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Mini review

Adipocyte biology and obesity-mediated adipose tissue remodeling

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ABSTRACT

Obesity has reached epidemic proportions, leading to an increase of associated pathologies such as insulin resistance, cardiovascular disease, some types of cancer and type 2 diabetes. The worldwide obesity epidemic has greatly increased interest in the biology and physiology of adipose tissues (AT), cells specialized in fat storage that all vertebrates possess. The last few decades have shown that adipocytes also play a critical role in sensing and responding to changes in systemic energy balance. White fat cells secrete sets of adipokines that influence processes such as food intake, insulin sensitivity, and insulin secretion. Brown AT instead induces fat accumulation and can produce energy as heat, thereby defending against hypothermia, obesity, and diabetes. There are two distinct types of thermogenic fat cells, termed brown and beige adipocytes. Adipocytes exist within AT, where they are in dynamic cross talk with immune cells. AT undergoes a continuous remodeling process in a fat-depot specific manner, that normally maintains tissue health, but may spin out of control and lead to adipocyte death in association with the recruitment and activation of macrophages, and systemic insulin resistance. In addition, AT is the major site of vitamin D storage and vitamin D affects directly the expression of the appetite regulating hormone, leptin as well as influencing adipocyte function. This review is intended to serve as an overview of white adipocyte biology and obesity-mediated AT remodeling by microbiome changes.

1. Background

Obesity has reached epidemic proportions. The worldwide obesity epidemic has greatly increased interest in the biology and physiology of adipose tissues (AT). Worldwide more than 1.9 billion adults are influenced by obesity, which represents a fast growing public health problem that contributes to higher mortality through an increase in hypertension, stroke, coronary heart disease, type 2 diabetes and some types of cancer (WHO, 2015; Adams et al., 2006; Bluher, 2013; Parvez et al., 2007; Mensah et al., 2004; Mokdad et al., 2003).

All eukaryotes from yeast to man are able to store calories in the form of lipid droplets, but only vertebrates have specialized cells that are recognizable as AT cells (adipocytes). AT is postulated to be a key player in regulating the process of obesity (Rosen and Spiegelman, 2006). The amount, distribution and changes of body fat have an impact on the onset and progression of obesity. Excess of fat is often characterized by a chronic state of low-grade inflammation with progressive immune cell infiltration into AT. AT undergoes a continuous remodeling process that may spin out of control and lead to adipocyte death in association with the recruitment and activation of macrophages, and systemic insulin resistance. There have been several pivotal discoveries that focused our interest on AT. One was the discovery of leptin in 1994 (Zhang et al., 1994). Total inability to produce leptin result in profound, early onset obesity with persistently excessive food intake, inappropriately decreased energy expenditure, severe insulin resistance, and genetic background–dependent diabetes (Zhang et al., 1994; Pelleymounter et al., 1995). Another discovery was the association between inflammation of AT depots and the development of obesity related metabolic diseases. Therefore AT is postulated to be a key risk factor in regulating the process of obesity. The amount, distribution and changes of body fat have an impact on the onset and progression of obesity. AT is distributed over multiple subcutaneous (SC) and visceral depots, typically accounting for 15–30% of total human body weight (Pi-Sunyer, 1998). This review is intended to give an overview to adipocyte biology function, obesity-mediated AT remodeling and discusses how changes in microbiota and vitamin D status seem to play a potential role in AT function and body weight regulation.

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2. Adipose tissue depots and function

AT is generally considered either 'white', characterized by adipocytes with a single lipid droplet for efficient energy storage, or 'brown', characterized by adipocytes with multiple lipid droplets, numerous enlarged mitochondria expressing uncoupling proteins (*UCP1)* for uncoupled oxidative phosphorylation and nonshivering thermogenesis, and increased vasculature for heat dissipation (Pope et al., 2016). White adipocytes are responsible for storing redundant calories as triglycerides within the lipid droplets (Konige et al., 2014). Brown fat is located mainly around the neck and plays an essential role in thermogenesis (Rutkowski et al., 2015). Some fat depots have both white and brown adipocytes and therefore called 'brite' or 'beige' AT (Walden et al., 2012). The appearance of these brite or beige adipocytes may involve transdifferentiation processes of white to beige cells.

The ability of adipocytes for lipid uptake and storage in form of triglycerides allows for expansion of AT, which significantly influences adipocyte biology. Result of excess triglyceride increase due to a positive energy balance is the growth in size (hypertrophy), whereas the increase in number (hyperplasia) results from the formation of new adipocytes from precursor cells (adipogenesis) (Bjorntorp, 1974). Hypertrophy of adipocytes results in loss of insulin sensitivity in lean and obese individuals, whereas AT hyperplasia has been shown to be protective against insulin abnormalities in obesity (Hoffstedt et al., 2010; Kloting and Bluher, 2014). The total amount of fat is distributed in multiple depots in the body, which are concentrated in three main areas – SC, dermal and intraperitoneal fat depots (Cinti, 1999). An excess of intraperitoneal fat is known as central or abdominal obesity and is characterized by excessive fat around the stomach and abdomen.

