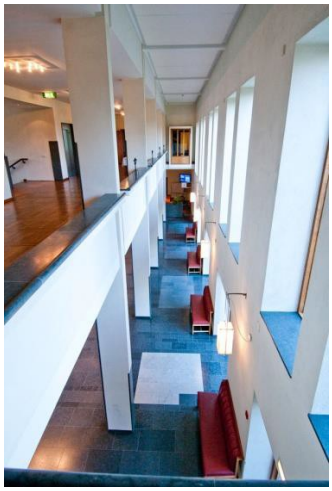
Nobelförsamlingen
The Nobel Assembly at Karolinska Institutet

Nobel Conference No. 62

Combat Metabolic Diseases – New Strategies

Nobel Forum, Karolinska Institutet, Stockholm, May 28 - 29, 2015



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The Nobel Assembly at Karolinska Institutet

Nobel Conference No. 62
Combat Metabolic Diseases – New Strategies
Nobel Forum, Karolinska Institutet, Stockholm, May 28 - 29, 2015

Day 1 Thursday 28th of May

08:15 - 09:00 Registration

09:00 - 09:10 **Welcome Note**
Per -Olof Berggren, Kerstin Brismar, Juleen Zierath

09:10 - 09:30 **Living with Diabetes**
Karin Hehenberger, Karolinska Institutet and Lyfebulb, NY, USA

Islet Cell Biology and Pathophysiology
Chair: Helena Edlund, Umeå University, Sweden

09:30 - 10:00 **Insight into Pancreatic Islet Cell Physiology/Pathology**
P-O Berggren, Karolinska Insitutet

10:00 -10:30 **Treating Types 1 and 2 Diabetes without Insulin: Rationale and Results**
Roger Unger, Southwestern Medical School, University of Texas, Dallas, TX, USA

10:30 - 11:00 COFFEE BREAK

11:00 - 11:30 **Genetic Insights into Human Beta Cells**
Andrew Hattersley, University of Exeter Medical School, Exeter, UK

Regulation of Metabolism through Specific Cell Signaling
Chair: Claes-Göran Östenson, Karolinska Institutet

11:30 - 12:00 **New Mechanisms of Insulin Receptor Signaling and Tissue Crosstalk in Insulin Resistance**
C Ronald Kahn, Joslin Diabetes Center, Harvard Medical School, Boston, MA, USA

12:00 - 13:30 LUNCH AT NOBEL FORUM

13:30 - 14:00 **FGF21: Fasting, Feasting and Pharmacology**
David J Mangelsdorf, Southwestern Medical School, University of Texas, Dallas,TX, USA

14:00 - 14:30 **AMP - Activated Protein Kinase: Regulating Energy Balance at the Cellular and Whole Body Levels**
Grahame Hardie, University of Dundee, Dundee, Scotland, UK

14:30 - 15:00 **Altered DNA methylation of glycolytic and lipogenic genes in skeletal muscle and liver from obese and type 2 diabetic patients**
Juleen Zierath, Karolinska Institutet

15:00 - 15:30 COFFEE BREAK

Regulation of Food Intake and Energy Balance
Chair: Martin Ingvar, Karolinska Institutet

15:30 - 16:00 **Leptin and the Neural Circuit Regulating Food Intake and Metabolism**
Jeffrey Friedman, Rockefeller University, NY, USA

16:00 - 16:30 **Metabolic Disease: Lessons from human genetics**
Sir Stephen O'Rahilly, Cambridge University, Cambridge, UK

16:30 - 17:00 **Role of Gut Microbiota in the Pathogenesis of Diabetes**
Fredrik Bäckhed, Wallenberg Laboratories Göteborg University, Sweden

Day 2 Friday 29th of May

Fat metabolism
Chair: Jan Nedergaard, Stockholm University

9:00 - 9:30 **Brown and Beige Fat: Mitochondrial Bioenergetics and a Novel Thermogenic Pathway**
Bruce Spiegelman, Dana-Faber Cancer Institute, Harvard Medical School, Boston, MA, USA

9:30 - 10:00 **Turnover of Human Fat Cells and their Lipid Content**
Peter Arner, Karolinska Institutet

