metabolic functions. Locally, AT immune cell cross-talk with progenitor cells modify their differentiation potentials including white and brite adipogenesis as well as myofibroblast potentials. In addition, interactions with mature adipocytes affect lipolysis and lipogenesis functions, and with endothelial cells modulate angiogenesis, leading to a global alteration of the adipose tissue buffering capacity to cope with excess fatty acids. Moreover, AT immune cells through the release of pro-inflammatory factors could also impact on systemic metabolic and inflammatory responses. Such local and systemic changes have repercussion on energy homeostasis. Therefore AT immune cells are major players in obesity-associated pathologies.

T1:S1:02
Adipose tissue expandability, lipotoxicity and the metabolic syndrome

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

T1:S1:03
HemeOxygenase and Met-inflammation

Esterbauer, H.*
Medizinische Universität Wien

No abstract submitted

T1:S1:04
Cellular origins of fibrosis

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Fibrosis occurs in many organs including the white adipose tissue (WAT) as a result of prolonged tissue injury with exaggerated extracellular matrix deposition. This phenomenon causes tissue disorganization and functional alterations. Whereas not completely understood, fibrotic transformation in several organs is mediated by cell activation towards a so-called myofibroblast phenotype, which includes matrix generation, high responsiveness to proinflammatory cytokines, active proliferation and sometimes resistance to apoptosis. In WAT depots from obese subjects, fibrosis is now seen as part of pathological alterations associated with inflammation and metabolic alterations. In the last years, our team provided description of WAT tissue remodelling and fibrosis in various forms of obesity and during weight changes. WAT fibrosis is linked to changes in tissue stiffness and both fibrosis and changes of stiffness appeared as contributors of metabolic deteriorations and of unfavourable clinical outcomes after weight loss-induced bariatric surgery in severe obesity. Ex vitro and in vitro experiments showed that fibrosis-embedded hypertrophied adipocytes displayed altered metabolic functions and increased expression/production of many inflammatory and fibrotic mediators partially via the stimulation of mechano-sensitive pathways. New data are now being produced regarding cell progenitors driving human WAT fibrotic phenotype and their phenotypic changes under various metabolic conditions and stress. New results will be presented on this matter.

Session 2: Brown and beige fat

T1:S2:02
BMP2, 4 and 7 exhibit distinct brite adipogenic potential according to the modulation of MSCA1 activity

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INSERM UMR1048/I2MC

Brite adipogenesis may be of potential interest to fight against obesity and to ameliorate metabolic parameters. Bone morphogenetic proteins (BMPs) have been described as potent brite inducers. Our previous study showed that MSCA1 is expressed by human bipotent committed progenitor cells and that MSCA1 activity is involved in brite adipogenesis. The present study aimed to characterize the impact of BMP2, 4 or 7 on MSCA1 activity and on the modulation of mitochondrial architecture as a readout of functional brite adipogenesis.

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Human native progenitor cells (CD45-/CD34+/CD31-) and preadipocytes (CD45-/CD34+/CD31-/MSCA1+) were isolated from human subcutaneous AT and cultured under adipogenic condition after 48h BMP pretreatment. Adipogenesis was assessed by lipid accumulation and adipogenic related gene expression. The mitochondrial network architecture was assessed by super-resolution microscopy BMP2, 4 or 7 pretreatment led to increased lipid accumulation and adipogenic-related gene expression.. BMP7 only increased the brite- related gene expression and MSCA1 activity. Isolated MSCA1+ preadipocytes pretreated with BMP7 exhibited fragmented mitochondrial network after adipogenic differentiation while preadipocytes pretreated with BMP2 or 4 exhibited elongated mitochondria.
The present study shows that among the tested BMPs, BMP7 only promotes the appearance of functional brite adipocytes
No conflict of interest is disclosed. Financial support: Sanofi, INSER

T1:S2:03
Brown and beige/brite Can both display a mammary myoepithelial cell phenotype in vivo

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There are at least 3 types of 'adipocyte': classic brown adipocytes, white adipocytes and beige/brite adipocytes. Beige/brite adipocytes are capable of displaying both brown and white phenotypes in different circumstances. Previous work has suggested white adipocytes may also show a mammary gland alveolar cell phenotype. It is however presently uncertain whether these 'white' adipocytes were in fact beige/brite adipocytes in their white phase. The capacities of the three different adipocytes to display a mammary cell phenotype are currently unknown. To investigate the potential adipocyte origins of mammary gland cells, we performed genetic lineage-tracing experiments of mouse brown adipose tissue and the mammary gland. Both mammary myoepithelium and luminal epithelium cells contained Fabp4^{+} lineage cells in the scapacular and inguinal mammary glands during reproduction. However, the classic brown adipose Myf5^{+}/Ucp1$^{+/-}$lineage and subcutaneous Brite/Beige Myf5^{-}/Ucp1$^{+/-}$lineage cells were only localized in the mammary myoepithelial population. These results demonstrates all three 'adipocytes' can display a mammary cell phenotype, although brown and brite adipocytes only reveal a myoepithelial mammary cell phenotype. Additionally we found mammary epithelial lineage Mmtv^{+} and K14^{+} cells expressed adipocyte markers after weaning demonstrating that mammary gland cells can revert to an adiopocyte phenotype after weaning.

T1:S2:04
The innervation of beige fat—a search for a unique neurochemical signature

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Monash University

Brown fat biology and the potential for brown fat to be recruited to combat overweight has recently moved to centre stage in obesity research. This has been driven by two factors, one being the recognition that brown fat exists in adult humans in levels inversely proportional to body weight and two, the fact that white fat may contain brown fat precursors or be transformed into "brown-like" or beige fat. It is likely that neural activation is integral to recruitment of brown and beige fat and therefore the therapeutic potential to promote energy expenditure in these end points is dependent on an understanding their innervation.
Male SD rats were housed either at 27 oC or 8oC for 7 days after which they were perfused with aldehydes or killed prior to removal of the inguinal (iWAT) or interscapular (isBAT) brown fat and their associated sympathetic ganglia (iWAT = T13/L1; isBAT = stellate). RNA was extracted from sympathetic ganglia and RNA seq was used to identify differential gene expression after cold exposure. At 8oC, iWAT expressed beige characteristics in the form of islands of UCP1+ve brown-like fat which attracted elevated levels of neural input and the T13/L1 ganglion took on a brown like neurochemical signature. Bioinformatics analyses revealed key candidate pathways and neurochemicals such as CGRP within ganglionic neurons that were specific to beige fat.
These data provide the first clear insights into the nature of the specific neural input to beige fat.

T1:S2:05
Cold exposure induces proliferation of mature brown adipocytes: Possible role of Beta3-adrenergic receptor stimulation

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Hyperplasia of brown adipose tissue (BAT) is fundamental to survival in the cold environment in rodents, but the mechanism behind the increase in number of brown adipocytes (BA) remains unknown. Thus, we examined cell type in BAT that proliferated in response to cold exposure. BAT was isolated from 6 weeks old C57BL/6J mice housed at 24°C (control group) or 10°C (cold-exposed group) for 1, 3 and 5 days. Histochemical analysis showed that the number of Ki67-positive proliferative cell was dramatically increased from the first day of cold exposure. To identify cell type of Ki67-positive cells, double-staining with Ki67 and antibody against monocarboxylate transporter 1 that exclusively located on the cell membrane was performed, so that BA could be distinguished clearly from stromal-vascular (SV) cells. The rate of Ki67-positive BA increased from Day1 (17.4±2.4%) compared to the control group (3.5±1.3%), whereas Ki67-positive SV cell was increased at Day5 of cold exposure. We also examined the effect of beta3-adrenergic receptor agonist CL316,243 (CL) for 5 days on cell proliferation in BAT. CL treatment raised the rate of Ki67-positive BA at Day1 (14.3±0.9%) compared to the control group (3.5±0.8%). However, the rate of Ki67-positive SV cell failed to change during the CL treatment. These results suggest that proliferation of mature BA is induced immediately after the beta3-adrenergic receptor stimulation and possibly contribute to cold-induced BAT hyperplasia.

T1:S2:06
Brown adipose tissue is involved in diet-induced thermogenesis and whole body fat utilization in healthy humans

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Background: Brown adipose tissue (BAT) is a potential therapeutic target against obesity and diabetes through thermogenesis and

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substrate disposal. The role of BAT in energy metabolism under cold conditions has well been established, while that under free-living and thermoneutral conditions remains unclear.
Aims: We assessed the contribution of BAT to energy expenditure (EE), particularly diet-induced thermogenesis (DIT) and substrate utilization in human adults.
Key Methods: BAT activity was evaluated in 21 male adults using 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography combined with computed tomography (^{18}F-FDG-PET/CT) after cold exposure (19°C). Subjects were divided into BAT-positive (N=13) and BAT-negative (N=8) groups according to the findings of ^{18}F-FDG-PET/CT. Twenty-four-hour EE, DIT, and respiratory quotient (RQ) were measured using whole-room indirect calorimeter at 27°C under semi-free living conditions 3 weeks after the ^{18}F-FDG-PET/CT sessions.
Results: Twenty-four-hour EE did not differ significantly between the groups, while DIT relative to total energy intake and RQ were significantly higher and lower, respectively, in the BAT-positive group than in the BAT-negative group.
Conclusions: DIT and fat utilization were higher in subjects with higher BAT activities even under thermoneutral conditions. Our findings enhance that BAT would be considerable as a target for treatment of obesity.

