Adipose tissue: from amorphous filler to metabolic mastermind

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Adipose tissue plays a central role in the control of systemic glucose homeostasis through two major mechanisms: fat storage and secretion of specific cytokines known as adipokines. Fat storage in adipose tissue is critically important, as it prevents lipid deposition in liver and muscle, which in turn results in insulin resistance and increased risk of type 2 diabetes. Secretion of adipokines, such as leptin, protects from fuel depletion through appetite control, and other adipokines control fuel distribution and utilization. Fat storage capacity of adipose tissue increases through two mechanisms, adipocyte hypertrophy and adipocyte hyperplasia. Adipose tissue depots expand differently in diverse individuals and confer varying degrees of metabolic disease risk. There are multiple adipocyte subtypes that together mediate the functions of adipose tissue. They do so through specialized functions such as thermogenesis, which burns fuel to maintain core temperature, and through selective secretion of different adipokines. Much progress has been made in understanding the mechanisms by which adipose tissue controls systemic metabolism, increasing our hope of developing new, effective therapies for metabolic diseases.

Adipose tissue revealed as key player in systemic homeostasis

One of the most remarkable discoveries in the history of medicine has been the action of insulin to control blood glucose levels. It never ceases to amaze that a simple injection of a single molecule can within minutes exert a profound systemic effect, a drop in circulating glucose levels, that can rapidly become the difference between life and death. It is also extraordinary that disruption of this single mechanism underlies one of the most consequential health challenges of our time, which is the global epidemic of type 2 diabetes (T2D). In a recent estimate, the global direct health expenditure on T2D is expected to reach a projected USD 825bn by 2030. Unlike type 1 diabetes, which arises from lack of insulin due to pancreatic β-cell destruction, T2D stems from insufficient responsiveness to secreted insulin, known as insulin resistance, which is followed by β-cell failure. Efforts over several decades to understand the causes of insulin resistance have led to our recognition of elaborate communication networks between tissues including liver, muscle and fat, which define cell-specific metabolic pathways that ultimately control whole-body metabolism.

One of the greatest surprises from research on insulin action was the major role of adipose tissue in the control of systemic glucose homeostasis. While it was known that insulin stimulated glucose uptake in both fat and muscle cells and that this effect resulted from translocation of a specific glucose transporter (GLUT4) to the cell surface, it came as a surprise that knockout of GLUT4 exclusively in adipose tissue had much greater effects on whole-body glucose homeostasis than its knockout in muscle. This finding was counter-intuitive, given that the mass of adipose tissue is typically much smaller compared to total muscle mass and that the large majority of glucose consumed by the body flows into muscle. This finding of an unexpected, key role of adipose tissue in the maintenance of glucose homeostasis was congruent with epidemiological studies showing an unequivocal relationship between weight gain and T2D risk. These findings initiated an exciting effort by many research groups to understand the mechanisms by which adipose tissue plays such a critical role in insulin action and diabetes pathogenesis.

Adipose tissue regulates metabolism through both fat storage and adipokine secretion

The relationship between adipose tissue and insulin sensitivity is complicated and often seems paradoxical, as individuals with either very small or very large amounts of adipose tissue can display similar impairments in insulin sensitivity. For example, genetic diseases that result in almost complete absence of adipose tissue, such as congenital lipodystrophies, result in extreme insulin resistance. Yet, in some individuals, only small degrees of excess weight lead to insulin resistance, and epidemiological data reveals an unequivocal correlation between prevalence of overweight and obesity and that...
of T2D. These observations in humans are reiterated in mouse models, where manipulations that eliminate adipose tissue, such as expression of diphtheria toxin in adipocytes, lead to very high insulin resistance, but so do increases in adipose tissue mass achieved through feeding high-calorie/high-fat diets that mimic the human Western diet. So, why do both deficiency and excess of adipose tissue result in the same outcome of impaired insulin sensitivity and glucose intolerance?

