DIGESTION, METABOLISM AND ENDOCRINE DISEASES

P04-01
FEEDBACK REGULATION OF CHOLESTEROL BIOSYNTHESIS: MECHANISTIC AND APPLIED STUDIES

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Cholesterol is synthesized from acetyl-CoA through a cascade of enzymatic reactions. The biosynthesis of cholesterol is tightly regulated, mainly through two feedback regulatory mechanisms: sterol-regulated degradation of HMG-CoA reductase (HMGCR) and maturation of sterol regulatory element-binding protein (SREBP). gp78 is a membrane-anchored ubiquitin ligase mediating the degradation of HMGCR and Insig-1. As a rate-limiting enzyme in cholesterol biosynthesis, HMGCR undergoes rapid sterol-promoted degradation. In contrast, destruction of Insig-1 releases its inhibition on SREBP and stimulates the expression of lipogenic genes. Thus, gp78 has opposite effects on lipid biosynthesis. We generated liver-specific *gp78* knockout (*L-gp78*$^{-/-}$) mice and showed that although the degradation of HMGCR was blunted, SREBP was suppressed due to the elevation of Insig-1/-2, and therefore the lipid biosynthesis was decreased. The *L-gp78*$^{-/-}$ mice were protected from diet- /age- induced obesity and glucose intolerance. The livers of *L-gp78*$^{-/-}$ mice produced more FGF21, which activated thermogenesis in brown adipocytes and enhanced energy expenditure. Together, the major function of gp78 in liver is regulating lipid biosynthesis through SREBP pathway. Ablation of *gp78* decreases the lipid levels and increases FGF21, and is beneficial to patients with metabolic diseases. We further performed high-throughput screening and identified betulin as an inhibitor for SREBP pathway. The mice treated with betulin showed similar beneficial phenotypes with *L-gp78*$^{-/-}$ mice.

P04-02
STEAROLY-COA DESATURASE IN LIPID METABOLISM

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Stearoyl-CoA desaturase (SCD) is a key enzyme in the biosynthesis of fat and energy homeostasis. Disruption of SCD in both mice and *C. elegans* significantly decreases the fat storage and body weight. On the contrary, overexpression of SCD leads to excess fat storage associated with obesity, type 2 diabetes, fatty liver, etc. Currently, we are using *C. elegans* and tree shrew to investigate the role of SCD in lipid metabolism and metabolic diseases. We found that SCD regulates the lipid droplet size to reduce the fat storage in *C. elegans*. Additionally, we have screened several genes that regulate the expression of SCD, and now are exploring the interactions of these SCD regulators and SCD in the regulation of lipid metabolism.

P04-03
GROWTH HORMONE AND OBESITY: A PHYSIOLOGICAL RESPONSE TO AN UNHEALTHY CONDITION

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Growth hormone (GH) is thought to modulate insulin-induced lipogenesis throughout periods of positive energy balance. It is thought that impaired GH secretion relative to dietary induced weight gain contributes to improved meal tolerance, insulin responsiveness, and consequently the maintenance of non-esterified free fatty acid (NEFA) flux.

To assess this notion, we investigated the relationship between pulsatile GH secretion and body weight, fat mass, circulating levels of insulin, and non-esterified free fatty acids (NEFAs) in male mice in response to dietary induced weight gain. Data were collected from wild type (WT) mice following 8 weeks of dietary intervention, and throughout progressive weight gain in hyperphagic melanocortin 4 receptor knock out (MC4R KO) mice. Observations demonstrate an inverse association between pulsatile measures of GH secretion and circulating levels of insulin. This relationship occurred alongside an increase in body weight and adiposity, and the maintenance of circulating levels of NEFAs. We confirm healthy release of GH in MC4R KO mice prior to the development of hyperphagia-associated hyperinsulinemia. GH secretion in MC4R KO mice decline rapidly alongside an elevation in circulating measures of insulin.