T1:S2:07
Fish oil intake induces UCP1 upregulation in brown and white adipose tissue via the sympathetic nervous system

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Brown adipose tissue (BAT) plays a central role in regulating energy homeostasis, and may provide novel strategies for the treatment of human obesity. BAT-mediated thermogenesis is regulated by mitochondrial uncoupling protein 1 (UCP1) in classical brown and ectopic beige adipocytes, and is controlled by sympathetic nervous system (SNS). Previous work indicated that fish oil reduces fat accumulation and induces UCP1 expression in BAT; however, the detailed mechanism of this effect remains unclear. In this study, we investigated the effect of fish oil on energy expenditure and the SNS. Fish oil intake increased oxygen consumption, with concomitant upregulation of UCP1 and the β adrenergic receptor, two markers of beige adipocytes, in interscapular BAT and inguinal white adipose tissue (WAT). Fish oil intake increased the elimination of urinary catecholamines and the noradrenaline turnover rate in interscapular BAT and inguinal WAT. Interestingly, β adrenergic blocker-treated and vagotomized mice showed the enhancement of UCP1 by fish oil was canceled, suggesting that afferent vagal nerve in gastrointestinal tract mediates the stimulatory actions of fish oil. Furthermore, the effects of fish oil on SNS-mediated energy expenditure were abolished in transient receptor potential vanilloid 1 knockout mice. In conclusion, fish oil can induce UCP1 expression in classical brown and beige adipocytes via the SNS, thereby attenuating fat accumulation and ameliorating lipid metabolism.

T1:S2:08
The association between brown adipose tissue thermogenesis and body composition and metabolic profile among Chinese adults

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An innovative technology by thermal imaging had been developed to monitor human brown adipose tissue(BAT). Previous studies associated the BAT thermogenesis with obesity among adolescents, however, no studies investigated fat composition and metabolic risk factors especially among adults.
To identify the association between BAT thermogenesis indicators and obesity, fat distribution indicators, and metabolic risk factors among Chinese adults.
A total of 454 adults were recruited. The metabolic indicators were from blood analysis and the body composition indicators were measured by DXA. Thermal imaging measurements were performed using the FLIR E60. The baseline temperature of supraclavicular region(TSCR) was calculated as a mean of the values before cold exposure, and the ΔTSCR was defined as the change from baseline to the peak TSCR after cold exposure.
Baseline TSCRs were negatively associated with anthropometry and fat distribution factors. The ΔTSCRs were negatively associated with most body indicators in women but not in men. The baseline TSCR in women and the ΔTSCR in men were positively associated with blood pressure. The ΔTSCRs in left site were negatively associated with HDL, LDL and total cholesterol in women.
The BAT thermogenesis was negatively associated with obesity, most fat indicators and metabolic indicators. The association was inconsistent between genders and sites of the measurement. Further studies were warranted to understand the mechanism for the correlation.

T1:S2:09
Adipocyte-specific overexpression of P27kip1 inhibits brown adipose tissue development in mice

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The number of adipocyte is drastically changed depending on the physiological conditions, and thought to be determined by the proliferation and differentiation of pre-adipocyte. It is controversial whether the mature adipocyte has an ability to proliferate or not. To investigate the possible proliferative ability of adipocyte, we generated transgenic (Tg) mice expressing p27^{kip1}, a cyclin-dependent kinase inhibitor that prevents the cell-cycle progression, under the control of mature adipocyte-specific aP2 promoter. At 12 weeks old, no obvious change was observed in white adipose tissue of Tg mice. However, brown adipose tissue (BAT) was strikingly reduced in Tg mice to 21.1% of the wild-type (WT) mice in weight. However, cellular morphology, lipid droplet content, or expression level of uncoupling protein 1 in BAT of Tg mice was similar to WT mice. Tissue DNA content was decreased in Tg mice to 20.2 % of WT mice, indicating that the smaller BAT size in Tg mice is due to the decrease in cell number. Immunostaining showed that approximately 8.7% of brown adipocytes in BAT expressed proliferation marker PCNA, and the ratio was significantly decreased in Tg mice. These results suggest that brown, but not white, adipocytes have proliferative ability even after the differentiation, and

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it contributes to the BAT development. (The authors declare no conflict of interest.)

T1:S2:10
Optimizing the methodology for measuring supraclavicular skin temperature for the detection of brown adipose tissue in adult humans using infrared thermography

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McMaster University

Background: The discovery of brown adipose tissue (BAT) in adults has sparked interest in its role as a therapeutic target in metabolic disorders. Infrared thermography (IRT) is a promising way to quantify this thermogenic organ located primarily in the supraclavicular (SCV) area in humans.
Aim: This study aims to establish a standardized protocol to measure thermal response to cold in the SCV area to detect BAT activity using IRT.
Method: IRT images were taken every 5 minutes in 28 healthy adult males (mean age 23.95±5.87 years) at each of 3 visits which included a 1 hour acclimation followed by a 1 hour exposure. SCV temperature at the control visit (room temperature (RT) acclimation and exposure periods) was compared to acclimation at 32°C or RT followed by torso cold exposure at 12°C.
Results: The SCV temperature stabilized after 45 minutes of acclimation at 32°C and then rose with cooling leveling off at 10 minutes. The delta SCV temperature in response to cooling was greater after 32°C compared to RT acclimation at 10 minutes of cooling (0.24±0.20 vs 0.10±0.20°C, p=0.007).
Conclusion: Based on these findings, measurement of SCV temperature change in response to cold (compared to RT response) is best done after a 32°C acclimation period for 45 minutes followed by 10 minutes of 12°C cooling with a measurable response.There is no conflict of interest. Funded by MAC-Obesity (McMaster University Faculty of Health Sciences & McMaster Children's Hospital Foundation).

T1:S2:11
Brown adipose tissue stimulation as a new approach to fight obesity and metabolic syndrome

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Foz/foz mice develop metabolic syndrome with non-alcoholic steatohepatitis as a key feature. The aim of the study was to decipher the mechanisms responsible for their metabolic phenotype.
A pair-feeding experiment was performed in which *foz/foz* mice received the same amount of high fat diet (HFD) consumed by WT. Physical activity level, oxygen consumption and thermogenic adaptation (18FDG PET-scan) were evaluated. Intermittent cold exposure (ICE), β3-adrenergic agonist treatment (CL-316,243) and brown adipose tissue (BAT) transplantation were performed to stimulate BAT.
Unlike in WT mice, 4 weeks of HFD induced obesity, insulin resistance, steatosis, liver and adipose inflammation in *foz/foz* mice. Although being hyperphagic compared to WT, caloric restriction to *foz/foz* mice failed to restore metabolic disturbances. Physical activity and basal metabolism were unaffected in *foz/foz* mice. By contrast, their thermogenic response to HFD or a cold exposure was impaired due to a lower mitochondrial density in brown adipocytes and a lower sympathetic tone. ICE, CL-316,243 treatment and WT BAT transplantation significantly increased cold-induced expression of thermogenic genes, improved glucose tolerance and decreased body weight gain in *foz/foz* mice.
In conclusion, impaired BAT activity drives HFD-induced obesity and metabolic syndrome in *foz/foz* mice. Induction of endogenous BAT function had a significant positive impact on obesity, glucose tolerance as well as on liver steatosis.

Session 3: Epigenetics in obesity

T1:S3:01
Epigenetic programming by maternal obesity

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It is widely recognised that events in early life can influence the risk of an individual developing conditions such as type 2 diabetes, insulin resistance and cardiovascular disease in later life. Early focus was directed towards the effects of maternal under-nutrition on the health of an individual. However in light of the current epidemic of obesity, including in women of child-bearing age, attention has now been directed towards understanding the effects of maternal over-nutrition during pregnancy and lactation on the offspring. To address this we have used a mouse model of maternal diet-induced obesity where pregnant and lactating mice are fed a diet rich in saturated fats and simple sugars (reflective of a human westernized diet) to induce obesity. This maternal dietary manipulation leads to cardiovascular dysfunction, insulin resistance and increased susceptibility to diet-induced obesity in the offspring. The insulin resistance is associated with post-transcriptional epigenetic programming of insulin signaling protein expression that may underlie these effects. As well as utilizing the mouse model as a tool to identify underlying mechanisms through which programming occurs, we have also utilized it to identify factors in the obese mother that mediate the detrimental effects on the offspring. Maternal hyperinsulinaemia, which is amenable to lifestyle interventions such as increased physical activity, has emerged as one important parameter. These findings in an animal model therefore provide important insight into rational intervention strategies that have the potential to prevent transmission of metabolic dysfunction between generations.

T1:S3:02
Neonatal nutrition, epigenetics and obesity complications

Jiménez-Chillarón, J.C.*
Hospital Sant Joan de Deu

The Developmental Origins of Health and Disease hypothesis proposes that early-life environmental exposures increase the risk of chronic diseases such as obesity and type 2 diabetes. The specific molecular mechanisms that lead to such long-lasting effects remain poorly characterized.
We have developed a mouse model of neonatal overfeeding by litter size reduction (Small Litter=4 pups/dam; Control=8 pups/dam). Neonatal overfeeding resulted in increased adiposity as early as 7 days and SL mice remained obese as adults and developed insulin resistance and hepatic steatosis. Increased adiposity in SL mice was characterized by adipocyte hypertrophy, which persisted until adulthood. In agreement, expression of lipogenic genes was increased, whereas the expression of adipogenic factors remained

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unaltered. Hypertrophic obesity is in part induced by impaired recruitment and differentiation of new adipocytes. Accordingly, SL mice showed altered expression of *Suvr39*, *Dlk1* and *Wisp2*, which together might impair adipogenesis and lead to hypertrophic obesity. We are currently exploring whether these long-lasting effects are mediated by epigenetic modifications.
In sum, we suggest that excessive nutrient availability during lactation results in storage of the energy surplus via lipogenesis leading to adipose tissue hypertrophy. Furthermore, rapid early hypertrophy determines adipose tissue dysfunction and metabolic derangements throughout life.

