Differences between white, brown and “brite” fat tissue

The latest results on the different metabolic pathways used by white and brown fat cells and potential transformations between the two cell types were discussed at the conference “Metabolism 2012: From Signalling to Disease” held on 15th and 16th November 2012 in Heidelberg. A special cell type, so-called “brite” adipocytes, may have the potential to be used in the treatment of obesity and related metabolic diseases such as diabetes.

The most widespread epidemic disease around the world is not AIDS or malaria or any other transmissible disease; it is obesity, now the major global disease. In contrast to around twenty years ago when obesity mainly affected Western industrial countries, it has now become a medical condition of major concern on all continents, especially in emerging countries such as China, India, Mexico and South Africa. Central (or abdominal) obesity is most commonly caused by excessive food energy intake and associated with a lack of physical activity. Obesity is one of the symptoms of a severe metabolic disorder called “metabolic syndrome”. Metabolic syndrome is also characterised by raised blood pressure, altered blood fat values (high triglyceride and reduced HDL cholesterol levels) and the insulin resistance of body cells, which is characteristic of type 2 diabetes, more commonly associated with adults but also on the rise in children and adolescents.

Metabolic diseases are associated with inflammatory reactions and arteriosclerotic depositions in the vascular walls, and sufferers have an increased risk of developing cardiovascular diseases and cancers such as liver cancer. The disrupted signal transduction pathways that cause various metabolic diseases such as obesity and diabetes were the topic of the international conference.
“Metabolism 2012: From Signalling to Disease”, which was organised by the German Cancer Research Center (DKFZ) and held in Heidelberg in November 2012. The principal conference organiser was Professor Dr. Stephan Herzig, who heads a research department on diabetes and cancer (Molecular Metabolic Control) that is jointly run by the ZMBH (Centre for Molecular Biology), Heidelberg University and Heidelberg University Hospital. The conference focused mainly on the functions of fat tissue.

The largest endocrine organ

Obesity is characterised by excessive amounts of white fat tissue, which mainly consists of adult white adipocytes whose major function is to store energy in the form of triglycerides. The adipocytes are located in large lipid-storage vacuoles in the cytoplasm; these vacuoles can take up as much as 95% of the entire cell volume. The storage (lipogenesis) and the provision (lipolysis) of energy are regulated by hormones, including insulin. This is why insulin-resistant diabetes is linked to metabolic disorders of the fat tissue. In addition to high blood glucose levels, the blood of people suffering from obesity contains high quantities of triglycerides, which is a hallmark of metabolic syndrome.

Relatively recently, scientists found that white fat tissue has a high secretory activity; the pharmacologist Professor Eugen Verspohl refers to white fat tissue as the “largest endocrine organ of the human body”. Adipocytes and the macrophages and monocytes that accumulate in the fat tissue secrete around one hundred different messenger substances and secretion products, including angiotensin, adiponectin and the PPARy (peroxisome proliferator-activated receptor gamma) receptor, which is the main regulator of white fat tissue and counteracts resistance to insulin. They also secrete inflammation markers such as TNFα (tumour necrosis factor alpha), prostaglandin E1, interleukin 6 and C-reactive protein, all of which suggest that there is a link between chronic inflammation and obesity.

Brown fat tissue

The conference dealt extensively with brown fat tissue. Brown adipocytes contain many small lipid vacuoles. In contrast to the univacuolary white fat cells, brown adipocytes contain a large number of vacuoles. The major function of fat tissue is the generation of heat (thermogenesis). Heat is generated as the fatty acids resulting from the metabolism of triglycerides in the mitochondrial respiratory chain activate a protein called UCP1 (uncoupling protein 1). This protein decouples the respiratory chain from the synthesis of energy-rich chemical compounds (ATP), resulting in the freeing up of energy in the form of heat. The darker colour of brown adipose tissue is due to the increased number of mitochondria, which have a high iron content.
Small hibernating mammals like dormice have large amounts of brown fat tissue. After many months of hibernation during which the animals’ body temperature is much lower than normal, these stores help the animals to rapidly reach their normal temperature of 37°C. Human infants are born with a large amount of brown fat, which is important to avoid the potential lethal effects of cold. Adults usually only have minute remnants of brown fat. However, recent studies have shown that adipocytes are still present in adults in the upper back and neck area and that adipocytes can continue to be produced a long time after birth. These cells are much more active in individuals who have adjusted to lower temperatures – i.e. room temperatures of 16°C rather than 22°C - and produce more heat.