Collectively, data confirms an inverse relationship between in circulating levels of GH and insulin, and the corresponding maintenance of circulating levels of NEFAs. Moreover, observations from MC4R KO mice highlight the potential role for insulin in sustaining low levels of GH following progressive weight gain, and in obesity. We propose that suppressed GH secretion in obesity does not occur in response to endocrine dysfunction, rather the suppression of GH throughout progressive weight gain is a physiological adaptation to sustain NEFA balance. We are now validating this premise, and addressing the mechanisms that may account for this interaction.

P04-04
ERYTHROPOIESIS, RED CELL DESTRUCTION AND IRON TURNOVER

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Iron is essential for the formation of red cells due to its key role in haemoglobin (Hb) synthesis. Since Hb represents the largest

pool of iron in the body, most body iron turnover involves iron uptake by immature erythroid cells and the recycling of that iron after senescent erythrocytes are phagocytosed by macrophages. The liver-derived iron-regulatory peptide hepcidin plays a central role in this cycle. Stimulated erythropoiesis reduces hepcidin expression, which in turn increases macrophage iron release and intestinal iron absorption to ensure an adequate supply of iron for Hb production. How erythropoiesis reduces hepcidin is unknown. Using a mouse model of chronic haemolytic anaemia, we have shown that stimulated erythropoiesis interferes with at least two steps in the Bmp/Smad signalling pathway, the main pathway affecting hepcidin expression. Haemolysis stimulates the expression of Bmp6, a positive regulator of hepcidin, but under these conditions Bmp6 is unable to alter the phosphorylation of Smad1/5/8, key signaling intermediates. Since hepcidin expression is reduced in the absence of changes in pSmad1/5/8, signaling steps downstream of pSmad1/5/8 must be compromised or an independent event must be overriding Bmp/Smad action. In our system, we have excluded the involvement of candidate 'erythroid factors' GDF15 and TWSG1, but have evidence that transferrin/transferrin receptor interactions may be involved. In certain chronic haemolytic anaemias, iron absorption is not elevated despite a high erythropoietic rate. To investigate this we have studied the RBC14 mouse, a novel model of chronic haemolytic anaemia without iron loading, and compared it to Hbbth3/+ mice, a model of an iron loading anaemia. Our data suggest that in low-grade chronic haemolytic anaemia, increased erythroid iron requirements can be met through enhanced macrophage iron release without the need to alter iron absorption or hepcidin, indicating that hepcidin is not the sole regulator of macrophage iron release.

P04-05
ENU-INDUCED MUTANT MICE MODELS TO IDENTIFY NOVEL MOLECULES THAT REGULATE BONE HOMEOSTASIS

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Over the past decade, progress in gene manipulation technologies has facilitated the use of mouse models to study bone homeostasis. Knockout, knock-in and transgenic mouse models have been widely used to identify genes that are vital in regulating bone homeostasis. More recently, chemical mutagenesis has been employed to develop and expand the repertoire of mutants for gene function studies. In this approach, *N*-ethyl-*N*-nitrosourea (ENU) mutagenesis, followed by screening methods to detect single-nucleotide substitutions within the targeted gene, represents a promising technology. We are currently screening mice for mutations that affect bone phenotype. We have identified several molecules that affect bone homeostasis in ENU-induced mutant mice; including CHKB, Roquin, BCL2 and Morc3. For example, choline kinase beta (chkb) mutant mice exhibit an osteoporotic phenotype as evidenced by microCT and histological assessment. *In vivo* and *in vitro* analysis reveals elevated osteoclast numbers in the mutant mice. Furthermore, osteoclasts from choline kinase beta mutant mice exhibit increased resorptive activity compared to those of littermate controls. Osteoclasts derived from choline kinase beta mutant mice showed decreased calcium signaling response to high extracellular calcium. This may account for the increased resorptive activity in osteoclasts derived from the mutant mice. Treatment with CDP-choline *in vivo* and *in vitro* reduces osteoclast numbers, thereby rescuing the osteoclast phenotype. *In vitro* assays show a reduction in bone mineralisation in osteoblast cultures derived from the bone marrow of mutant mice. Taken together, our data document, for the first time, that choline kinase beta plays an important role in bone homeostasis. Overall, this phenotype-driven screening approach enables us to utilize a novel and unique tool for the discovery of gene function in bone biology. The high-throughput sequencing-based screening technique will help unveil novel mutations that cause dysfunction of bone homeostasis, and potential molecular mechanism(s) underlying the fundamental activities of bone cells.