T1:S3:03
Stochasticity and inter-generational epigenetic effects in obesity

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Max Planck Institute of Immunobiology and Epigenetics

Though progress has been made in explaining genetic predisposition for obesity, much of the high heritability remains enigmatic. Our lab focuses on understanding how chromatin state biases can be established to generate or modify disease susceptibility. In recent studies in flies, mice and humans we have begun to dissect how core chromatin regulatory systems can impact metabolic phenotypes, and in specific, obesity. In the first, we develop a fly model of paternal-diet-induced intergenerational metabolic reprogramming (IGMR) and show paternal sugar to be a physiological suppressor of variegation, capable of desilencing chromatin-state-defined domains in both mature sperm and in offspring embryos. In the second study, we identify a Trim28-sensitive epigenetic switch that triggers obesity stochastically and in an apparently 'On/Off' manner. Using genetic dissection and transcriptome analyses, we map this phenotype to control of a series of metabolically potent imprinted genes. We find that human children present in similarly distinct sub-populations stratifying by *Trim28* expression, imprinted gene dysregulation, and profoundly distinct transcriptome organization. To the best of our knowledge, the latter data provide the first evidence of *polyphenism* in mouse and humans and test assumptions made in our understanding of complex trait genetics, evolution and medicine.

T1:S3:04
Role of noncoding RNAs in imprinting disorders

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Parental imprinting is a form of epigenetic regulation by which genes are expressed exclusively according to their parent-of-origin. In humans, aberrations of imprinted genes are linked with several diseases, developmental disorders and malignancies. To analyze the role of parental imprinting in human embryogenesis, we generated parthenogenetic human induced pluripotent stem (iPS) cells, having only maternal chromosomes. By comparing the gene expression profile of parthenogenetic and normal pluripotent stem cells, we have identified multiple novel imprinted genes, among them are several types of non-coding RNAs, and uncovered their potential targets. In addition, in-vitro and in-vivo differentiation assays were conducted to examine the developmental potential of these cells. The major genetic disorder that involves loss of expression of paternally imprinted genes is Prader-Willi syndrome (PWS). One of the main features of PWS is excessive eating and life-threatening obesity. To model PWS in humans we generated patient-derived iPS cells, and studied molecular aspects of this disease. Unexpectedly, our analysis uncovered up-regulation of maternally imprinted genes residing on chromosome 14. Subsequently, we determined that IPW, a long non-coding RNA in the critical region of the PWS locus, is a regulator of the maternal genes, as its over-expression in PWS and parthenogenetic iPSCs resulted in down-regulation of the genes in this locus. Our results suggest that a subset of PWS phenotypes may arise from dysregulation of an imprinted locus distinct from the PWS region by a long non-coding RNA. Our results emphasize the role of non-coding RNA in imprinting disorders.

Session 4: Genes, epigenomics and nutrigenomics

T1:S4:01
New insights into the control of obesigenic pathways- a comprehensive proteomics and genetics data integration approach

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Over the last decade many genes and proteins influencing bodyweight, like leptin or adiponectin have been identified and characterized. While they have enriched our understanding of the pathways involved in obesity enormously, many aspects of how these genes/proteins are controlled on the molecular level remain unknown. Many of these proteins show large inter-individual variability but it is not clear if this mainly stems from environmental influences or systemic biological differences.
In order to address some aspects of these questions we performed a large scale proteomics screen (1200 plasma proteins) in one of the largest weight loss trials, the Diogenes study. We identified proteins, known like leptin and new ones, the levels of which associated with BMI at baseline but more importantly with weight loss after LCD. We then performed protein quantitative trait locus (pQTL) GWAS to identify SNPs that associated with the plasma levels of these proteins. Our results show that the baseline levels of many proteins known to be associated with obesity are determined to a large degree by cis or trans-acting pQTL's. We also show that some of the changes in protein levels that occur during weight loss are under genetic control through trans-acting pQTLs. We identified trans-acting SNPs that associate with changes in plasma leptin levels and influence success of weight loss. The proteins associated with these trans-SNPs maybe new regulators of leptin.

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T1:S4:02

ExomeChip meta-analysis of 525,508 individuals identifies novel protein altering variants associated with body mass index (BMI)

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Genome-wide association studies (GWAS) have identified >90 common variants associated with BMI, which are mostly non-coding with small effects. New strategies aimed to analyze low-frequency variants (LFV) (minor allele frequency <5%) with greater effects on traits. We estimated the contribution of coding and splicing variants on BMI by meta-analyzing exome array data from 526,508 individuals. Using single variant meta-analyses (223,648 variants), we have identified ~60 significant (P<2E-07) novel loci or independent of known BMI loci; 7 of them were driven by LFV. These LFV loci targeted known (MC4R; rs13447324, P=2.4e-11, EAF=0.01%, β[SE]=0.64[0.10] SD/allele) or novel BMI-associated genes; RAPGEF3 (rs145878042, EAF=1%, P=5.2E-14, β[SE]=0.074[0.010]), PRKAG1 (rs1126930, EAF=3%, P=2.6E-12, β[SE]=0.040[0.005]) and KSR2 (rs56214831, EAF=0.8%, P=5.0E-8, 0.062[0.011]). Meta-analyses aggregating LFV based on functional annotations (16,222 genes) identified another novel BMI locus, GIPR (P=6.8E-9), whose effect was independent of the common GWAS proxy in this gene. By interrogating coding and splicing LFV in a large sample set, we have identified additional genes and variants associated with BMI, some of which may be causal. These loci may highlight further pathways regulating BMI, other than the central nervous system, such as insulin secretion (RAPGEF3, GIPR), and metabolism of energy, fatty acids and glucose (PRKAG1, KSR2). Replication and functional studies are underway.

T1:S4:03

Positive selection at 9/37 single nucleotide polymorphisms (SNPs) associated with body mass index (BMI)

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The thrifty gene hypothesis suggests that genes favoring fat storage were positively selected during our evolutionary history - particularly since the advent of agriculture. A direct test of the thrifty gene hypothesis would be detection of signatures of positive selection at loci linked to obesity. We chose 37 body mass index (BMI) associated single nucleotide polymorphisms (SNPs) from genome wide association studies to identify the signatures and timing of selection events, using public available databases (HapMap Phase III and 1000 Genomes project Phase 1) in multiple populations. We characterized the linkage disequilibrium (LD) patterns and multiple indices of positive selection through a *database of recent positive selection across human populations* (dbPSHP). We found evidence of positive selection at nine BMI associated SNPs (rs3810291 , rs12597579, rs206936 , rs2206734 , rs1244979 , rs2890652 , rs29941, rs11847697 and rs2241423) (p<0.05). However, these signatures were detected in estimators that measure selection events around 80,000 y to 250,000 y ago e.g. Tajima's D, and may be susceptible to artefacts due to population expansion. There was no strong evidence of positive selection in the last 20,000 years. Our data provide little support for the widely held belief that obesity provided a selective advantage during our recent evolutionary history to survive periods of famine leading to strong positive selection of BMI linked SNPs.

T1:S4:04

Triglyceride and cholesterol levels in severely obese subjects are influenced by TOMM20 methylation quantitative trait loci

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Background: The translocase of outer mitochondrial membrane 20 homolog gene (*TOMM20*) has a key role in maintaining mitochondrial biogenesis and function. Previously, we identified this gene as differentially expressed between severely obese patients with and without metabolic syndrome (MS).
Aims: To identify methylation quantitative trait loci (meQTL) within the *TOMM20* gene and to test them for associations with MS risk factors in obese patients.
Methods: Single nucleotide polymorphisms (SNPs) within the *TOMM20* gene were genotyped in a population of 1749 severely obese patients and DNA methylation analysis was conducted in a subset of 31 subjects. Logistic regression was used to test identified meQTLs for associations with MS risk factor groups in the entire cohort.
Results: We identified three SNPs as significant meQTLs for the CpG site cg16490124, namely rs4567344 (P=0.03), rs11301 (P=0.02) and rs4551650 (P<0.0001). The carriers of the rare allele of rs4567344 (A>G) and rs11301 (T>C) showed a significant decrease in methylation and increased susceptibility to exhibit high plasma triglycerides (TG≥1.69mmol/L; P=0.005 and P=0.02, respectively). On the other hand, rare allele carriers of rs4551650 (G>A) showed a significant increase in methylation and lower risk of high total cholesterol levels (total-C≥6.2mmol/L; P=0.03).
Conclusions: These results suggest that *TOMM20* meQTLs are associated with MS-related lipid alterations in obese subjects, particularly TG and total-C levels.

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T1:S4:05

FTO hypermethylation is associated with polycystic ovarian syndrome and non-alcoholic fatty liver disease, but not pre-diabetes, in obese youth

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Variation in DNA methylation is implicated in several complex phenotypes. Methylation levels within FTO gene have previously been linked to a range of obesity-related comorbidities (ORC) in adults, such as impaired glucose tolerance/type 2 diabetes (IGT/T2DM). However, little data exist in relation to early onset obesity and ORC. We investigated associations between FTO methylation and ORC in a cohort of obese youth.
Data were collected (with ethics approval) from 239 obese youth (mean±SD age;10.9±3.6 years, BMI-Z; 2.5±0.4, 47% male). Comorbidities assessed were IGT/T2DM, hypertension, hyperlipidaemia, non-alcoholic fatty liver disease (NAFLD), obstructive sleep apnoea, and polycystic ovarian syndrome (PCOS). FTO methylation (CpG site Chr16:52366732 [hg18]) was examined using Sequenom MassARRAY MALDI-TOF MS. Data were statistically analysed using chi-squared, one-way ANOVA and logistic regression.
Hypertension was present in 118 patients, NAFLD in 83, IGT/T2DM in 65 and PCOS in 18 females. FTO hypermethylation was associated with NAFLD (OR 1.05 [1.0-1.1], p=0.039 adjusted for age, sex and total percentage body fat) and PCOS (OR 1.32 [1.0-1.7], adjusted p=0.019) but not other parameters (IGT/T2DM (p=0.633).
Associations were seen between FTO hypermethylation with PCOS and NAFLD, independent of age, sex and total body adiposity. Whether this marker could be used in the future to predict the development of these comorbidities now needs to be examined in longitudinal studies.