10:00 - 10:30 **Human Brown Fat as a Therapeutic Target**
Sven Enerbäck, Göteborg University, Sweden

10:30 - 11:00 COFFEE BREAK

Late Complications
Chair: Mikael Rydén, Karolinska Institutet

11:00 - 11:30 **Diabetes Complications, New Mechanisms**
Kerstin Brismar, Karolinska Institutet

11:30 - 12:00 **Genetics of Diabetic Nephropathy**
Karl Tryggvason, Karolinska Institutet, Duke-NUS Graduate Medical School, Singapore

12:00 - 13:30 LUNCH AT NOBEL FORUM

13:30 - 14:00 **Immune Modulation of Lipoprotein Metabolism and Atherosclerosis**
Göran Hansson, Karolinska Institutet

14:00 - 14:30 **Epigenetic Changes, Oxidative Stress and Vascular Disease in Diabetes**
Francesco Cosentino, Karolinska Institutet

14:30 - 15:00 **Insulin: the Diabetes-Cancer connection**
Lewis Cantley, Weill Cornell Medical College, NY, USA

15:00 - 15:30 COFFEE BREAK

15:30 - 16:15 **Discussion and conclusions**

Combat Metabolic Diseases – New Strategies

Thursday 28th of May, 9:00-9:30

Welcome Note

Per-Olof Berggren, Kerstin Brismar, Juleen Zierath
Karolinska Institutet



LIVING WITH DIABETES

Karin Hehenberger, MD, PhD
Karolinska Institutet and Lyfebulb, NY, USA

Living with diabetes is more than just injecting insulin multiple times daily and closely monitoring your blood sugars. It requires a comprehensive approach to life, including working with a team of professionals and reassessing your approach to diet, exercise, stress and relationships. It can often be daunting to have a disease that just never gives you a break, one cannot take a vacation from diabetes. Diabetes affects your body and emotions, and the consequences of not dealing with it correctly or appropriately, are sometimes more serious than the disease itself. I have studied the disease from a multitude of perspectives, as a patient for more than 25 years, as a clinician, medical scientist and a life sciences professional assessing new treatments and solutions, but one of my major discoveries came after speaking to others who have the disease and sharing my ups and downs. Therefore I recommend to people living with diabetes to try to connect with people in a similar situation, in addition to become educated and associate with a great team of caregivers.

Islet Cell Biology and Pathophysiology

Thursday 28th of May, 9:30 - 11:30

Chair: Helena Edlund, PhD
Umeå University, Sweden

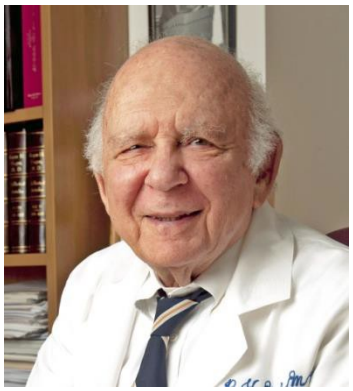
Field of interest: Beta cell function and type 2 diabetes

INSIGHT INTO PANCREATIC ISLET CELL PHYSIOLOGY/PATHOLOGY
Per-Olof Berggren, PhD
Department of Molecular Medicine and Surgery, Karolinska Institutet

Two major challenges in islet biology are to understand regulation of islet cell function and survival in the living organism and the extent to which experimental work in rodents reflects the human islet. By using the anterior chamber of the eye as a transplantation site and the cornea as a natural body window we can image islet cell biology *in vivo*, non-invasively, longitudinally and at single cell resolution. I will discuss novel aspects of this *in vivo* imaging approach involving metabolic islet imaging, reporter islet imaging, cell signaling, immune biology as well clinical islet transplantation. I will also discuss how this approach can be applied to human/non-human primate islets enabling direct comparison with rodent islets in terms of key regulatory steps in, for example, the insulin secretory process. Finally, I will share a few thoughts on future applicability of the living window approach.