Stephan Herzig and his team at the DKFZ found that brown adipocytes accumulated within the white fat tissue in mice that were kept at low temperatures. These adipocytes are referred to as “brite” (brown in white) adipocytes. [In analogy to brite adipocytes, brown fat cells that were discovered in skeletal muscles are referred to as “bruscle” (brown in muscle) adipocytes]. Working with German and Swiss scientists, the Heidelberg researchers found that the fat tissue of cold-
adapted mice contains higher than normal levels of the enzyme cyclooxygenase 2 (COX-2; eds. note: elevated levels of COX-2 are found during inflammation). The researchers found that the raised COX-2 production in the fat tissue was associated with an increase in UCP1, a decoupling protein that is typical for brown tissue. The experimental overexpression of COX-2 (irrespective of coldness) also resulted in the accumulation of brown adipocytes in white fat tissue.

In contrast to control animals, these mice (as well as the cold-adapted mice) did not gain weight despite being fed high-calorie food. COX-2 catalyses the key step in prostaglandin biosynthesis. Prostaglandins regulate inflammatory mediation and are also involved in the onset of pain. The researchers have been able to show that prostaglandins trigger the development of “brite” cells, i.e. cells located within white fat tissue which have the properties of brown adipocytes. Together with the discovery of cold-activated brown fat tissue in adult individuals, these results open up a fascinating perspective for the treatment of obesity. If it were possible to stimulate an increase in the number of brown fat cells in obese people, this could lead to a new method of weight loss, since the energy consumption of such patients resulting from the elevated lipolysis of white fat could be considerably increased.

How do “brite” cells develop?

The transplantation of brown fat tissue has also been discussed as a potential therapy for obesity. However, a lot of basic research is still required before this could actually happen. While it was previously assumed that white and brown adipocytes could be converted into one another, new results suggest that the actual scenario is much more complicated. Professor Jan Nedergaard, a pioneer in this field of research, and his team at the Wenner-Gren Institute at the University of Stockholm believe that white and brown fat cells have different developmental lineages and cannot simply be converted into one another. Professor Barbara Cannon from Nedergaard’s group of researchers gave a talk at the Heidelberg conference, in which she reported that brown adipocytes are much more closely related to skeletal muscle cells. The research done by the Swedish researchers suggests that the two cell types arise from a common precursor cell called adipomyocyte. The researchers also found two types of white fat cells that can be derived from a common precursor cell (adipoblast): the “genuine” white adipocytes and the “brite” adipocytes, which express the decoupling protein UCP1 (a property which up until now was regarded as the only marker of brown adipocytes).

While the Swedish researchers base their hypotheses mainly on cell culture experiments, recent results obtained from cold-adapted mice show that the individual fat storage depots of the animals have different marker gene expression patterns: storage depots of classical brown fat tissue, storage depots of “brite” fat tissue (sometimes also referred to as beige tissue) and storage depots of genuine white tissue.

Other scientists believe that the “brite” adipocytes develop mainly from transdifferentiating white fat cells. Further evidence for this assumption comes from findings obtained by Bruce Spiegelman’s team of researchers at the Dana Faber Cancer Institute at the Harvard Medical School in Boston, USA, who discovered a new hormone called irisin. Spiegelman, who is another one of the big names in research into the fat metabolism, discovered the nuclear receptor PPARy, which controls fat development and the development of type 2 diabetes. In a recent publication (Nature 2012, Jan 11), Spiegelman’s group of researchers reports that some effects of exercise on muscle are mediated by the transcriptional co-activator PPARy co-activator-1 α (PGC1-α). PGC1-α expression in muscle stimulates an increase in expression of FNDC5, producing irisin. This hormone induces uncoupling protein 1 (UCP1) expression, thereby enhancing metabolic
uncoupling and caloric expenditure due to its effect on white adipocytes. As a result, white fat cells are converted into “brown in white”, i.e. “brite” adipocytes.

In addition, PPARγ activation has been linked to beneficial antidiabetic effects, which is why synthetic PPARγ ligands are already used for the medical treatment of patients suffering from type 2 diabetes. Future research will need to focus on the identification of the receptor’s endogenous factors. Greater understanding of the complex molecular signalling pathways that control the sugar- and fat metabolisms as well as adipocyte differentiation, have the potential to open up new therapies for obesity and diabetes.