P04-06
CROSS TALK BETWEEN ER STRESS AND *DE NOVO* LIPOGENESIS AND ITS IMPLICATIONS FOR INSULIN RESISTANCE AND FATTY LIVER DISEASE

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The endoplasmic reticulum (ER) has been proposed as a 'nutrient-sensing' apparatus that regulates carbohydrate, lipid and protein metabolisms linking inflammation and stress pathway networks. When ER stress occurs it triggers the unfolded protein response (UPR) and this has been suggested to contribute to hepatic insulin resistance and fatty liver disease. We first investigated the role of ER stress in the development of hepatic steatosis and insulin resistance induced by commonly seen nutrients (high carbohydrate and high fat) for these metabolic conditions. Our results showed that ER stress is coupled with excess *de novo* lipogenesis (DNL), hepatic steatosis and insulin resistance induced by high carbohydrate. Among the three branches of the UPR pathways the IRE1/XBP1 arm is the key link to DNL and hepatic insulin resistance. Along with up-regulation of lipogenic enzymes, autophagy pathway was reduced, indicating an inhibition of protein degradation. These data suggest a cross talk of ER stress presumably in response to protein metabolism to DNL which can lead to hepatic lipid accumulation and insulin resistance. As activation of PPARα is known to be the therapeutic target of the lipid-lowering drug fenofibrate which attenuates hepatic insulin resistance, we further investigated whether the insulin sensitising effect of PPARα activation may be related to a relief of ER stress. Intriguely, the effect of fenofibrate to attenuate hepatic insulin resistance was found to be closely associated with activation of the IRE/XBP1 and PERK/eIF2α arms of UPR pathways and elevated DNL. The results suggest that the UPR upstream pathways may be required to mediate PPARα induced metabolic effects. This presentation will discuss the possible

implications of the cross talk between ER stress and lipid metabolism for insulin resistance and fatty liver disease.

P04-07
NOVEL USES OF BIOLUMINESCENCE RESONANCE ENERGY TRANSFER TECHNOLOGIES TO STUDY MOLECULAR ENDOCRINOLOGY

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Bioluminescence resonance energy transfer (BRET) is a technology that enables protein-protein interactions to be monitored in live cells and in real time. It utilises luciferase enzymes, genetically fused to proteins of interest, as energy donors that emit blue light upon oxidation of a substrate. When in close enough proximity to a complementary energy acceptor genetically fused to another protein of interest, less blue light is emitted and some of the energy is transferred in a non-radiative manner to the fluorescent acceptor, resulting in the emission of light of longer wavelengths from the acceptor. My laboratory is a leader in the use of the BRET technology to study receptor complexes in the membranes of our cells. In particular, we have focused upon monitoring receptor complexes largely involved in the regulation of the endocrine system, the perturbation of which can lead to disease. We have increasing evidence to suggest that different receptor types can functionally interact with each other and modulate various aspects of receptor activity, a process known as heteromerisation. This has potentially important implications, both for disease etiology and pharmaceutical intervention. Indeed, it is entirely possible that certain side effects from pharmaceuticals emanate from unforeseen modulation of other signalling pathways as a consequence of heteromerisation. Therefore understanding the nuances of these functional interactions enables strategic use of combination therapies, as well as the potential for development of compounds exhibiting beneficial heteromer-selective pharmacology for a range of disorders.