TREATING TYPES 1 AND 2 DIABETES WITHOUT INSULIN: RATIONALE AND RESULTS

Roger Unger, MD,
Southwestern Medical School, University of Texas, Dallas, TX, USA



Insulin replacement maintains life in insulin-deficient type 1 diabetic (T1D) patients, but does not normalize glucoregulation or hemoglobin A1C (HgbA1C). Even optimally controlled subjects exhibit extreme glycemic volatility and HgbA1C values above 6%. Here we elucidate the mechanism of the glycemic volatility and propose a strategy to prevent it. In normal human islets 90% of the alpha cells are juxtaposed to beta cells. The functional implication of this juxtaposition was revealed by perfusing normal pancreata with a neutralizing anti-insulin serum and showing an immediate 150% rise in glucagon levels. In T1D islets, beta cells are absent and hyperglucagonemia is uncontrolled. Endogenous paracrine insulin levels are estimated at ~10 times the portal vein insulin levels and 100-fold above peripheral vein levels. Exogenous insulin levels following subcutaneous injection usually peak at 10% of portal vein concentrations. Thus, hyperglucagonemia is unsuppressed and its actions on the liver unopposed by sufficient hyperinsulinemia. Indeed, peripheral injected insulin fails to suppress the gluconeogenic enzyme, PEPCK, whereas endogenously secreted insulin, when stimulated by a complete glucose load suppresses. Neutralization of the glucagon receptor with a potent anti-glucagon receptor antibody also eliminates hepatic PEPCK protein expression as completely as secreted insulin, maintains a stable normal glycemia for over 10 days, and lowers HgbA1C to nondiabetic levels below 5% with no hypoglycemic episodes. These results indicate that normalization of glucoregulation and HgbA1c in T1D diabetes requires a bihormonal strategy that eliminates the alpha cell paracrinopathy.

GENETIC INSIGHTS INTO HUMAN BETA-CELLS

Andrew Hattersley, FRCP, FMedsci, FRS
University of Exeter, Exeter, UK

In neonatal diabetes the marked improvement in treatment by replacing insulin with sulphonylurea tablets for the 50% of patients with beta-cell potassium channel mutations has meant every case of neonatal diabetes should be referred rapidly for genetic testing. Exeter offers rapid and free testing for all patients diagnosed before 6 months and has received over 1400 referrals from 84 countries worldwide. The large number of referrals combined with the advances in sequencing methodology, has allowed us to identify many new monogenic subtypes (23 genetic aetiologies to date).

Patients with neonatal diabetes have fundamental problems with their beta-cells either due to reduced numbers (impaired development or early destruction) or from reduced function in each beta-cell. These accidents of nature are effectively human models akin to knockout animals and can give complementary scientific insights. This lecture will review recent advances in our knowledge of the beta-cell that have come from gene discovery and in depth phenotyping of patients with neonatal diabetes. The similarities and differences with rodent models will be discussed. A combined approach of animal models and observations in human monogenic diabetes is crucial to help our understanding of the human beta-cell.

Regulation of Metabolism through Specific Cell Signaling

Thursday 28th of May, 11:30 – 15:00

Chair: Claes-Göran Östenson, MD, PhD
Karolinska Institutet

Field of interest: Type 2 diabetes - Pathogenesis, prevention and novel treatment

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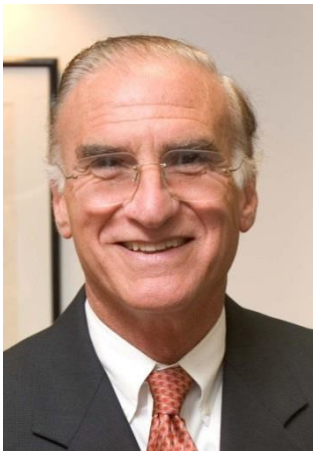
NEW INSIGHTS INTO INSULIN ACTION AND INSULIN RESISTANCE
C. Ronald Kahn, MD
Joslin Diabetes Center and Harvard Medical School, Boston, MA, USA



Insulin and IGF-1 have highly homologous receptors and signaling systems. To determine how insulin and IGF-1 receptors (IR and IGF1R) and their downstream signaling molecules regulate muscle and fat metabolism, and whole body physiology, we generated mice with combined muscle-specific or fat-specific knockout of either IR, IGF1R or both. While the single IR and IGF1R muscle knockouts show no effect on muscle growth, the double knockout MIGIRKO mice showed a >60% decrease in muscle mass. Interestingly, MIGIRKO mice also displayed fasting hypoglycemia due to increased basal glucose uptake in muscle. This was secondary to increased

levels of glucose transporter (Glut1 and Glut4) protein and translocation. On the other hand, transgenic overexpression of a kinase inactive IGF1R in muscle (MKR), which has been shown to act as a dominant negative for both IGF1R and IR, induced glucose intolerance and elevated triglycerides in both normal and MIGIRKO mice.

