Review

CellPress

Insulin resistance and impaired adipogenesis

Birgit Gustafson, Shahram Hedjazifar, Silvia Gogg, Ann Hammarstedt, and Ulf Smith

The Lundberg Laboratory for Diabetes Research, Department of Molecular and Clinical Medicine, Sahlgrenska Academy at the University of Gothenburg, SE-41345 Gothenburg, Sweden

The adipose tissue is crucial in regulating insulin sensitivity and risk for diabetes through its lipid storage capacity and thermogenic and endocrine functions. Subcutaneous adipose tissue (SAT) stores excess lipids through expansion of adipocytes (hypertrophic obesity) and/or recruitment of new precursor cells (hyperplastic obesity). Hypertrophic obesity in humans, a characteristic of genetic predisposition for diabetes, is associated with abdominal obesity, ectopic fat accumulation, and the metabolic syndrome (MS), while the ability to recruit new adipocytes prevents this. We review the regulation of adipogenesis, its relation to SAT expandability and the risks of ectopic fat accumulation, and insulin resistance. The actions of GLUT4 in SAT, including a novel family of lipids enhancing insulin sensitivity/secretion, and the function of bone morphogenetic proteins (BMPs) in white and beige/brown adipogenesis in humans are highlighted.

Insulin resistance: a major driver of the global type 2 diabetes epidemic

Diabetes, and particularly type 2 diabetes (T2D), is increasing at an epidemic scale worldwide. In China alone it was recently estimated that 11.6% of the adult population, around 136 million people, has diabetes [1]. Globally, it is expected to afflict around 500 million people by 2030. The epidemic of T2D is attributed to our changed life-style, with less physical activity and fast-food consumption ultimately leading to obesity. T2D develops when the insulin secretory capacity is unable to compensate for the obesity-related increase in insulin resistance.

Obesity as defined by body mass index (BMI) is a heterogeneous condition and around 30% of obese individuals do not show the associated metabolic complications and are considered metabolically healthy obese [2], although also this may not be an entirely benign condition [3]. However, a similar number of non-obese individuals exhibit markers of a dysmetabolic state and reduced insulin sensitivity [4]. Thus, BMI *per se* is not a sufficiently sensitive marker of individual risk for obesity-related metabolic complications. In addition, adipose tissue distribution is important and an abdominal distribution, defined as a large waist circumference, markedly enhances both cardiovascular and diabetes risk for a given BMI [5,6].

The molecular abnormalities associated with obesity-induced insulin resistance in insulin-responsive tissues and organs (i.e., skeletal muscle, adipose tissue, and the liver) have been investigated extensively and are well established. Increased lipids plays an important role and can promote insulin resistance through the activation of various signaling pathways including protein kinase C (PKC), ceramide, and other lipid molecules and the accumulation of lipids in target tissues can induce insulin resistance (lipotoxicity) [7]. One important factor that precipitates this is the inability to store excessive lipids in SAT, which leads to 'lipid overflow' into ectopic sites that are able to accumulate lipids but at the expense of inducing lipotoxicity and negative metabolic consequences associated with insulin resistance.

Here we review current knowledge about the ability of SAT to store excess lipids and prevent accumulation in ectopic sites, as well as the possibility that white adipose tissue (WAT) under appropriate signaling conditions can assume an oxidative beige/brown phenotype and thereby also promote weight loss and increase insulin sensitivity.

SAT expandability and consequences for ectopic fat accumulation and insulin resistance

SAT is the largest adipose tissue depot in humans and also the preferred site to store excess fat. However, it has limited ability to expand and, when its storage capacity is exceeded, fat is stored in other metabolically more harmful ectopic lipid depots, including intra-abdominal/visceral sites, liver, myocardium, epi/pericardial and perivascular sites, and skeletal muscles. The importance of SAT expansion in accommodating excess lipids safely has been clearly demonstrated in several different genetically engineered animal models. For instance, overexpressing adiponectin in adipose tissue in mice leads to profound subcutaneous obesity, but with hyperplastic 'healthy' adipose tissue, and the mice are at least as insulin sensitive as their lean littermates [8]. Similarly, inhibiting adipose tissue development in lipoatrophic or lipodystrophic animal models leads to marked insulin resistance, ectopic liver fat accumulation, and reduced glucose tolerance similar to what is seen in human lipoatrophic/lipodystrophic diabetes [9]. This concept was supported by a recent study using isotope-based tracing of murine adipogenesis *in vivo*. It was shown that age-dependent inhibition of SAT hyperplastic potential in obesity was associated with the

Corresponding author: Smith, U. (ulf.smith@medic.gu.se).
Keywords: obesity; type 2 diabetes; insulin resistance; BMP4; Gremlin1; adipogenesis.

1043-2760/
 http://dx.doi.org/10.1016/j.tem.2015.01.006

development of insulin resistance and thus that hypertrophic SAT is an important link to obesity-induced metabolic dysfunction [10].

The individual 'set point' and ability to expand SAT is probably both genetically determined and modified by prepubertal lifestyle factors [11]. At present, it can be determined only indirectly from, for instance, SAT cell size in relation to the amount of body fat/BMI and/or the accumulation of ectopic fat. In contrast to males, females seem to maintain an ability to recruit new cells in the thigh/gluteal region in adulthood [12], which is consistent with the reduced accumulation of ectopic visceral fat in obese women compared with obese men [7]. By contrast, a reduced ability to expand SAT is seen in Asian populations and this is accompanied by early accumulation (i.e., at low BMI) of ectopic visceral fat [13].