Beside the main functions of AT as energy storage, mechanical protection and thermal insulator, AT has been recognized as an endocrine organ, which secretes more than 600 different hormones, so-called adipokines (Bluher, 2014; Kershaw and Flier, 2004; Lehr et al., 2012). Adipokines are involved in regulation of various metabolic processes, for instance appetite and satiety, fat distribution, adipogenesis, energy metabolism, inflammation, which are directly linked to body weight (Bluher, 2014; Bluher and Mantzoros, 2015). Secretion of adipokines may be influenced by fat distribution or may contribute to several fat distribution subtypes (Schleinitz et al., 2014). Both AT depots produce and secrete both pro- and anti-inflammatory molecules that influence local and systemic inflammation. The balance of pro- and anti-inflammatory adipokines is dictated by many different factors, including the nutritional/metabolic status of the host, genetic factors, the presence of infection or systemic inflammation, oxidative stress, smoking status, age, and gender (Bluher, 2016; Mancuso, 2016).

3. Obesity-mediated adipose tissue remodeling

Obesity-associated AT remodeling has been first described by Cinti in 2005 as the existence of significant numbers of so-called "crown-like structures (CLS)", consisting of macrophages surrounding dead adipocytes in both obese mice and humans (Cinti et al., 2005). The high number of CLS is highly correlated to AT inflammation, metabolic disorder as well as considered to be pathological lesions in AT of obese subjects (Aouadi et al., 2013). With excess of fat, extreme increases in adipocyte size are accompanied by an elevated frequency of adipocyte death and a phenotypic switch in AT macrophage (ATMs) polarization and recruitment (Lumeng et al., 2007). The elevated adipocyte death rate could partly be explained by hypoperfusion causing an inadequate supply of oxygen in the face of expanding AT (Patel et al., 2013). Long-term imaging of ATMs in live AT explants have shown that the accumulation of ATMs around a dying adipocyte (formation of CLS), the migration of ATMs toward the CLS and out of the CLS, different migratory behaviors of ATMs, and the degradation of dead adipocytes are very dynamic processes (Gericke et al., 2015). High-fat feeding (60% of calories as lard) provoke a nearly complete remodeling of the epididymal (visceral) fat depot of male mice. Interestingly, AT of female mice are far less susceptible to high-fat diet–induced adipocyte death and AT remodeling. This gender difference is dramatic in the gonadal (parametrial vs. epididymal), but also holds for SC inguinal fat depots (Strissel et al., 2007). Similar depot differences are observed in genetic obese models (Nishimura et al., 2008). The mechanisms underlying depot differences in rates of remodeling are not well understood. DiGirolamo and co-workers showed that next to anatomy, growth characteristics and extra cellular matrix composition differ substantially among fat depots. While the SC fat grows in response to a high-fat diet mainly by increasing the number of adipocytes, the hyperplastic capacity of the visceral fat is far lower (DiGirolamo et al., 1998). Despite the close association of adipocyte death with macrophage infiltration, it remains unclear to what extent macrophages respond to or contribute to adipocyte death. Lee et al. hypothesized that the small molecules released by dead adipocytes may activate toll-like receptors (TLRs) on the macrophages and neighboring adipocytes, inducing a release of pro-inflammatory factors (Lee et al., 2010).

In obesity, unusual expression of extra cellular matrix (ECM) components, proteases and fragments derived from AT-remodeling processes can influence immune cell recruitment and activation, actively contributing to inflammation (Catalan et al., 2012).

There are obesity induced fat depot differences in adipocyte size and AT progenitor pool (AP) between SC and visceral AT (VAS) (Table 1). Therefore, it is not unexpected that plasticity is also differently affected, particularly when stressed by positive energy intake (Pellegrinelli et al., 2016). The percentage of small cells is higher in SC and omental VAT in healthy individuals compared to subjects with diabetes and obesity (Fang et al., 2015).

Recently, high-fat feeding time course experiments in mice revealed intra-depot differences in immune cell composition in relation to white AT (WAT) expandability (van Beek et al., 2015). This mice study also suggests that VAT is the primary fat depot that expands during the initial phase of obesity, followed by the subcutaneous AT (SAT) and mesenteric VAT. Once the mice had reached a body weight of about 40 g, gonadal VAT stopped expanding further, in contrast to SAT and mesenteric VAT. Interestingly, reaching this maximal expansion coincides with increased adipocyte death rate and formation of CLS, inflammation and tissue dysfunction associated with insulin resistance and liver damage (Strissel et al., 2007).

Similarly, another study has suggested that increased visceral mass predominantly results from adipocyte hypertrophy whereas hyperplasia is predominantly seen in SAT (Joe et al., 2009). The resistance to differentiation observed in VAT APs and the fact the

Table 1
Differences of WAT depots undergoes remodeling in obesity.

Remodeling process	SAT vs VAT
Adipocyte hypertrophy	<
Production of inflammatory factors	<
Crown like structure	<
Fibrosis deposition with decreased tissue plasticity	>
Expansion	>
SVF differentiation capacity	>

SVF = stromal vascular fraction, WAT = white adipose tissue, SAT = subcutaneous adipose tissue, VAT = visceral adipose tissue.