P04-08
ROLE OF LIPID DROPLETS IN METABOLIC DISEASES

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The aberrant storage of neutral lipids in lipid droplets has been linked to human metabolic syndrome that can increase the risk of type 2 diabetes and cardiovascular diseases. To study how lipid droplets are involved in these health problems, we have carried out studies on lipid droplets of skeletal muscle, liver, heart, and *C. elegans* by isolation and proteomic analyses of the organelle. We found one way that monounsaturated fatty acid utilizes lipid droplets to prevent skeletal muscle cells from saturated fatty acid-induced ER stress and insulin resistance, and the other way that decrease of triglyceride hydrolysis in heart lipid droplets was involved in the development of heart failure. We identified several lipid droplet-associated proteins that promote formation of supersized lipid droplets in both human fatty liver and *C. elegans*. These studies not only identified the lipid droplet-associated proteins that were involved in metabolic disease progress but also provide more information that facilitates lipid droplet research, in general.

P04-09
MICE LACKING PGC-1α IN PANCREATIC β-CELLS HAVE IMPAIRED GLUCOSE TOLERANCE

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PGC-1α is an important co-activator regulating the expression of genes for oxidative phosphorylation in a number of tissues including skeletal muscle, liver and adipose tissue. Previous *in vitro* and *in vivo* studies using adenoviral mediated overexpression and shRNA approach showed that PGC-1α suppressed beta-cell energy metabolism and negatively regulated insulin secretion. In contrast, a recent study using isolated human islets showed that PGC-1α promotes insulin secretion and that PGC-1α expression in human islets is down-regulated in Type 2 diabetic patients. Our study is designed to determine the requirement for PGC-1α in regulating beta-cell function using beta-cell specific PGC-1α knockout mice. The beta-cell specific PGC-1α knockout mice were generated by crossing RIP-cre/+ mice with PGC-1α flox/flox mouse line. Glucose tolerance test and insulin tolerance test were performed in the mice. RIP-cre/+ or PGC-1α flox/flox mice were used as controls. The mice lacking PGC-1α in beta-cells developed modest impaired glucose tolerance at 8 weeks of age compared to RIP-cre/+ or PGC-1α flox/flox control mice. RT-qPCR analysis showed that insulin and Pdx-1 mRNA were significantly reduced in the islets isolated from PGC-1α knockout mice compared to control mice, whereas there was no difference in the expression of MafA, NeuroD1, NKx6.1, IRS-2 and Glut2 between the two groups. Immunohistochemistry analysis showed that islet sizes were reduced in HFD fed PGC-1α KO mice compared to control HFD fed mice. Taken together, PGC-1α in beta-cells is necessary for beta-cell function, Pdx-1 and insulin expression. PGC-1α deficiency reduces islet size to cause impaired glucose tolerance.

P04-10
NFATC3 IS REQUIRED FOR PANCREATIC BETA-CELL FUNCTION AND REPLICATION

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How fatty diet and obesity trigger diabetes has long been the subject of intense scientific research. Calcineurin activates NFAT

(Nuclear Factor of Activated T-cells) transcription factors by dephosphorylation of NFAT, resulting in nuclear translocation of NFAT. There are 4 members of NFAT genes, c1 to c4, whose functions in beta-cells are unknown. We found that NFATc3 was the major isoform expressed in beta-cells and its expression was down-regulated in mouse pancreatic islets in high fat diet (HFD) fed mice. Min6 cells were infected with Adenovirus expressing NFATc3 and Calcineurin, and gene expression profiles were determined by cDNA microarray. Overexpression of NFATc3 in Min6 cells activated a great number of genes important for beta-cell function and increased Cyclin D1 protein expression and Min6 cell proliferation; Overexpression of NFATc3 in the cultured mouse islet cells activated a number of transcription factors such as FoxA2 and HNF1a, and promoted insulin secretion stimulated by high glucose; NFATc3(-/-) C57BL/6 mice and wild type controls were fed with HFD. There were no differences in glucose tolerance test between NFATc3 null mice and wild type mice fed with normal chow. However, NFATc3 (-/-) mice fed with HFD for 2 weeks showed more severe glucose intolerance than HFD-fed wild type mice; In the isolated islets of NFATc3 (-/-) mice compared to those of WT mice, a number of important beta-cell genes were significantly down-regulated, including Pdx-1, MafA, NeuroD1, Neurogenin3, NFATc2, NFATc4, FoxA2, HNF1a, PPARg, Insulin and Glu-2, whereas Nkx6.1 and IRS-2 were unchanged; Pancreatic islet numbers and size were reduced in HFD-fed NFATc3-null mice compared to WT HFD-fed mice. Conclusions: These results demonstrate that NFATc3 is required for beta-cell gene expression and plays an important role in maintaining beta-cells function and islet mass expansion under HFD-induced increased metabolic demand. Moreover, down-regulation of NFATc3 by HFD in beta-cells may be one of the mechanisms by which HFD induces beta-cell dysfunction in the pathogenesis of Type 2 Diabetes.