To investigate the physiological role of adipose specific insulin resistance in adult mice, we established an experimental mouse model in which we inactivated genes for the insulin receptor (named FindIRKO), IGF-1 receptor (FindIGKO) or both (FindIGIRKO) in adult mice with mice using a tamoxifen-inducible Cre ERT2 transgene under control of the adiponectin promoter. Both FindIRKO and FindIGIRKO, but not FindIGKO, mice showed acute, severe systematic insulin resistance with marked hyperglycemia and hyperinsulinemia, marked glucose intolerance, and severely impaired insulin tolerance tests as early as 2 days after induction of recombination. Thus, disruption of insulin signaling in adipose tissue can produce a syndrome of severe lipoatrophic diabetes. Insulin and/or IGF-1 receptor signaling is muscle, on the other hand, is required for maintenance of muscle mass, but not for normal glucose tolerance. Nonetheless, presence of a dominant negative IGF1R in muscle, even in the absence of functional IR or IGF1R, induces dysglycemia, indicating interactions between these receptors and other proteins in muscle is required for normal regulation of glucose homeostasis.

FGF21: FASTING, FEASTING, AND PHARMACOLOGY

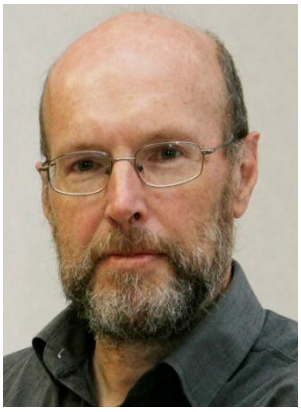
David J. Mangelsdorf, PhD
Howard Hughes Medical Institute, *University of Texas Southwestern Medical Center, Dallas, TX,USA*

Fibroblast growth factor 21 (FGF21) is a hepatokine that during fasting plays an important role in the adaptive response to starvation. However, in the setting of obesity and nutrient excess, FGF21 has potent pharmacologic effects that include weight loss and improved insulin sensitivity due in large part to FGF21's ability to mobilize oxidative substrates (the fuel) and stimulate a robust thermogenic response (the fire). In addition to these beneficial effects, FGF21 also inhibits growth, causes bone loss, and suppresses female reproduction. Attempting to dissociate the beneficial versus detrimental effects has revealed the existence of a complex peripheral and neural endocrine circuit, which coordinates the diverse physiologic and pharmacologic actions of FGF21.

AMP-ACTIVATED PROTEIN KINASE – MAINTAINING ENERGY HOMEOSTASIS AT THE CELLULAR AND WHOL BODY LEVELS

D. Grahame Hardie, FRS, FRSE, FMedSci

University of Dundee, Dundee, Scotland, UK



Almost all energy-requiring processes carried out by cells are driven by the high cellular ratio of ATP to ADP, analogous to the chemicals in an electrical cell or battery. The AMP-activated protein kinase (AMPK) monitors the state of this "battery charge" by sensing the ratios of AMP:ATP and ADP:ATP. If these ratios rise (signifying a fall in cellular energy), AMPK is activated and acts to maintain energy homeostasis by switching on catabolic pathways that generate ATP, while switching off biosynthetic pathways and other energy-requiring processes to conserve ATP. Genes encoding the three subunits of the AMPK heterotrimer are found in the genomes of essentially all eukaryotes, and it is clear that the system evolved to sense nutrients and regulate energy balance at the single cell level. However, in multicellular organisms the system has also adapted to respond to hormones that maintain whole body energy balance by modulating energy intake (i.e. feeding) and expenditure. Due to its critical role in maintaining energy balance at these twin levels, AMPK is involved in several chronic human diseases. For example: (i) the drug metformin, the primary treatment for type 2 diabetes, now appears to exert its insulin-sensitizing effects by activating AMPK; (ii) the upstream kinase required for AMPK activation, LKB1, may exert some of its tumour suppressor effects via AMPK; (iii) the natural product salicylate (from which aspirin was derived) activates AMPK, and this may account for at least some of its anti-inflammatory effects.