T1:S4:06

Indipendent effects of hypocaloric dietary intervention on global DNA methylation status of overweight Italian adults

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Epigenetic DNA methylation can be a determinant of body weight as it represents the mechanism by which environmental factors, including nutrients intake, modulate the expression of individual genotype.
We analysed the blood global DNA methylation profile of overweight subjects.
Aims were:1)evaluate whether DNA methylation is associated with anthopometric characteristics and metabolic serum biomarkers; 2)investigate if hypocaloric dietary intervention modulates epigenetic signature.
42 adults were examined; 32 F (mean age: 43,2yrs;mean BMI:28,2) and 10 M (40,9yrs; 29,2) received a balanced -30% energy diet (48% carb, 26% lipid, 26% proteins) for 4 weeks.
BMI, body composition, and serum parameters were determined at baseline and endpoint; Long Interspersed Nuclear Element-1 (LINE1)CpG sites were analysed as a surrogate of global DNA methylation.
Pearson was used for association of LINE1 levels with anthropometric and metabolic variables; generalized linear model was conducted to assess effect of nutritional intervention.
At baseline no significant associations between LINE-1 and any variables was found. LINE1 increased after hypocaloric diet (β−0.4708, p0.036). Magnitude of this change augmented after adjustment for antropometric and metabolic parameters (β−0.9187, p0.001).
Our results showed epigenetic modification in overweight subjects after a hypocaloric diet and indicated that nutritional intervention modulate DNA methylation regardless baseline characteristics and weight loss.

T1:S4:07

LEPR polymorphism may affect neuropeptides among Brazilians obese adolescents

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Background: Little is known about the effect of *LEPR* polymorphism on orexigenic and anorexigenic neuropeptides.
Aims: To verify the impact of *LEPR* polymorphism on orexigenic and anorexigenic neuropeptides among obese adolescents.
Methods: Seventy-six adolescents with obesity were enrolled in one year of weight loss therapy including clinical, nutritional, psychological and exercise-related. Blood samples were collected to analyze neuropeptides and *LEPR* genotyping. Visceral fat was measured by ultrasound and body composition was measured by pletismography. Adolescents were grouped according to genotype (TT or CT+CC group).
Results: Effect of the weight loss therapy was analysed through ANOVA and Wilcox, according to normality. Statistic value was set at < 0.05. The results revealed that C-allele carriers have the orexigenic neuropeptides (NPY, AgRP and MCH) statistically higher when compared with wild type, at baseline. Furthermore, wild type group seems to respond better to the therapy by a greater delta on BMI. Indeed, the data suggest a concomitant increased of AgRP in CT+CC genotypes, confirming our hypothesis that genetic alterations on *LEPR* may influence the energy balance in obese adolescents.
Conclusion: Our results suggest that leptin receptor polymorphism impact neuroendocrine regulation of energy balance by increasing orexigenic factors and hampering leptin reduction during weight loss therapy among adolescents with obesity. (FAPESP 2013/08522-6; 2015/14309-9)

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T1:S4:08

The association between the 'Fat mass and obesity associated gene (FTO)' and obesity-linked eating behaviours in adults and children: A systematic review

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FTO has been recognised as one of the principle candidate genes predisposing to common obesity in humans and numerous weight-associated single nucleotide polymorphisms (SNP) of FTO have been identified. However, understanding of the mechanism of action by which FTO contributes to obesity is limited. The objective of this systematic review is to investigate the hypothesis that weight-associated variants of the FTO gene elicit their effect on adiposity by influencing eating behaviour. To achieve this objective, an exhaustive database search was conducted, with 16 studies selected for analysis after rigid relevance screening. The effects of five FTO SNPs were assessed across the 16 studies: rs9939609, rs1421085, rs17817449, rs1121980 and rs9939973. All five of the SNPs were significantly associated with increased adiposity in at least one study. The rs9939609 SNP was significantly related to multiple appetitive behaviours with the potential to predispose to obesity, including: increased energy and fat intake, risky eating behaviour, decreased satiety responsiveness and preference for energy-dense foods. The effects of the rs9939609 variant on appetite were predominately observed in children. The rs1421085, rs17817449, rs1121980 and rs9939973 variants were not linked to eating behaviour in either children or adults. These results provide insight into one possible mechanism by which FTO may contribute to obesity, specifically in children.

T1:S4:09

The effects of weight loss in very-low carbohydrate and low-fat isoenergetic diets in diet-induced obese mice

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Objectives: Obesity is caused by excessive fat or carbohydrate intake. Both low-carbohydrate diet (LCD) and low-fat diet (LFD) are used to achieve weight loss in humans. To clarify the mechanisms underlying LCD-induced weight loss, we investigated the effects of a very-low carbohydrate diet (VLCD) in diet-induced obese (DIO) mice.
Methods: DIO ddY mice were divided into high-fat diet (HFD), and isoenergetic VLCD and LFD groups. Pair-feeding was performed in the VLCD and LFD groups. Three weeks later, the body, liver, white adipose tissue (WAT) and brown adipose tissue (BAT) were weighed and the serum and hepatic lipids, the mRNA expression levels in each tissue, and energy metabolism were analyzed.
Results: The caloric intake of the VLCD-fed mice was initially reduced. There was a similar decrease in the BW of the VLCD- and LFD-fed mice. The browning of WAT was observed to a greater extent in the VLCD-fed mice. Moreover, in the VLCD-fed mice, BAT activation, the decrease in the weight of the BAT, and the increase in the expression of G-protein-coupled receptor 120 were observed. The energy expenditure of the VLCD- and LFD-fed mice did not differ. Hepatic TG accumulation was reduced in LFD-fed mice but not in the VLCD-fed mice. The proinflammatory macrophage ratio was increased in the WAT of VLCD-fed mice.
Conclusions: After 3 weeks, the isoenergetic VLCD- and LFD-fed DIO mice showed similar weight loss, health-related biomarkers and the browning of WAT.

T1:S4:10

Analysis of circulating angiopoietin-like protein 3 and genetic variants in lipid metabolism

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Angiopoietin-like protein 3 (ANGPTL3) is suggested to play an important role in the lipid and lipoprotein metabolism.
This study examined the effect of circulating ANGPTL3, and the main and dietary interaction effects of *ANGPTL3* rs12048208 and rs10789117 on BMI and plasma lipid profile.
The study was based on data from the DIOGENES study (NCT00390637). Participants who lost ≥8% of their initial body weight after 8 weeks low caloric diet were randomized to one of five 5 *ad libitum* diets differing in glycemic index (GI) and dietary protein content for 6 months. Plasma ANGPTL3 was measured using SomaLogic™ and genotyping was done using Illumina 660 quad and humanCore array. Linear regression models and assumption of additive effects of the minor alleles were used for analyses. P-values <0.05 were considered significant.
Plasma ANGPTL3 concentrations were not associated with total cholesterol, HDL-C, LDL-C, triglycerides or free fatty acid (FFA) at baseline (n=594). After weight loss, plasma ANGPTL3 were positively associated with BMI (P=0.03) and FFA (P=0.01). *ANGPTL3*rs12048208 and rs10789117 were not associated with ANGPTL3 plasma concentrations, BMI or lipid profile. Neither of the SNPs showed effects on the lipid profile during weight maintenance *per se* or by interaction with GI or dietary protein.
In conclusion, plasma ANGPTL3 is associated with changes in FFA concentration independently of weight loss.

T1:S4:11

The association between TFAP2B Rs987237 and plasma adipokine and hormone concentrations in children

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Background: *TFAP2B* encodes a transcription factor controlling expression of adipokines and hormones involved in appetite regulation, body weight homeostasis and adipose inflammation. Interestingly, *TFAP2B* rs987237 is associated with BMI and waist circumference in children and adolescents.
Aim: To test whether rs987237 is associated with adipokine and hormone concentrations in 393 boys and 361 girls aged 8 – 11 years.
Methods: One-way ANOVA and linear regression were used to analyse baseline data from the OPUS School Meal Study (NCT01457794), a randomized, controlled trial exploring the health effects of school meals based on the New Nordic Diet. Concentrations of plasma leptin, ghrelin, insulin, adiponectin, C-reactive protein and IL-6 were determined in fasting blood samples.

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DNA was extracted from buffy coats and genotyped using KASP™ technology.
Results: Compared to wild-type children, fasting ghrelin concentrations were significantly lower in children heterozygote (P = 0.002) and homozygote (P = 0.048) for the minor allele of rs987237. For each minor allele present, an 8% decrease in ghrelin concentration was observed. We did not detect an effect of rs987237 on any of the other hormones measured.
Conclusion: rs987237 might influence body weight in 8 – 11 years old children by modifying the interaction between TFAP2B and the orexigenic hormone ghrelin.
Conflicts of interest: None.
Funding: The OPUS project was supported by a grant from the Nordea-Foundation, Denmark.