P04-11
MICRORNA-29A-C REGULATE MITOCHONDRIAL BIOGENESIS AND FUNCTION VIA INHIBITION OF PGC-1β

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MicroRNA-29a-c are small endogenous, non-coding RNAs which regulate expression of target genes through translational repression or degradation of target mRNAs, and has been considered to be related to skeletal muscle disease and dysfunction, diabetes. It has been reported that PGC-1 family members regulate numerous processes including hepatic gluconeogenesis, fatty acid β-oxidation, adaptive thermogenesis and mitochondria biogenesis which were involved in the forementioned situation, especially our group also reported that PGC-1β regulate mitochondrial biogenesis and function. We therefore hypothesized that microRNA-29a-c is related to inhibit PGC-1β to regulate mitochondrial biogenesis. The C2C12 myoblast cell lines were maintained to differentiate into myobubes, which were infected with recombinant adenovirus expressing miR-29a-c. Expression of PGC1β was also studied in DuaL-Luciferase Reporter gene Assays. Meanwhile, labeling of mitochondria and flow cytometry, measurement of oxygen consumption were performed to detect mitochondrial biogenesis and function. Realtime analysis showed that adenovirus-mediated overexpression of miR-29a-c in C2C12 myotube cells decreased mRNA level of PGC-1β. Also, DuaL-Luciferase Reporter gene Assays showed that transcriptional activity of PGC-1β was down regulated by microRNA-29a-c. Overexpression of microRNA-29a-c diminished PGC-1β-induced mtDNA, COXI transcript and subsequently mitochondrial biogenesis. Our data suggests that the mechanism of miR-29a-c regulate mitochondria biogenesis and function via inhibition of PGC-1β, which is association with the dysregulated oxidative metabolism, may facilitate the development of novel regimen for metabolism disorders.

P04-12
ACETYLATION OF HEPATIC FOXO1: A MECHANISM OF THE SUSTAINED CORRECTION OF HYPERGLYCEMIAFOLLOWING THE ADMINISTRATION OF OLEANOLIC ACID IN DIABETIC MICE?

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We have recentlydemonstrated that administration of the triterpenoidoleanolic acid (OA) to diabetic mice produces a sustained correction of hyperglyceamia post OA treatment (>4 weeks) with liver as the responsible site. To identifythe mechanism underlying thispersistenteffect, the present study examined the changes of key regulators on FoxO1 in the liver during the period of OA administration in diabetic mice induced by high fat feeding plus low doses of streptozotocin in comparison with those post OA treatment. Treated with OA (100 mg/kg/day for 4 weeks) reduced hyperglycaemia in diabetic mice by ~87% ($P < 0.01$ vs. untreated group) and this effect was largely (~70%) maintained even 4 weeks after the removal OA administration ($P < 0.01$). During the OA treatment, the acetylation and phosphorylation of FoxO1 in the liver were both markedly increased (by 1.5–2.5 fold) while G6Pase mRNA was suppressed by ~80% (all $P < 0.05$). HAT1 content was increased (>50%) and Class IIa histone deacetylases (HDACs) 4 and 5 were reduced by 30–50%. The OA-induced changes in FoxO1, G6Pase, HAT1 and HDACs persisted even 4 weeks after the removal of its administration whereas the increased phosphorylation of AMPK, SIRT1 content and reduced liver triglyceride were subsided. These results suggest that the anti-hyperglycaemic effects after the removal of OA may result from persistent acetylation of FoxO1 to suppress the hepatic gluconeogenic pathway. Our study provides a plausible concept of targeting epigenetic regulation of key proteins in the liver as a feasible approach for the treatment of T2D.