Elucidating this paradox requires an understanding of fuel storage mechanisms (Figure 1). Calories consumed in excess of immediate energetic needs are converted into fat by liver and must be subsequently transported to adipose tissue for storage. If adipose

Figure 1. Adipose tissue protects liver and muscle from lipotoxicity and insulin resistance.
tissue is absent, such as in lipodystrophy, fat accumulates in non-adipose tissues, including liver and muscle, producing lipotoxicity and tissue insulin resistance. If adipose tissue is present, but its volume is insufficient to store the totality of the fat generated from excess caloric intake, lipotoxicity and insulin resistance also ensue. If, however, adipose tissue expands sufficiently in response to excess calorie intake, lipotoxicity is prevented and insulin sensitivity is maintained. These later conditions lead to obesity, but not to metabolic abnormalities. This explains why insulin resistance and high fasting glucose can occur in some individuals with small degrees of weight gain, while other individuals maintain normal insulin sensitivity despite much larger weight gain.

In addition to the critical role of preventing lipotoxicity through fat storage, adipose tissue controls systemic metabolism through secretion of cytokines (adipokines) that exert powerful metabolic effects. This endocrine role of adipose tissue was revealed through the discovery of leptin, a hormone secreted specifically by adipose tissue that acts in the brain and peripheral tissues to monitor and control fuel levels and utilization. Adiponectin is also secreted specifically by adipose tissue and exerts pleiotropic actions on many tissues. Like leptin, adiponectin exemplifies the tight relationship between fat storage and endocrine function of adipose tissue; while leptin levels increase with increasing fat mass, adiponectin levels decrease with weight gain. Other factors secreted by adipose tissue include ANGPTL4, which regulates lipid partitioning between organs through its effects on lipoprotein lipase.

Both ectopic fat accumulation and secreted cytokines can contribute to insulin resistance. For example, in muscle cells, mitochondrial metabolism of excess fat results in abnormal accumulation of metabolites that can impair energy production, increase oxidative stress, and secondarily impact insulin signal transduction and GLUT4 trafficking, resulting in impaired glucose transport. In liver cells, excess fatty acid oxidation can affect gluconeogenesis, leading to excessive liver glucose output, directly contributing to high blood glucose levels. There are also direct effects of ectopic fat to affect synthesis of other lipids, e.g., ceramides, that can affect membrane composition, cholesterol metabolism or signal transduction. In addition, fat accumulation results in stress signaling leading to immune cell activation and inflammation. Maladaptive inflammation can result in consequences beyond insulin and glucose homeostasis. For example, in the liver, a clear progression from fat accumulation to inflammation and fibrosis underlie non-alcoholic steatohepatitis (NASH). NASH increases the risk of hepatocellular carcinoma, and liver failure associated with NASH comprises the largest current need for liver transplantation.

### Distinct roles and properties of different adipose depots

There are multiple different adipose tissue depots throughout the body. The mass of these depots and the adipokines they secrete into the circulation differ greatly, and therefore each adipose depot can be considered to have specialized functions. For example, mesenteric adipose tissue surrounds the viscera and plays an important role in immune defence; perivascular adipose tissue surrounds blood vessels and plays an important role in controlling blood flow; thermogenic adipose tissue is distributed in the supraclavicular and paravertebral region and plays an important role in maintaining core temperature upon cold exposure. Subcutaneous adipose tissue resides under the skin, which is the largest organ in the body, and comprises the largest capacity for fat storage. Indeed, epidemiological studies indicate that the abundance of subcutaneous adipose tissue is inversely correlated with risk of T2D.