ALTERED DNA METHYLATION OF GLYCOLYTIC AND LIPOGENIC GENES IN SKELETAL MUSCLE AND LIVER FROM OBESE AND TYPE 2 DIABETIC PATIENTS

Juleen R. Zierath, PhD

Department of Molecular Medicine and Surgery, Karolinska Institutet

Metabolic diseases such as diabetes and obesity are associated with profound alterations in gene expression, caused by genetic and environmental factors. Epigenetic regulation of gene expression by DNA methylation has become increasingly recognized as an important component in the etiology of metabolic disease. DNA methylation is a major epigenetic modification controlling gene expression in physiological and pathological states. Environmental factors at all ages can modify DNA methylation in somatic tissues, suggesting that DNA methylation is a more dynamic process than previously appreciated. Given the importance of lifestyle factors in metabolic disorders, DNA

methylation provides a mechanism by which environmental factors, including diet and exercise, can modify genetic predisposition to disease. Thus, we have performed genome-wide methylome and transcriptome analysis in skeletal muscle and liver from severely obese patients with or without type 2 diabetes to discover aberrant pathways underlying the development of insulin resistance. Severely obese non-diabetic and type 2 diabetic patients have distinct alterations in the skeletal muscle and hepatic methylome and transcriptome. In skeletal muscle, obesity was associated with altered expression of a subset of genes enriched in metabolic process and mitochondrial function. After weight loss, the expression of the majority of the identified genes was normalized to levels observed in normal weight healthy controls. In liver, obesity shifts the epigenetic program towards increased lipid production, which may exacerbate the development of hepatic insulin resistance. In conclusion, dynamic changes in DNA methylation may be an early event controlling transcription of metabolic genes involved in the regulation of insulin sensitivity in human obesity. Our results highlight the importance of environmental factors in forming the metabolic memory of somatic cells.

Regulation of Food Intake and Energy Balance

Thursday 28th of May, 15:30-17:00

Chair: Martin Ingvar, MD, PhD
Karolinska Institutet

Field of interest: Patient/health care - interaction and the neurophysiology of health seeking behaviour

LEPTIN AND THE NEURAL CIRCUIT REGULATING FOOD INTAKE AND METABOLISM
Jeffrey Friedman, MD, PhD
Rockefeller University, NY, USA

It has been known since the work of Claude Bernard that the CNS can regulate peripheral glucose metabolism. To identify specific neural populations that regulate plasma glucose, we first generated mice that express cre specifically in neurons that express glucokinase, a key enzyme

in glucose sensing. To probe the effect of modulating the activity of these (and other) neurons, we have developed a novel method that enables the modulation of neural (and other cell) activity using radio waves or magnets. This method referred to as NICR, Non-Invasive Cell Regulation, uses radiowaves (RF) or magnetic fields (MF) to modulate neural activity. The system is composed of two components; ferritin and TRPV1. In transduced cells, the targeted neurons express modified ferritin which generates 5-8nm iron oxide nanoparticles. Ferritin is tethered to TRPV1, a temperature sensitive, cation channel. RF and/or MF penetrate tissue resulting in heating, motion and/or a voltage change of the nanoparticle thus opening the channel leading to Ca++ and Na+ entry and neural activation. Furthermore, point mutations of TRPV1 channel (TRPV1Mutant) alter its ion conductance from cations to chloride ions thus allowing non-invasive silencing of neurons. We find that activation of glucokinase cre neurons in the ventromedial hypothalamus (VMH) using NICR doubles blood glucose by increasing plasma glucagon while inhibiting these neurons decreases blood glucose by half and increasing plasma insulin. We also find that activation of glucokinase neurons in the VMH by exposing animals to a magnetic field increases food intake. These studies reinforce the importance of neural populations in the CNS to control peripheral metabolism and also provide a general method for the non-invasive regulation of cellular activity in adult and developing animals. This approach also has translational potential, which is currently being explored.