P04-13
NONALCOHOLIC FATTY LIVER DISEASE FIBROSIS SCORE PREDICTS 6.6 YEARS OVERALL MORTALITY OF CHINESE PATIENTS WITH NAFLD

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Background: Nonalcoholic fatty liver disease (NAFLD) fibrosis score (NFS) has emerged helpful as a long-term outcome predictor for NAFLD patients. We evaluated the predictive performance of NFS for overall mortality in a Chinese population with NAFLD.
Methods: All ultrasonography-diagnosed NAFLD patients at Xixi hospital of Hangzhou between January, 1996, and September, 2011 were retrospectively recruited. The outcome was obtained by interview and the causes of death were further confirmed by medical records. Area under receiver operating characteristic curve (AUC) was used to determine the predictive accuracy of NFS, BARD, FIB-4 and aspartate aminotransferase/platelet ratio index (APRI) for mortality.
Results: A total of 180 eligible patients (median age 39 years; 96 males) were analyzed, with 12 deaths (malignancy 5, cardiovascular disease 3, cirrhosis 2, stroke 1, and infection 1) over a median follow-up of 6.6-year. By Cox model analysis, NFS as a continuous variable other than 3 other scoring systems or any of individual variables was identified as the only predictor for all-cause mortality [hazard ratio 2.743, 95% confidential interval (CI) 1.670~4.504]. NFS yielded the highest AUC of 0.828 (95% CI 0.728~0.928, $p < 0.05$), followed by FIB-4, APRI and BARD with their AUCs of 0.806, 0.732 and 0.632 respectively ($p < 0.05$, except for BARD). Although the original cutoff of NFS for excluding advance fibrosis (-1.455) was capable of differentiating patients with increased death risk or not, cutoff of -1.836 showed a higher accuracy with a sensitivity of 83.3% and a specificity of 61.9%.
Conclusions: NFS is a useful predictor of 6.6-year all-cause mortality for Chinese patients with NAFLD.

P04-14
THE EFFECT OF TLR4 SIGNAL PATHWAY ON DYNAMIC PATHOPHYSIOLOGICAL PROCESS OF NAFLD INDUCED BY HIGH FAT AND HIGH FRUCTOSE DIET IN MICE

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Background: NAFLD (Non-alcoholic fatty liver disease) is an orchestrated, multi-step process in response to hepatic fat accumulation and oxidative stress, the acknowledged steps include simple steatosis, non-alcoholic steatohepatitis and Cirrhosis.
Objective: The aim of the present study was to establish a stable model of natural pathophysiological processes of NAFLD induced by high fat and high fructose diet, and observe the effect of TLR4 signal pathway in different stage of NAFLD.
Method: One hundred and twenty mouse were divided into the following groups: TLR4-WT SC group, TLR4-WT HFHFr group, TLR4mut-SC group, TLR4mut- HFHFr group, were fed a normal diet(SC) or high fat and high fructose (HFHFr) diet for 4, 8, 16 weeks respectively, and then assessed for simple steatosis, steatohepatitis and fibrosis by Oil Red O staining, hematoxylin-eosin (H&E) and Masson's trichrome. Immunohistochemistry and quantitative real time PCR were implemented to determine the activation of TLR4 signal pathway through both myeloid differentiation factor 88 (MyD88) dependent and MyD88-independent road, and the negative feedback mechanism between activin A and TLR4 signal pathway.
Result: The mice model induced by high fat and high fructose diet reappeared natural pathophysiological progress of NAFLD well, including typical stage of simple steatosis, steatohepatitis and hepatic fibrosis at the time point of 4, 8, 16 weekend respectively. TLR4 signal pathway is activated and it expresses different mRNA level in different stage of NAFLD, signal molecules of TLR4 signal pathway in TLR4-WT mouse liver had significantly increased after fed with HFHFr diet for 4 weeks, it augment more remarkably for 8 weeks, while for 16 weeks, with the growing of fibrosis, signal molecules of TLR4 signal pathway had a reductive tendency compared with 8 weeks. Interestingly, activin A has gradually increased from 4 weeks to 16 weeks. Lipid accumulation, inflammation launching, fibrosis and correlative live injury of TLR4 mutant mice had dramatically alleviated.
Conclusions: TLR4 signal pathway plays an crucial role in dynamic pathophysiological process of NAFLD induced by high fat and high fructose diet in mice, and there is a negative feedback mechanism between activin and TLR4 signal pathway which is important to form hepatic fibrosis.