T1:S4:12

Adipose tissue expression of genes involved in melanin synthesis and oxidative stress of black and white South African women and the association with insulin sensitivity

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Black South African women are more insulin resistant than white women for given body mass indices (BMI), but involving unclear mechanisms. We hypothesise that increased oxidative stress is associated with greater insulin resistance in black women, and that melanin is expressed in adipose tissue and associates with antioxidant activity.
Body composition and insulin sensitivity (FSIGT) were assessed in 60 normal-weight and obese, black and white women. Total RNA was isolated from gluteal (GLUT), superficial and deep abdominal SAT (SSAT, DSAT) depots. The expression of oxidant gene: endothelial nitric oxide synthase (*eNOS*); antioxidant genes: Superoxide dismutase 1 (*SOD1*) and Catalase (*CAT*) and melanin synthesis-related genes: Microphthalmia-associated transcription factor (*MITF*), Tyrosinase related protein 1 (*TYRP1*), Dopachrome Tautomerase (*DCT*) were measured using quantitative polymerase chain reaction.
Insulin sensitivity(SI) was lower in black compared to white women. DSAT expression of *SOD1* and *CAT* was negatively associated with SI in white women only, independent of fat mass (kg). GLUT expression of *TYRP1* was negatively associated with SI in black women only. DSAT expression of *eNOS* was positively associated with *DCT* and *MITF* in black and white women.
We demonstrate, for the first time that melanin synthesis genes are expressed in the SAT of SA women, and that this expression differed by adipose depot and ethnicity. Further analysis at the protein level is being conducted.

T1:S4:13

Differential plasma concentrations of MicroRNA-16-5p and MicroRNA-19b in Brazilian lean and obese children

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Circulating microRNAs (miRNAs) are been considered valuable biomarkers of many metabolic diseases, such as obesity, and potential promising targets for the diagnosis and clinical monitoring of adiposity and its complications. Our objective was to investigate whether circulating miRNAs levels differ between lean and obese preschooler children in southern Brazil. Nine plasma miRNAs were assessed by quantitative polymerase chain reaction in 38 children aged 6.2 years (18 lean and 20 obese). We compared miRNA expression between lean and obese children and performed correlation analyses with anthropometric and biochemical measurements. Two circulating miRNAs were differentially expressed, with decreased levels of miR-16-5p (P=0.008) and miR-19b (P=0.046) in obese children compared to the lean group. The plasma concentrations of these two miRNAs were inversely correlated with body mass index, and miR-16-5p was significantly correlated with plasma insulin levels. Our findings contribute to a better understanding of the role of miRNAs in physiopathology of obesity and suggest a potential role of circulating miR-16-5p and miR-19b in childhood obesity as novel biomarkers for the early prevention and to improve the diagnostic power of obesity-associated metabolic complications. To our knowledge, this study provides the first evidence of obesity-related circulating miRNAs in South American children.

T1:S4:14

Resveratrol induced changes in hepatic triacylglycerol metabolism in rats fed a high-sucrose high-fat obesogenic diet are mediated by modifications in MicroRNAs

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The epigenetic mechanisms of action of resveratrol as an anti-obesity molecule have not been fully addressed so far. MicroRNAs (miRNA) have been proposed as regulators of lipid metabolism in white adipose tissue and liver. The aim of the present study was to assess changes produced by resveratrol in miRNAs related to *de novo* lipogenesis and beta-oxidation, in liver obtained from rats fed an obesogenic diet supplemented with resveratrol.
Sixteen male Sprague-Dawley rats (6 weeks old) were divided into two groups, a control group and a group treated with resveratrol (30 mg/kg body weight/d), both fed a high-sucrose high-fat diet, for 6 weeks. After checking miRecords Database (www.http://omictools.com) and the literature, several miRNAs involved in *de novo* lipogenesis and in beta-oxidation were selected. miRNAs gene expressions were assessed by qRT-PCR. Statistical analysis was carried out by using Student's t test.
Resveratrol treatment induced a decrease in liver fat (data previously published). The expression of mir-103-3p, mir-107-3p, mir-122-5p and mir-335 (related to the regulation of carnitine palmitoyltransferase 1a, sterol regulatory element-binding protein 1 and fatty acid synthase) were down-regulated by resveratrol intake ($P<0.05$). In conclusion, resveratrol modifies miRNAs in liver, indicating a possible involvement of epigenetic mechanisms in the anti-obesity effect of this polyphenol.

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T1:S4:15

Interferon activated gene (Ifi202b) promotes obesity by improving adipogenesis and triglyceride storage

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Background: Obesity is a polygenic metabolic disease. Recently we have identified *Ifi202b* as a novel obesity gene by positional cloning. *Ifi202b* is mainly expressed in white adipose tissue of obese NZO but absent in lean B6 mice due to a loss of function mutation.
Aims: To characterize the mechanisms how Ifi202b affects fat mass, adipocyte function and metabolism.
Methods: *Ifi202b* was overexpressed in 3T3-L1 cells and in B6 mice by generating mice carrying *Ifi202b* in the ROSA26 locus.
Results: *Ifi202b*-overexpression in 3T3-L1 fibroblasts resulted in an improved differentiation into adipocytes; as indicated by an increased expression of adipogenic markers (e.g. *Pparγ*, *Plin1*) and higher triglyceride levels. Accordingly, fat precursor cells from *Ifi202b*transgenic mice showed an increased adipogenic potential. On a high-fat diet (45 kcal% from fat) *Ifi202b* transgenic female mice developed an elevated fat mass in comparison to B6-Wt mice which was accompanied by a marked adipocyte hypertrophy. Male *Ifi202b*transgenic mice showed an impaired glucose tolerance, elevated liver triglycerides and hepatic insulin resistance, whereas female mice were protected and exhibited increased insulin sensitivity in white adipose tissue.
Conclusions: We conclude that *Ifi202b* action depends on estrogen (E2); it promotes fat accumulation by an induction of adipogenic genes in the presence of E2, but induces hepatic insulin resistance when E2 is low (males).
Funding: BMBF, DZD, grant 01GI0922

T1:S4:16

Fructose-induced metabolic syndrome: Transcriptome-wide analysis of gene expression by next generation sequencing (RNA-Seq)

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An obesity epidemic is associated with overconsumption of added sugars containing fructose. Recently, we showed that high fructose diet caused in mice a variety of effects consistent with the metabolic syndrome, which was prevented in mice lacking ketohexokinase (KHK, KHK-KO). Here, we analyze transcriptome-wide changes in gene expression caused by exposure of C57BL/6 mice to high fructose.
WT and KHK-KO mice were fed with standard diet with or without adding 30% fructose to drinking water for 12 weeks. Liver poly-A RNA was sequenced using Illumina HiSeq2500. The datasets were analyzed with DNAstar Genomics and Ingenuity pathway analysis (IPA) platforms.
We detected expression of 20208 mRNA. 3201 mRNAs were significantly affected by fructose diet with 2354 mRNAs upregulated and 847 mRNAs downregulated. Gene ontology analysis showed that in addition to genes related to metabolism, especially fat accumulation, substantial part of affected genes was related to function of cell organelles (nucleus, endosomes, lysosomes and Golgi). IPA analysis demonstrated that in addition to genes related to fat accumulation, pathways leading to cell transformation (abdominal neoplasms), atherosclerosis, vascular damage, intestinal and hepatic diseases were highly affected ($P<10^{-6}$-10^{-10}).
In summary, we demonstrated that fructose consumption triggers a complex array of pathways responsible not only for metabolic syndrome but far more complex variety of pathological responses that we believed so far

T1:S4:17

A randomized controlled trial of a gluten-free weight loss diet in HLA DQ2 or D8 positive subjects

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We know that the vast majority of people with biopsy-proven celiac disease carry either HLA-DQ2 or HLA-DQ8 genes but these "celiac disease genes" appear in about 35-40% of the overall population. Having the genes does not mean necessarily they develop celiac disease, it simply means they have a genetic potential to do so. Some observations have reported that the presence of DQ2 or DQ8 may be linked to weight, irrespective of the celiac disease status.
The HLA DQ2 and 8 proteins are involved in presenting gluten derived peptides to the immune system.
We analyzed 221 patients who were genotyped with a nutrigenetic panel, including the HLA genes (Eurogenetica –NutriGene+).
Of 221 patients, 215 were overweight or obese and 69 patients were found to have at least one allele for DQ2 or DQ8. 64 were overweight and were randomly divided into two groups. Both groups were prescribed a 1800 kcal/day diet and one group was gluten free.
Patients were monitored, both weight and BIA, at one month, 3 months and 6 months. The differences were significant at 3 months and at 6 months and the gluten-free group showed a significant weight loss compared to patients with gluten included in the diet (at 3m: 14% vs 8% and 6m: 25% vs 14%).
Also the rate of loss over the 6 months was significantly greater in the gluten free group.
Conclusion: A gluten elimination diet in patients with at least one risk allele for gluten sensitivity was correlated with significantly more weight loss than in a standard diet.

T1:S4:18

Caveolin 1 (CAV1) gene polymorphisms associated to body mass index, hypertension and obesity-related disorders, in adults from Caribbean population

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Caveolin-1 (CAV1) gene has been found to be associated to insulin resistance, hypertension and metabolic syndrome, hence it has been proposed as a promissory therapeutic target. Thus, this study was aimed to determine the association between CAV1,obesity and related diseases in population from Colombian Caribbean Coast. A cross-sectional study was carried out in urban population. Fasting serum concentrations of glucose, triglycerides, total cholesterol and HDLc were determined from peripheral blood samples. Six polymorphisms in CAV1 were genotyped (rs926198, rs3779512, rs10270569, rs11773845, rs7804372 and rs1049337). Genetic associations were determined by age- and sex-adjusted logistic regression and ANOVA. A total of 604 subjects were genotyped. The BMI was associated to locus rs3779512 after *post-hoc* adjustment (p=0,02), and there was a nominal association with abdominal obesity (p=0.01). There was association of rs11773845 with hypertriglyceridemia (OR=0,89, p=0,002) and serum triglycerides (p-

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adj=0.01). High blood pressure was marginally related to rs3779512 (OR=1.44, p=0.03), systolic pressure was associated to rs3779512 (p-adj=0.01) and rs926198 (p-adj=0.03), and diastolic pressure was also associated to rs3779512 (p-adj=0.01) and rs926198 (p-adj=0.01). The metabolic syndrome was marginally associated to rs11773845 (p=0,04) and rs1049737 (p=0,04). These findings might be pointing out to a physiopatologic interaction between genetic markers and obesity-related diseases.