The association between increased visceral fat, the various metabolic complications of obesity, and the risk of developing diabetes and cardiovascular disease is well established and waist circumference is used as an easily measured clinical indicator of this [5,6]. There is also a close correlation between the amounts of fat accumulated in the various ectopic depots, indicating that they are all used for storage when SAT is unable to accommodate more excess fat [14]. This multicompartmentalization of ectopic fat also amplifies the dysmetabolic consequences associated with insulin resistance as seen in the MS, with, for instance, increased hepatic very-low-density lipoprotein (VLDL) cholesterol and triglyceride (TG) release and lower high-density lipoprotein (HDL) cholesterol levels [15]. Consistent with this concept, the large Dallas Heart Study showed that the amount of ectopic fat rather than the amount of SAT correlated with the metabolic complications, including degree of insulin resistance and the prospective risk of developing T2D in obese individuals [16].

SAT adipose cell size and phenotype are related to insulin resistance and T2D

The capacity of SAT to accommodate excess fat is regulated by the ability of the existing adipose cells to expand (hypertrophy) and/or recruit precursor cells into adipogenic differentiation (hyperplasia). Large clinical studies have shown that SAT adipose cell size expansion is limited to an upper maximal size and that hypertrophic, rather than hyperplastic, obesity is associated with insulin resistance and dyslipidemia also for a given BMI [17,18]. Inability to recruit new adipose precursor cells (both mesenchymal stem cells and committed preadipocytes) during caloric excess leads to inappropriate expansion of the available adipose cells and induction of the associated negative metabolic consequences.

Many studies, both in humans and in animal models, have shown that hypertrophic expansion of SAT adipose cells leads to a dysfunctional adipose tissue associated with increased tissue fibrosis, infiltration and activation of immune/inflammatory cells, increased lipolysis, local and systemic insulin resistance, and altered adipokine secretion [19]. As expected, hypertrophic obesity and adipose cell size are also related to the various aspects of the MS [17–20] (Figure 1). Waist circumference, a well-established marker of ectopic visceral fat accumulation and future risk of developing T2D [6,16], is also positively correlated with SAT adipose cell size.

In a detailed study of obese individuals with and without insulin resistance, Kloting *et al.* [2] demonstrated that insulin-sensitive obesity is characterized by smaller SAT adipocytes, higher secretion of the adipocyte differentiation marker adiponectin, and reduced adipose tissue inflammation and number of infiltrating macrophages. The strongest predictor of insulin sensitivity was the combination of circulating adiponectin and infiltrating macrophages in the adipose tissue [2].

An important finding relating SAT adipogenesis to insulin sensitivity and risk of T2D came from looking at individuals with a family history of T2D. Healthy first-degree relatives (FDRs) of individuals with T2D have a larger waist circumference and inappropriately enlarged SAT adipose cells for a given BMI compared with matched subjects lacking known heredity for T2D or having heredity for overweight/obesity [21]. These findings are consistent with reduced SAT adipogenesis and ability to recruit new adipose cells during caloric excess and would thus

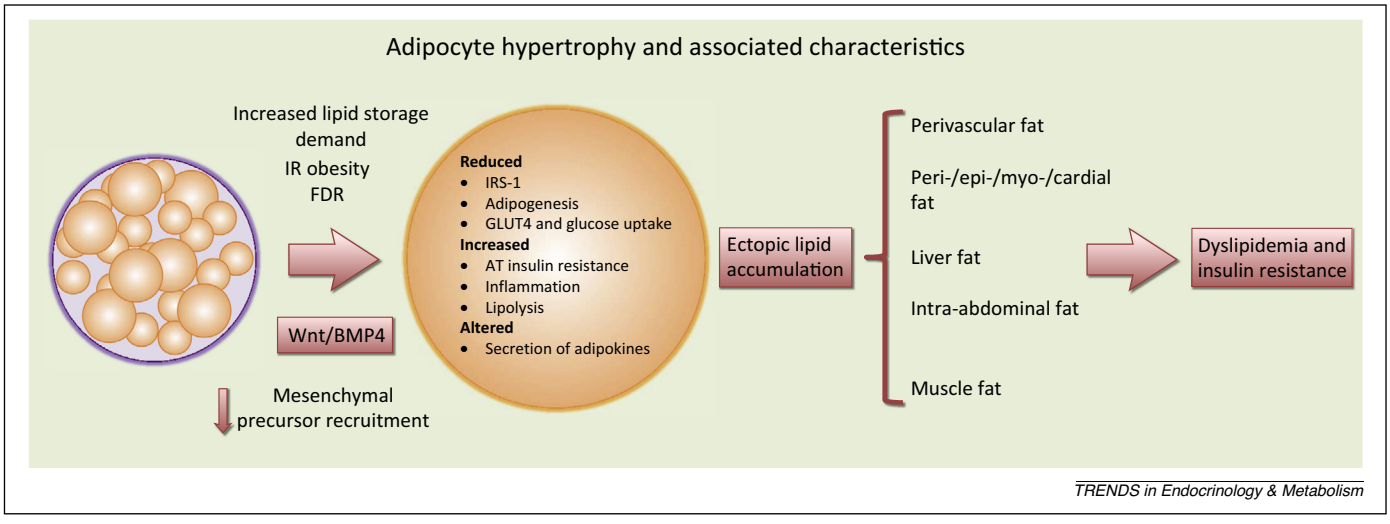

Figure 1. Characteristics of adipocyte cell hypertrophy. Adipocyte expansion with dysregulated subcutaneous adipose tissue (SAT) promotes ectopic fat accumulation and the metabolic syndrome. Adipocyte hypertrophy characterizes the SAT of insulin-resistant obesity and nondiabetic first-degree relatives of type 2 diabetes (T2D) patients.