P04-15
CENTRAL CONTROL OF METABOLIC SYNDROME AND AGING

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The hypothalamus is a converging point that integrates metabolic, neural, neuroendocrine, and neuroimmune signals to affect the whole body physiology. The research interest of my research is to investigate the role of neural dysregulations, in particular in terms of neural inflammation in the development of metabolic syndrome and aging. Our recent observations demonstrated that the hypothalamus contains adult neural stem cells, and IKK/NF-kB activation affects the fate of these cells and cause disease consequences in relation with aging development and metabolic dysfunctions. Taken together, we have established several conceptual models addressing the central mechanism of metabolic diseases and aging, and identified the involved mechanisms that are mediated by the integrative actions of neural, neuroendocrine and immune systems. We also have generated strategies for combating metabolic diseases and aging-related diseases through targeting the neural inflammatory molecular pathways.

P04-16
NRF2 AND ADIPOSE FUNCTIONS

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Nrf2 is referred to as the "master regulator" of the antioxidant response, modulating the expression of large numbers of genes that participate in the anti-oxidant and detoxification process. Aging is associated with hypoxia and oxidative stress in adipose tissue. After specific knockout of Nrf2 in the adipose tissue of mice, a slow-down of animal growth, increase of energy expenditure, lowered blood glucose level and higher macrophage infiltration in the visceral fat were observed under high-fat diet condition, accompanied especially by increase of FGF21, IGF1, NOS3, LPL, MGL and decrease of IGF1R gene expression in the visceral fat of Nrf2-knockout mice. Taking together, it suggests that Nrf2 may exercise its anti-oxidant effects in adipose tissues by enhancing adipose storage, decreasing hydrolysis of lipid and slowdown energy expenditure along with its anti-inflammatory effects.

P04-17
ADIPOCYTE DIFFERENTIATION, FUNCTION AND REGULATION

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Adipose tissues, including white adipose tissue (WAT) and brown adipose tissue (BAT), play important roles in the maintenance of the body's energy homeostasis. Recent studies have uncovered a specific type of "brown" cells or so called "beige" cells in WAT that exert protective function against obesity, diabetes and other metabolic diseases. During the past 10 years, a great progress has been made on our understanding of the mechanisms regulating adipocyte differentiation and the "browning" of WAT at the transcriptional level. However, the upstream signaling pathways that promote or inhibit the browning process remain largely unclear. My presentation will briefly summarize our recent progress on the regulation of brown adipocyte differentiation and function as well as the browning process of WAT, focusing on the mTOR signaling pathway and its effect on adipocyte function.