METABOLIC DISEASE: LESSONS FROM HUMAN GENETICS

Sir Stephen O'Rahilly MD FRS FMedSci
University of Cambridge, Cambridge, UK

The genetic component of quantitative metabolic traits is complex with a mixture of common alleles of small effect and rarer alleles of larger effect. We have principally focused on finding the latter through the study of extreme human phenotypes of obesity and insulin resistance, including lipodystrophy. By applying both candidate and hypothesis-free genetic approaches we have identified multiple different genetic variants that cause highly penetrant forms of these diseases. Through detailed phenotypic studies in humans and relevant murine and cellular models, these disorders continue to provide new insights into the physiology and pathophysiology of energy balance and metabolism.

ROLE OF GUT MICROBIOTA IN THE PATHOGENESIS OF DIABETES

Fredrik Bäckhed, PhD

Wallenberg laboratories, University of Gothenburg, Sweden

The human gut is inhabited with trillions of bacteria, gut microbiota, that have co-evolved with us and affect our physiology within and outside the gut. The gut microbiota has recently been suggested as a novel contributor to obesity and related comorbidities, such as type 2 diabetes (T2D) and cardiovascular diseases (CVD). We recently found that the gut microbiota is altered in patients with CVD and T2D and that we can classify patients and T2D patients based on the microbiota. Using germ-free mice we have causally linked the gut microbiota to obesity and insulin resistance and have recently found that the gut microbiota modulates adipose inflammation, bile acid signaling, and enteroendocrine cell function. However, the underlying mechanisms(s) by which the gut microbiota induces signaling is yet to be dissected. By combining defined microbial communities, multi-omics approaches with genetically modified mice we are beginning to clarify host microbial interactions and their metabolic responses.

Fat metabolism

Friday 29th of May, 9:00-11:00

Chair: Jan Nedergaard, PhD

Stockholm University

Field of interest: brown adipose tissue – uncoupling protein(s) - thermogenesis

BROWN AND BEIGE FAT: MITOCHONDRIAL BIOENERGETICS AND A NOVEL THERMOGENIC PATHWAY

Bruce Spiegelman, PhD
Harvard Medical School, Boston, MA, USA

We have identified several key regulators in the adipose lineage over the past few decades, including PPARγ PGC1α and PRDM16. These studies have led to the conclusion that there at least 3 distinct fat cell types: white, brown and beige. Increases in the amounts or activities of classical brown fat or beige fat in experimental models can have anti-obesity and anti-diabetes effects. We have approached the function of beige fat by purifying mitochondria from both brown and beige fat and asking about difference through the use of isobaric-tagging linked protein mass spectrometry. We show now that the beige fat has a second thermogenic pathway, in addition to the UCP1-mediated thermogenesis. Mitochondria from beige fat run a novel and robust futile cycle of creatine-a creatine phosphate cycle, which dissipates chemical energy via hydrolysis of the high energy phosphate on creatine. We call this pathway the creatine futile cycle (CFC). Beige but not brown fat cell mitochondria are stimulated to respire when supplied with creatine and this creatine acts sub-stoichiometrically, with regard to ADP. There is also phosphocreatine phosphatase activity in extracts of beige mitochondria. Finally, the proteins of this creatine-PO3 cycle are induced when UCP1 KO mice are adapted to the cold. Moreover, chemical interference with this creatine cycle in UCP1 KO mice causes a dramatic drop in body temperature without an alteration in shivering. These data illustrate a novel and robust pathway of energy expenditure centered on creatine metabolism in beige adipose tissues.

TURNOVER OF HUMAN FAT CELLS AND THEIR LIPID CONTENT

Peter Arner, MD, PhD
Department of Medicine, Karolinska Institutet

Human fat cells are in a highly dynamic state. On average 10% of all the fat cells are renewed every year throughout adult life. This process is influenced by body weight status and individual variations in the turnover rate determine if you have many small (hyperplasia) or few large fat cells (hypothrophy). The latter is associated with several metabolic disorders. Recently some genes have been identified which regulate size and number of fat cells in humans and they are potential treatment targets for metabolic disorders such as type 2 diabetes. A potential source for human fat cells is bone marrow which may pay the way in the future for using modified bone marrow cells to treat metabolic disease by targeting adipose tissue. The turnover of the lipids in the fat cells is even higher

than fat cells themselves. During the life span of a human fat cell its lipid content is renewed about 6 times. Lipid turnover is also influenced by body weight status and low turnover is associated with insulin resistance as well as genetic and common forms of dyslipidemia. Preliminary data suggest that genetic variations influences lipid turnover and also that there are regional differences in this turnover between inner (visceral) and outer (subcutaneous) fat. Therapies that enhance lipid turnover in fat cells might also be used to combat metabolic disorders.