Session 5: Mitochondria and disease

T1:S5:01
Role of mitochondrial fusion proteins on metabolic homeostasis

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Mitochondrial fusion and fission are key processes regulating mitochondrial morphology. Mitochondrial fusion is catalyzed by Mitofusins (Mfn1, and Mfn2) and OPA1 proteins in mammalian cells. Mfn2 protein seems to play a complex set of functional roles. It regulates mitochondrial morphology, and in addition, it also controls endoplasmic reticulum morphology and function.
Mfn2 expression is exquisitely regulated in tissues. It is upregulated in skeletal muscle response to chronic exercise and upon cold exposure. Cold also upregulates Mfn2 in brown adipose tissue. In contrast, Mfn2 is repressed in tissues such as muscle, liver or hypothalamus upon a high-fat feeding. Furthermore, Mfn2 is downregulated in obese or in type 2 diabetic patients.
In turn, changes in Mfn2 expression have a marked impact on mitochondrial metabolism. Thus, skeletal muscles obtained from Mfn2 knockout mice show a reduced respiratory control ratio, reduced glucose oxidation, and diminished expression of some OXPHOS subunits. Additional evidence indicating that Mfn2 deficiency causes mitochondrial dysfunction comes from studies in muscle cells in culture. Livers or POMC hypothalamic neurons also show a defective mitochondrial metabolism upon ablation of Mfn2. Mfn2-deficient muscle and liver tissues also show susceptibility to develop insulin resistance. In keeping with this, a defective insulin signaling is detected in livers or in muscles upon ablation of Mfn2. In all, available data indicate that Mfn2 regulates metabolism and insulin signaling in tissues, and it may contribute to the pathophysiology in obesity and type 2 diabetes.

T1:S5:02
Mitochondrial dynamics and energy expenditure

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Boston University School Medicine

T1:S5:03
The mitochondria and cristae shaping protein Opa1 impinges on fat browning to control insulin sensitivity

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Mitochondria-shaping proteins modulate bioenergetics, apoptosis, Ca2+ signalling and autophagy. The inner membrane pro-fusion and cristae shaping protein Optic atrophy 1 (Opa1) protects multiple tissues from damage by regulating cytochrome c release and mitochondrial respiratory efficiency, but whether this is mirrored by systemic changes in intermediary metabolism is unknown. Here we identify Opa1 as a key regulator of insulin sensitivity and adipose tissue function. Controlled Opa1 overexpression in the mouse reduces weight, improves glucose metabolism and insulin sensitivity, by reducing fat depots and favoring brownization of white adipose cells in vivo and in vitro. Adipocyte-specific Opa1 deletion triggers a lipodystrophic phenotype with hyperglycemia, insulin resistance, brown adipose tissue whitening and hepatosteatosis. Our findings identify the genetic and metabolic basis for Opa1 role in a lean and insulin-sensitive phenotype, paving the way for novel therapeutic strategies to treat obesity and diabetes.

T1:S5:04
Boosting mitochondrial function as a target for the treatment of type 2 diabetes: Insight from human intervention studies

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Maastricht University

Type 2 diabetic patients are characterized by a reduced mitochondrial function, and boosting mitochondrial function is considered an important target to improve muscle insulin sensitivity. Indeed, exercise training has strong beneficial effects on muscle mitochondrial function and insulin sensitivity, and increases the activity of PGC1, AMPK and SIRT1, important transcriptional factors involved in the regulation of skeletal muscle mitochondrial function. In recent years, the interest in non-exercise means of stimulating muscle mitochondrial function has been large, and human intervention studies have suggested that compounds like resveratrol may have exercise-like beneficial effects on muscle metabolism. In this lecture, the current status of mitochondrial function as a target to prevent or treat diabetes by (non)-exercise interventions will be discussed.

Session 6: Molecular and cellular biology of non-adipocytes

T1:S6:01
Effects of resveratrol, energy restriction and the combination of both on diet-induced insulin resistance in rats

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Although energy restriction is commonly used for insulin resistance treatment, the usefulness of biomolecules present in foodstuffs is being actively studied. Resveratrol, which shows energy restriction-like effects, seems a good candidate. The aim of this study was to compare the effects of resveratrol and energy restriction on diet-induced insulin resistance. Potential synergistic effects were also analyzed.
The obese group (O) was fed a high-fat high-sucrose diet for 12 weeks. Four groups were fed a high-fat high-sucrose diet for 6 weeks and then a standard diet for 6 weeks: control group (C), resveratrol group (RSV, resveratrol 30 mg/kg/d), restricted group (R, 12.5% energy restriction) and mixed group (both treatments together). HOMA-IR and glucose tolerance (GTT) test were analyzed. Insulin, leptin and adiponectin were measured by using commercial kits. GLUT4, IR1, p-IR1, Akt and p-Akt were assessed

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in muscle by western blot. ANOVA I and Newman-Keuls as *post-hoc* test were used.
HOMA and adiponectin/leptin values were reduced in C, RSV, R and RR groups. In the case of GTT, reductions in RSV, R and RR groups were higher than that in C group. An increase in p-IR1/IR was observed in RSV and RR groups. GLUT4 was increased in C, RSV, R and RR groups. No differences were observed Akt and p-Akt ratio among treated groups. In conclusion, resveratrol induced changes in glycaemic control similar to those induced by a mild energy restriction. No sinergistic effects were observed.

T1:S6:02
Endothelial dysfunction (ED) and changes in inflammatory status precedes the increase on systolic blood pressure (SBP) in obesity rat model

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Background: Obesity is associated with low grade inflammation, ED and hypertension that increase the rates morbidity and mortality.
Aim: Investigate during the development of obesity in rats the progresses of inflammatory status, ED and SBP.
Methodology: Wistar male rats were divided in 2 groups: CT (n-30) fed with standard diet and HFD (n=30) fed with high fat diet during 24 weeks. Each 6 weeks systolic blood pressure was measured vascular reactivity studies was performed in aortic rings and serum IL-6, TNF-α and Adiponectin was measured.
Results: With the growing of fat mass at 6 weeks, already can observed a decrease in endothelial relaxant effect by acetylcholine, accompanied by an increase of IL-6 and TNF- α, and decrease of adiponectin serum concentrations. At 12 weeks, the HFD groups showed an increased in SBP.
Conclusion: Endothelial dysfunction and increase inflammation status precedes development of hypertension and this state is strongly correlates with progress of obesity.
Conflict of Interest: None Disclosed.
Funding: CNPq (140056/2013-0)

T1:S6:04
Role of P38MAPK in palmitate-induced inflammation in C2C12 muscle cells

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INRA

The saturated fatty acid palmitate (PAL) is now recognized as an inducer of inflammation in many types of cells, including adipocytes and muscle cells, whereas n-3 polyunsaturated fatty acids (n-3PUFA) have anti-inflammatory properties. Meanwhile, PAL induces muscle insulin resistance (IR) and n-3PUFA are suggested to reverse it. We investigated n-3PUFA effects on palmitate-induced inflammation and the potential link between inflammation, P38MAPK activation and IR in C2C12 myotubes. After 16 hours incubation with 500μM PAL without or with SB203580, a specific inhibitor of p38MAPK, 50μM of alpha linolenic acid (ALA), eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA), myotubes were harvested and submitted to mRNA quantification or immunoblotting. IL-6, TNF-a and COX-2 mRNA levels were significantly increased by PAL treatment and reversed by EPA and DHA. Inhibition of p38MAPK significantly prevented the effect of PAL on these regulations although it had no significant effect on PAL-induced IR. Additional study should be performed to explore the involvement of NFKB signalling. Our results suggested that p38MAPK activation by PAL is crucial to induce inflammation in C212 muscle cells, independently of IR. Among n-3PUFA, only EPA and DHA reduced p38MAPK activation and improved IR. Additional studies are currently performed to explore the involvement of NFKB signalling in the effect of PAL on myotube inflammation and the impact of n-3 PUFA on this pathway.

T1:S6:05
CD271 is involved in myofibroblast differentiation of human native adipose progenitor cells

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Obesity is associated with adipose tissue (AT) fibrosis. Our previous work showed that human AT progenitor cells (CD45-/CD34+/CD31-) expressed myofibroblast phenotype in response to tumor growth factor β (TGFβ). The present study aims to identify the progenitor cell subset (based on CD271 and MSCA1 expression) and pathways involved in myofibroblast differentiation (MD). Experiments were performed on paired biopsies of subcutaneous and visceral AT from patients candidate to bariatric surgery and on subcutaneous dermolipectomy. Progenitor cell subsets were studied by cell sorting, flow cytometry and in vitro approaches. MD was assessed by protein and gene expression analyses.
In addition to increased expression of ECM gene expression, TGFβ treatment of progenitor cells led to the nuclear translocation of CD271. Inhibition of such a process by the use of γ-secretase inhibitor abolished the profibrotic effect of TGFβ. The native progenitor subset CD271+/MSCA1- expressed at the higher levels transcriptsrelated to MD and was the sole progenitor subset to express MD markers in response to TGFβ. Finally CD271+MSCA1+ subset was more abundant in vAT compared to paired sAT and was associated with higher MD capacities of vAT progenitor cells. The present study identifies the human progenitor subset CD271+/MSCA1- as the myofibroblast precursor highlights the role of CD271 in such a process.
No conflict of interest is disclosed. Financial support: Sanofi, INSERM, regi

T1:S6:06
SHBG-C57BL/ksJ-db/db: A new mouse model to study SHBG regulation during obesity development. SHBG role in adiposity and NAFLD development