P04-18
TRACING MAMMALIAN IRON BALANCE FROM MOUSE TO HUMAN

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Iron is an essential element for most living organisms on earth, including human beings. An inability to maintain iron homeostasis may lead to death or a disease. In fact, it is estimated that nearly one quarter of population worldwide are suffered from iron deficiency anemia. In contrast, iron overload induces hemochromatosis, and many neurodegenerative diseases. Therefore, maintenance of iron homeostasis is crucial for human health. Recently, emerging evidence supports iron transporters play important roles in regulate iron homeostasis. However, the underlying molecular mechanisms are not well defined. To explore the mechanistic network of iron regulators in maintenance of iron homeostasis, we initiated our investigations with knockout mouse models and epidemiology. Recently significant findings are listed as followings: By using macrophage Fpn1 deletion mouse models, they provided solid data to support Fpn1 plays important roles in macrophage iron release and in modulating innate immune responses; Functionally characterized Fpn1 as a major iron exporter in hepatocytes, and further defined hepatocyte Fpn1 as one of the important players in iron mobilization, iron storage, and intestinal iron absorption to maintain systemic iron homeostasis; We observed metalloreductase Steap3 coordinates with Fpn1 to regulate systemic iron homeostasis and inflammatory responses; Defined significant association between TMPRSS6 polymorphisms and decreased iron status, and refined genetic risk factors for iron deficiency and iron-deficiency anemia; Discovered TMPRSS6 variants, which mediated by plasma ferritin, were significantly associated with lower risk of type 2 diabetes in Chinese Hans. Furthermore, we measured the level of hepcidin expression in cultured cells treated with sixteen different medicinal plant extracts, all of which are used to treat anemia-related disorders in traditional Chinese medicine. Among the extracts tested that of *Caulis Spatholobi*, also called *Jixueteng*, showed the most potent inhibitory effect on hepcidin and was therefore selected for further mechanistic study. Our data indicated that the

extract of *Caulis Spatholobi* as a novel, potent hepcidin inhibitor, which may be further modified and optimized to become an effective herb supplement or treatment option for diseases in which hepcidin is overexpressed, such as ACD or IRIDA. We believe our studies pave ways to translate the findings to therapeutic target stratification in iron metabolism related diseases.

P04-19
ANTIOXIDATIVE STRESS BY SLC7A11 IS NECESSARY FOR IRON HOMEOSTASIS IN HEMOLYTIC ANEMIA

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Iron is an essential element for normal cellular function. However, iron is also a pro-oxidant, which causes oxidative stress by catalyzing Fenton reaction to generate reactive oxygen species (ROS). *Slc7a11* is a gene encoding the light-chain subunit of glutmate/cystine exchange transporter, which exports glutmate and uptakes cystine to generate glutathione (GSH) to protect cells from oxidative stress. But whether *Slc7a11* plays roles in iron metabolism is unknown. We found that iron stimulation can upregulate *Slc7a11* expression by qPCR *in vitro* and *in vivo*. When challenged with phenylhydrazine (PHZ), $Slc7a11^{-/-}$ mice showed more severe hemolytic anemia, delayed recovery and higher ROS level in hematopoietic system compared with wild type. Moreover, $Slc7a11^{-/-}$ macrophage showed impaired erythrophagocytosis and increased apoptosis. Our data indicate that antioxidative stress by Slc7a11 is necessary for iron metabolism in hemolytic anemia.

P04-20
HFE AND HEMOJUVELIN HAVE DISTINCT FUNCTIONS IN ACUTE IRON REGULATION OF HEPCIDIN

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Mammalian iron metabolism is delicately regulated by many modulators. Among them, hepcidin is the key hormone that negatively modulate iorn hemeostasis. Hepcidin induces internalization and further degradation of ferroportin1 (mammalian iron exporter), thus reduce iron absorbtion in intestinal and iron efflux in macrophages. Hepcidin deficiency leads to iron overload in major organs, which is the main reason that cause human hemochromatosis. Thus, hepcidin is a critical therapeutic target for curing hemochromatosis. The study of hepcidin regulation has great potentiality for the above subject, and is been launched for decades. HFE and hemojuvelin (herefor after HJV) are two hepcidin modulators discovered in the past 10 years. They are so important that defects of either will cause hemochromatosis in human and in mice. However, in one aspect of hepcidin regulation— acute iron regulation, the two regulators have controversial roles. HFE is proposed as a component in acute regulatory system, but HJV is not. However, in our study, we discovered that, in $Hfe^{-/-}$ mice, acute iron regulation was partially reserved while in $Hjv^{-/-}$ mice it was completely blocked. The hepcidin expression and the signal pathway were consistent with our observations. Either that unknown regulators synergize with HJV, or that HJV alone is enough to respond to acute iron stimulation and maintain basal hepcidin expression. Thus, this study further delineates the mechanisms controlling the regulation of hepcidin and provides evidence for the further therapeutic studies.