HUMAN BROWN FAT AS A THERAPEUTIC TARGET

Sven Enerbäck, MD, PhD

Department of Medical Genetics, University of Gothenburg, Sweden

The metabolic role of BAT in humans is far from being fully understood, but once we have defined the mechanisms involved we may have exciting opportunities to develop new therapies for obesity and obesity-related diseases such as type 2 diabetes, cardiovascular diseases, and cancers. New data suggest that even other diseases that are not immediately associated with metabolic disturbances, such as neoplastic disease, asthma and poor bone quality, are linked to obesity – emphasizing the urgent need to develop effective treatments. The key challenge is now to gain new insights that will ultimately lead to novel, effective treatments by stimulating BAT formation and activity in humans. Such studies will make use of BAT as a unique organ with an inherent ability to safely convert chemical energy to heat, and thus help to restore a healthy metabolism in a hypercaloric environment.

Late Complications

Friday 29th of May, 11:00-15:00

Chair: Mikael Rydén, MD, PhD

Karolinska Institutet

Field of interest: Human adipose tissue and its link to metabolic complications

DIABETES COMPLICATIONS, NEW MECHANISMS

Kerstin Brismar, MD, PhD
Department of Molecular Medicine and Surgery, Karolinska Institutet

There is an epidemic global increase of diabetes followed by increased risk for cardiovascular disease, kidney failure and slow-healing foot ulcer/amputation. Several studies have shown that 70-80% of subjects with cardiovascular disease have diabetes or pre-diabetes as an important cause of the disease. *Today there is no effective prevention or treatment* for many of the late complications. *We have established new principles that explain the mechanisms* behind the development of diabetes complications which make new treatment strategies possible.

Our main hypothesis based on our and others research is that high glucose leads to capillary hypoxia, increased production of free radicals and impaired adaptation both to low oxygen (impaired HIF activation) and increased production of radicals as well as impaired activity of Notch and the IGF/IGFBP system. These pathological changes lead to neuropathy and arterial disease via local arterial inflammation and oxidative stress. Impaired IGF/IGFBP system causes disturbed tissue repair and regeneration. Lost adaptation to increased expression of radicals is due to the fact that high glucose is associated with insufficient antioxidant defense, e.g. a low production of the antioxidants coenzyme Q and carnosine. *By normalizing HIF-I and Notch activity and the endogenous antioxidant capacity* we have shown in animal models of diabetes that *we can prevent late diabetes complications*.

DIABETIC NEPHROPATHY SUSCEPTIBILITY GENES – A POPULATION GENETICS AND WHOLE GENOME SEQUENCING APPROACH

Karl Tryggvason, MD, PhD
Karolinska Institutet, Stockholm and Duke-NUS Graduate Medical Singapore, Singapore

Diabetic nephropathy (DN) underlies half of all chronic kidney disease cases worldwide. Epidemiological studies have revealed that DN is partially genetically regulated, such that only 30-50 % of diabetic patients develop progressive kidney disease that requires dialysis or kidney transplantation. DN is usually associated with retinopathy, the most common cause of blindness in adult, as well as limb amputations and general angiopathy. Thus far, candidate gene and GWAS approaches have not identified any

DN genes, but whole genome linkage analyses suggest a locus on chromosome 3q. Finns have the highest incidence of type 1 diabetes (T1D) and about 30 % of them develop DN. Since the Finnish population is highly homogeneous and has been useful for identifying a number of disease genes, we decided to search for susceptibility genes in Finns with T1D. A discovery cohort of 90 sib pairs with T1D discordant for nephropathy (DSP) has been collected and subjected to whole genome sequencing which has yielded a large amount of potential candidate genes only found in cases or controls. Mutated candidate genes are validated in a Finnish T1D replication cohort containing >3,000 unrelated T1D patients discordant for nephropathy. The candidate genes are subsequently validated in a T1D diabetic zebrafish line, as well as mice harboring the mutations generated with the CRISPR/Cas9 genome editing system. Initial results of this project will be presented. This work has been has been carried out together with the groups of Per-Henrik Groop, University of Helsinki and Enrico Petretto at Duke-NUS, Singapore.