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Low plasma SHBG levels are present in obese subjects of all ages and in overweight individuals are a biomarker for the metabolic syndrome and predict type 2 diabetes and cardiovascular disease risk. There are no in vivo models to study SHBG expression and regulation during obesity development, since rodents unlike humans do not express the SHBG gene in their livers. In the present study, we have developed a unique mouse model that expresses the human SHBG and it develops obesity, by crossing the human SHBG transgenic mice with the C57BL/ksJ-db/db mice. The characterization of this SHBG-C57BL/ksJ-db/db mouse model have allowed us to determine: (1) the molecular mechanisms and transcription factors causing the SHBG downregulation during obesity

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development, which involved changes in liver HNF-4α and PPARγ mRNA and protein levels. These results were further confirmed in human liver biopsies; (2) that SHBG overexpression protects against body weight increase, adiposity and NAFLD development. The SHBG overexpression in C57BL/ksJ-db/db mice significantly reduced adipose tissue and liver weight. Overall, we have created the first mouse model that resembles what occurs in human obese subjects in terms of SHBG expression and regulation. More importantly, our results point out to SHBG as a protective factor against adiposity and NAFLD. Therefore, SHBG could be a new therapeutic target whereby increased expression may reduce obesity and NAFLD

T1:S6:07
A comparison of the effect high-fat diet feeding on liver lipogenesis in Wistar and Sprague-Dawley rats

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Introduction: Some researchers have proposed important variations in adipose tissue among different strains in response to a high-fat diet (hf). Although in some cases a direct comparison was made between Wistar (W) and Sprague-Dawley (SD) strains, unfortunately no mechanistic data for the different fat accumulation was evaluated so far on liver. The aim of the present research was to evaluate the effect of hf diet feeding on liver lipogenesis in W and SD rats.
Methods: 16 W and 16 SD rats were assigned to 2 experimental groups for 6 weeks: normal-fat (nf) and hf diet groups. Liver was dissected and weighted, and hepatic triglyceride content was measured spectrophotometrically. Liver sterol regulatory element-binding factor 1c (*srbef1c*), acetyl-CoA carboxylase (*acx*), and fatty acid synthase (*fasn*) expressions, as well as FAS activity, were measured.
Results: A tendency towards increased liver weights were observed in both strains (Wnf *vs* Whf and SDnf *vs* SDhf $P<0.01$ by Student's *t* test). This fact was associated with enhanced triglyceride content in SD (+62%) and W rats (+42%). No diet*x*strain interactive effect was observed in the analyzed gene expression. Strain effect was observable in the case of *fasn* and *srbef1c* mRNA levels. Hepatic FAS activity was raised by hf-diet feeding in both strains.
Conclusion: No differential hf-diet feeding effect exists on liver lipogenesis between Wistar and Sprague-Dawley strains.

Session 7: Origins and functions of adipocytes

T1:S7:01
Cellular and metabolic plasticity of adipose tissues

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Cold exposure or direct activation of β3-adrenergic receptors (ADRB3) induces metabolic and cellular remodeling of adipose tissues, including the appearance of new multilocular adipocytes that express UCP1, the prototypic marker of brown adipocytes (BA). Genetic lineage tracing using Pdgfra-CreERt2 and Adiponectin-CreERt2 indicates that cold-induced BA arise from the proliferation and differentiation of PDGFRa+ progenitors in classic interscapular brown adipose tissue (iBAT), whereas most newly-observed UCP1+ adipocytes in adult inguinal white adipose tissue (ingWAT) were derived from pre-existing unilocular adipocytes. Direct activation of ADRB3 did not induce de novo brown adipogenesis in either iBAT or ingWAT despite intense metabolic activation, but did trigger brown adipogenesis in gonadal WAT (gWAT). Here the primary targets of ADRB3 agonists were widely-dispersed white adipocytes that succumbed to agonist treatment. Progenitor proliferation and differentiation appears to be driven by local signals from M2-polarized macrophages, which recruit PDGFRa+ progenitors and generate proadipogenic PPARg ligands. Lastly, sustained activation of ADRB3 triggers massive triglyceride turnover in brown, beige, and white adipose tissues that includes simultaneous induction of fatty acid oxidation and de novo lipogenesis. This catabolic remodeling is entirely dependent on lipolysis, but largely independent of UCP1. Given the central role of lipolysis in catabolic reprogramming of adipocytes, direct activation of adipocyte lipolysis could provide a novel therapeutic avenue for treating obesity-related diseases.

T1:S7:02
Brown adipocytes: Origin and functions

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Brown adipocytes are not really adipocytes - at least not if we then think of them as being closely related to the "real" white adipocytes. Rather, they are muscle-like cells that at an early stage in their development diminished their expression of many of the genes that we normally associate with muscle. However, they retained one of the characteristics of red muscle cells: their ability to exhibit a high density of mitochondria. However, whereas muscle mitochondria are extremely good at producing ATP, brown adipocyte mitochondria suppressed the amount of ATP synthase and instead acquired the unique "uncoupling" protein UCP1. Around 90 % of all of the body's UCP1 is found in brown adipocytes (at least in mice), and it is thus in these cells that the overwhelming capacity for burning food directly to heat is found. The brown adipocytes are readily recruited, i.e. when more combustion capacity is needed, a series of recruitment processes are initiated, involving generation of more UCP1 per mitochondrion, more mitochondria and, importantly, many more brown adipocytes. Working together, they have the potential to diminish obesity and possibly also to lower both blood glucose and blood lipid levels. Thus, if they become possible to recruit therapeutically, they are inborn anti-metabolic-syndrome fighters.

T1:S7:03
Origin and regulation of beige/ brite adipocytes

Feldman, B.*
Stanford University

Adipose tissue integrates an array of homeostatic processes and plays a crucial role in metabolism. Classical brown adipose tissue (BAT), the key site of thermogenesis in mammals contains brown adipocytes characterized by a high number of mitochondria, small lipid droplets and robust expression of the pathognomonic uncoupling protein 1 (UCP1) enabling the uncoupling of b-oxidation that results in dissipation of energy as heat. Brown adipocytes are innervated by sympathetic nerve fibers that release norepinephrine (NE) in response to cold to activate thermogenesis. Interestingly, it was discovered that white adipose tissue (WAT) could display properties of BAT at the molecular and functional levels. This is driven by the development of 'brown-like' adipocytes in the WAT, which are often referred to as either 'beige' or brown-in-white (brite) cells. Brite cells are most abundant in the subcutaneous WAT depot in mice and various stimuli, such as cold exposure and b-adrenergic signaling, increase their abundance and activity. Increasing the activities of brown and beige adipocytes is linked to

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resistance to obesity and improvements in glucose and lipid homeostasis. Therefore, increasing the amount of beiging is an attractive strategy for combating obesity and metabolic diseases. Reciprocally, factors that reduce beige fat abundance or function may have adverse implications.

T1:S7:04
Regulation of brown fat formation

Wolfrum, C.*
ETH Zurich

Obesity is defined by an expansion of adipose tissue mass, however in recent years it has become evident that not only the mass, but also the quality of adipose tissue is important. Adipose tissue can be subdivided into two distinct types, namely white and brown fat. White fat is specialized in the storage of lipids, however, under obese conditions it transforms into a diseased and injured tissue which contributes to the development of obesity associated co-morbidities. Brown fat, in contrast, releases energy in the form of heat through uncoupling, leading to an enhanced basal energy expenditure. Therefore, brown adipose tissue has received tremendous interest in recent years as a target organ to improve metabolism. At the moment it remains controversial how brown adipocytes are formed and become activated in response to external cues. On the one hand, it is well established that brown fat cells can develop from adipocyte precursors, nevertheless a large body of evidence suggests that brown adipocytes can acquire a "white adipocyte like phenotype" under un-stimulated conditions suggesting a certain degree of plasticity within the adipose tissue organ.

Session 8: White adipose tissue: Development, products and function

T1:S8:01
Meteorin-like (METRNL) decreases during human adipogenesis and is associated with hypertrophic adipose tissue accumulation and hyperinsulinemia by inhibiting adipocyte differentiation in humans

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Meteorin-like (METRNL) is a recently described adipokine that affects energy metabolism in mice.
We systematically evaluated METRNL expression during human adipogenesis and the association with obesity, browning and hyperinsulinemia in children. In addition, we assessed the functional relevance of METRNL on human adipogenesis.
We show that METRNL is down-regulated during human adipocyte differentiation. METRNL expression is higher in adipocytes of obese than in lean children and correlates with adipocyte size as an indicator of hypertrophy, whereas in SVF METRNL expression correlates with the proliferation capacity. Concordantly, overexpression of METRNL inhibited human adipocyte differentiation while downregulation promoted adipogenesis. Proliferation, in contrast, was advanced by METRNL overexpression. Clinically, we observed association of METRNL expression with hyperinsulinemia and AT inflammation in children. METRNL was not associated with UCP1 in WAT or induction of browning by rosiglitazone or BMP7.
Hence, our findings of down-regulation of METRNL during adipogenesis and functional effects of METRNL on increased proliferation in SVF cells with concomitant inhibition of adipocyte differentiation result in hypertrophic AT accumulation. As obese children have larger adipocytes, this may also explain our observations of increased METRNL expression in adipocytes but not SVF cells in obese compared to lean children and the subsequent hyperinsulinemia.