The protective role of subcutaneous adipose tissue may reside in its capacity to undergo hyperplasia, i.e., to expand by making new adipocytes. Adipocytes are uniquely capable of increasing their size; indeed, only a few days of exposure to high-calorie diets can induce a doubling in adipocyte diameter, corresponding to an eight-fold increase in fat storage capacity (Figure 2). However, there appears to be a species-defined limit on maximal adipocyte size, after which cellular stress is triggered. Cellular stress is associated with maladaptive inflammatory responses and tissue fibrosis, compromising overall tissue function. Thus, while adipocyte hypertrophy can accommodate temporary and limited excess caloric intake, hyperplasia can accommodate larger amounts, resulting in obese but metabolically normal phenotypes. Interestingly, limits on subcutaneous adipose tissue expansion resulting in relatively higher abdominal adipose tissue mass are seen more frequently in some ethnic groups such as South Asians. This distribution of fat in the abdominal region is strongly associated with metabolic disease risk. Elucidating the mechanisms that lead to adipose tissue expansion by either hypertrophy or hyperplasia, and to its relative distribution among different depots, is an important area of research.

### Different adipocyte subtypes are involved in adipose tissue function

Recent studies have revealed that the different properties and functions of adipose tissue depots are associated with distinct adipocyte subtypes. The adipocyte subtypes that have been identified differ in their expression of secreted cytokines such as leptin and adiponectin, in their...
capacity to undergo lipolysis, and in other important features associated with adipose tissue functions. The finding of specialized adipocyte subtypes changes our general concept of how adipose tissues operate and of mechanisms that could underlie the pathophysiology of metabolic disease. For example, alterations in adipose tissue function, which have been previously attributed to metabolic alterations occurring to a homogenous population of cells, may instead arise from adjustments in the relative abundance of different adipocyte subtypes.

Figure 2. Adipose tissue hypertrophy can store large, but limited amount of fat.

Figure 3. Different models for adipose tissue adaptation, based on existence of single or multiple adipocyte subtypes.
Diabetes (Figure 3). This is conceptually analogous to the evolution of our thinking of the immune system, where we now distinguish multiple populations of lymphocytes with very specific roles, and find phenotypes dictated by the relative proportion of specialized lymphocyte populations.

There are already clear indications that certain adipocyte subtypes are associated differently with T2D risk. For example, the abundance of thermogenic adipocytes, defined as expressing the mitochondrial uncoupling protein UCP1, has been found to correlate with decreased T2D risk. In adult humans, thermogenic adipocytes are found interspersed within adipose tissue depots localized to the supraclavicular and paravertebral region. Experiments to determine whether there is a cause–effect relationship between thermogenic adipocyte abundance and systemic energy metabolism have involved implantation of human thermogenic adipocytes into mice. Results from several groups, using either primary or genetically engineered thermogenic adipocytes, concur in finding a strong effect of these cells on glucose homeostasis. These effects occur with no major changes in the mass of endogenous mouse adipose tissue, indicating that thermogenic adipocytes can exert powerful actions on systemic metabolism independently of their role in fat storage, possibly through secretion of specific adipokines yet to be fully identified.

The relative importance of different adipocyte subtypes in controlling metabolism has triggered much interest in understanding their development and functions. Adipocytes arising from multipotent mesenchymal progenitors remain present in many tissues through adulthood and retain the capacity to differentiate into multiple lineages, including adipogenic, osteogenic, and chondrogenic. Only a small number of progenitor cells are present in adult tissues, making them challenging to study. However, over the past decade, different approaches have found that progenitors are closely associated with the microvasculature, and human mesenchymal progenitor cells proliferate under conditions that stimulate angiogenesis. This has made it possible to grow large numbers of human adipocyte progenitors in vitro and analyse the mechanisms that regulate their proliferation and differentiation. Elucidating the mechanisms that control the differentiation of mesenchymal progenitors into different adipocyte subtypes is an exciting challenge for future research.

While much remains to be discovered, there has been great progress in our understanding of the role of adipose tissue in systemic metabolism, and of specific mechanisms by which it contributes to the pathogenesis of T2D. Current efforts to further define the adipocyte subtypes that compose major human adipose tissue depots and how these subtypes differ between subjects with or without T2D will provide clearer insights into adipose tissue development and T2D pathogenesis, and hopefully point to new, exciting strategies to mitigate the global burden of metabolic disease.

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