IMMUNE MODULATION OF LIPOPROTEIN METABOLISM AND ATHEROSCLEROSIS

Göran K Hansson, MD, PhD

Center of Molecular Medicine and Department of Medicine; Karolinska University Hospital Karolinska Institutet

Atherosclerosis is a chronic inflammatory condition initiated by retention and accumulation of cholesterol-containing lipoproteins, in particular low-density lipoprotein (LDL), in the artery wall. This triggers pathological responses of immune cells that lead to atherosclerotic plaque formation. T cells are present during all stages of the disease, and play an essential role in the initiation and progression of plaques. A significant proportion of them are CD4+ cells that recognize components of LDL as autoantigen. Whereas most T effector cell responses have been suggested to aggravate atherosclerosis, regulatory T cells (Tregs) have been shown to limit inflammation and inhibit the formation of lesions. In addition to their effects on the local pathological process, T cells and their released mediators modulate systemic lipid metabolism and can increase risk of CVDs. T cell dependent antibody responses, as well as natural IgM antibodies, may also modulate disease development by removing LDL or through effector responses.

Modulation of immune responses by vaccination, antibody therapies, dendritic cell based-therapies, and using metabolites involved in immune regulation has shown benefits against atherosclerotic plaque progression in animal models. This holds promise for development of novel prevention and therapy against atherosclerotic cardiovascular disease.

EPIGENETIC CHANGES, OXIDATIVE STRESS AND VASCULAR DISEASE IN DIABETES

Francesco Cosentino, MD, PhD
Department of Medicine, Karolinska University Hospital, Karolinska Institutet

Type 2 diabetes is associated with increased cardiovascular disease risk, even after intensive glycemic control. Oxidative stress is a prominent feature of cardio-metabolic disturbances leading to endothelial dysfunction and atherosclerosis. Understanding redox signaling in the context of diabetes is of paramount importance for the development of mechanism•based therapeutic strategies. Adverse chromatin remodeling is emerging as a key driver of vascular damage and may play a role in this setting.

INSULIN: THE DIABETES-CANCER CONNECTION

Lewis C. Cantley, PhD
Weill Cornell Medical College, New York, NY, USA

Phosphoinositide 3-Kinase (PI3K) is a central enzyme in a signaling pathway that mediates cellular responses to insulin and other growth factors. The generation of PIP_3 at the plasma membrane in response to activation of PI3K by growth factors results in the initiation of downstream signaling cascades that control a variety of cellular responses. The AKT/TORC1 signaling pathway downstream of PI3K is highly conserved from worms and flies to humans and genetic analysis of the pathway has revealed a conserved role in regulating glucose metabolism and cell growth. Based on deletion of genes encoding the catalytic or regulatory subunits of PI3K in the mouse, PI3K mediates insulin dependent regulation of glucose metabolism, and defects in activation of this pathway result in insulin resistance. In contrast, mutational events that lead to hyperactivation of the PI3K pathway result in cancers. Activating mutations in PIK3CA, encoding the p110alpha catalytic subunit of PI3K or inactivating mutations in PTEN, a phosphoinositide 3-phosphatases that reverses the effects of PI3K, are among the most common events in solid tumors. PI3K driven tumors are FDG-PET positive and turning off PI 3-Kinase with PI3K inhibitors that are in human clinical trials results in an acute decline in FDG-PET signal that precedes tumor shrinkage. Importantly, there is increasing evidence that some tumors express high

levels of insulin receptor and activate PI3K due to elevated serum insulin in patients with insulin resistance. These results suggest that elevations in serum insulin may partially explain the link between obesity, diabetes and cancers. The role of PI3K inhibitors for treating cancers in mouse models and in human trials will be discussed.