T1:S8:02
Effects of pterostilbene and hesperidin on adipogenesis in 3T3-l1 cells

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Obesity has reached epidemic proportions worldwide. Noticeable attention has been paid in recent years to natural bioactive molecules, such as polyphenols, present in foodtuffs. Very few data are available in the literature concerning the anti-adipogenic effects of hesperidin and pterostilbene. Thus, the aim of the present study was to analyze the effects of these polyphenols on adipogenesis, a process involved in obesity development.
For this purpose 3T3-L1 pre-adipocytes were treated from day 0 to day 8 of differentiation with 25μM of pterostilbene or hesperidin. Triglycerides were measured by spectrophotometry. Protein measurements were performed using the BCA reagent. *Cebp/α*, *cebp/β*, *pparγ*, *srebp-1c and lpl* gene expression was assessed by RT-PCR. Cell viability was analyzed by using a commercial kit. Comparisons between each treatment and control cells were performed by using Student's *t*-test.
The percentages of reduction in adipocyte triglyceride content were 57.1± 5.6 for pterostilbene and 53.9±6.5 for hesperidine. No cytotoxic effects were induced by these molecules. With regard to gene expression, pterostilbene reduced *cebp/β*, *pparγ* and *srebp-1c*. In the case of hesperidin, only *srebp-1c* was significantly reduced. In conclusion, both polyphenols show an anti-adipogenic effect, but the mechanisms underlying this effect are different. While hesperidin acts by inhibiting the early stage of adipogenesis, pterostilbene inhibited both the early and the later stages.

T1:S8:03
Elucidation of suppressive mechanism of betulinic acid on adipogenesis using global gene expression profiling

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Betulinic acid (BA) is a plant-derived triterpenoid with known anti-obesity activities, yet the action mechanisms are not well defined. In this study, we investigated the suppressive effect of BA on adipogenesis and the underlying mechanisms during 3T3-L1 differentiation. BA treatment during 3T3-L1 differentiation significantly inhibited adipogenesis as shown by Oil Red O staining and reduced expression of key adipogenic genes. Detailed molecular mechanisms of BA on adipogenesis were assessed by global gene expression profiling of fully differentiated adipocyte with BA treatment. The results identified 869 up- and 852 down-regulated genes using Rank Product method. Gene ontology (GO) analysis revealed that the target genes were highly enriched in regulation of lipid metabolic process ($P < 0.01$). To confirm microarray data, qPCR analysis was

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performed for selected genes by GO analysis and literature-based associations with obesity. The potential therapeutic effects of BA through modification of lipid metabolism were examined in high-fat diet-fed mice (HFD). Mice treated with BA for 12 weeks showed significantly ameliorated body weight, epididymal fat mass, and serum triglyceride levels compared to those of HFD. BA-treated mice also showed decreased adipogenic and lipogenic gene expression in epididymal fat. In conclusion, the suppressive effect of BA on adipogenesis, and thus obesity, is likely mediated by alteration of expression of lipid metabolic pathway-related genes.

T1:S8:04

Metalloproteinase inhibition does not modify metabolic or inflammatory alterations in adipose tissue induced by weight loss

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São Francisco University

Extracellular matrix (ECM) changes are necessary during the process of expansion and regression of adipose tissue (AT). GM6001 (GM) is considered a matrix metalloproteinases (MMPs) inhibitor and we assessed the GM effects upon ECM remodeling in adipose tissue (AT) during weight loss (WL) in high-fat diet (HFD) obese mice. Swiss mice were fed a HFD to induce obesity and after they were subjected to caloric restriction to induce WL and treated with GM (WLGM; 100 mg/kg/day). Obese (Ob) and lean (NC) mice group was used as controls. Body weight (bw) and adiposity was monitored. Glucose homeostasis was evaluated by insulin tolerance test. MMPs, adipokines and ECM components in AT were quantified. MMP activity was analyzed by zymography. After caloric restriction, WL mice presented bw, adiposity and glucose homeostasis similar to NC group. Inflammation assessed by adipokine levels was not present, but MMP-2 (114±25 and 334 ±58 ng/mg protein for NC and WL, respectively, $p<0.05$), as well as MMP-3, MMP-8, MMP-12 levels and MMP activity on AT remained increased after WL. GM treatment resulted in a reduction in MMP activity and an increasing of collagen, laminin and fibronectin content, but it did not modify local inflammation or glucose homeostasis. In conclusion, obesity induces tissue remodeling in AT and it remains active after weight loss. Interferences with tissue remodeling do not result in alterations in glucose homeostasis or local inflammation during weight loss.

T1:S8:05

Meta-analysis of insulin resistance based on gene expression datasets in human adipose tissues

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To elucidate genetic markers involved in development and treatment of insulin resistance (IR), an approach of meta-analysis can be adopted using a public database integrating multiple heterogeneous microarray datasets. To our knowledge, this is the first study showing meta-analysis on IR in white adipose tissue. In this analysis, Rank Product (RP) algorithm for meta-analysis was applied to identify differentially expressed genes (DEGs) by combining multiple microarray datasets with batch effects adjustment in omental and subcutaneous adipose tissue. A total of 7 GEO datasets, including 83 IR and 52 normal glucose tolerance (NGT) samples, were accessible for the meta-analysis. We identified 670 (482 up- and 188 down-regulated) DEGs using RP method, and found KEGG (Kyoto Encyclopedia of Genes and Genomes) pathways related to inflammation such as phagosome, Toll-like receptor signaling pathway, rheumatoid arthritis and cytokine-cytokine receptor interaction ($P < 0.01$) via pathway enrichment analysis. Furthermore, protein-protein interaction (PPI) network analysis indicated that 217 (147 up-, 70 down-regulated) proteins and 358 edges had interaction with one another in a network, with a putative hub protein, EEF1A1 (degree=22), that did not significantly stand out previous single study analysis. In conclusion, the identified DEGs may be considered as useful robust genetic markers or potential therapeutic targets.

T1:S8:06

In vitro effects of hypoxia on human adipose tissue lipoprotein lipase activity and lipolysis

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Background: Adipose tissue (AT) plays a pivotal role in buffering postprandial lipid metabolism by storing dietary fat through lipoprotein lipase (LPL)-mediated hydrolysis of exogenous triglycerides, and by inhibiting delivery of endogenous non-esterified fatty acid to nonadipose tissues (intracellular lipolysis). Should these functions of adipose tissue be impaired, other organs such as the liver and skeletal muscles could be exposed to an excess of lipids, potentially leading to metabolic disorders. Animal studies suggest that hypoxia reduces AT LPL activity and stimulates lipolysis. Available data on the effects of hypoxia on AT lipolysis in humans are conflicting, while the effects of hypoxia on AT LPL activity in humans are unknown.
Aims: To investigate the effects of hypoxia on human AT LPL activity and intracellular lipolysis.
Methods: Differentiated human preadipocytes were exposed to hypoxia (3% oxygen) and normoxia (21% oxygen) for 24h.
Results: Acute hypoxia (AH) induced a 6-fold reduction in LPL activity ($p<0.001$). Basal lipolysis levels were significantly higher during AH session ($p<0.05$). No difference in isoproterenol- and epinephrine-stimulated lipolytic responses were observed in subcutaneous abdominal preadipocytes between normoxia and AH.
Conclusions: This study demonstrates that hypoxia impairs the buffering of lipids in adipocytes by impairing AT LPL activity and increasing basal lipolysis.

T1:S8:07

Serum resistin is associated with adipocyte hypertrophy, inflammation and metabolic complications of obesity in South Asian women

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South Asian individuals develop metabolic complications of obesity at lower levels of adiposity compared to their western counterparts. Hence, the aim of the current study was to investigate BMI (Body Mass Index)-dependent changes in serum adipokines in Sri Lankan

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women and determine their association with metabolic complications of obesity.
Adult females who underwent routine abdominal surgery at Teaching Hospital, Peradeniya were recruited (n=59). Anthropometric measures and fasting pre-operative blood samples were obtained while ultrasound scanning was performed to detect hepatic steatosis. During surgery, white adipose tissue (WAT) samples were obtained from the omentum and anterior abdominal wall. Histological sections of WAT were used to measure the adipocyte area and identify the crown-like structures (CLS).
Overweight or obese women had significantly higher serum resistin levels, CLS and adipocyte area compared to normal weight women, while no significant difference in serum adiponectin levels was observed among the different groups. Moreover, serum resistin had significant positive correlations with age, waist circumference, number of CLS in WAT and mean omental WAT area. Individuals with hepatic steatosis and impaired fasting glucose also had significantly higher serum resistin levels compared to women without these derangements. In conclusion, the adipokine resistin may be important in the pathogenesis of obesity-related metabolic complications in South Asians.

T1:S8:08

Effect of high intensity exercise training on insulin-stimulated glucose uptake in various adipose tissue depots of pre- and postmenopausal women

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Background: Female sex steroids influence storage of fatty acids, and the loss of estrogen during the menopausal transition might contribute to increased accumulation of adipose tissue in the abdominal depots in postmenopausal women. Since abdominal obesity is associated with insulin resistance and cardiovascular disease, this change in female body composition is undesirable. Physical exercise is known to reduce adipose tissue accumulation and prevent metabolic and cardiovascular diseases, but it is suggested that postmenopausal women have a blunted response to exercise. Therefore, our **aim** is to investigate the effect of high intensity exercise training on insulin-stimulated glucose uptake in various adipose tissue depots in pre- and postmenopausal women, to elucidate the interaction between physical exercise and menopause. **Subjects:** Pre- (n=17) and postmenopausal (n=19) women, 45 to 57 years, healthy and non-smoking, with no use of medication, sedentary and normal- to overweight (BMI: 18.5 – 30 $kg{\cdot}m^{-2}$), are participating in a 3-month exercise intervention comprising spinning three times per week.
Methods: Body composition is determined by DXA- and MRI-scans. [^{18}F]FDG uptake in abdominal, gluteal and femoral adipose tissue is determined by PET/CT-scanning during a hyperinsulinemic euglycemic clamp (40 $mU{\cdot}m^{-2}{\cdot}min^{-1}$) at baseline and after the intervention.
Results: The study is ongoing until the end of 2015 and data will be presented at the conference.

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