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Adipose tissue remodeling in pathophysiology of obesity

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Abstract

Purpose of review—Recent studies demonstrate that adipose tissue undergoes a continuous process of remodeling that is pathologically accelerated in the obese state. Contrary to earlier dogma, adipocytes die and are replaced by newly-differentiated ones. This review will summarize recent advances of our knowledge of the mechanisms that regulate adipose tissue remodeling and highlight the influences of obesity, depot, and sex, as well as the relevance of rodent models to humans.

Recent findings—A substantial literature now points to the importance of dynamic changes in adipocyte and immune cell turnover, angiogenesis, and extracellular matrix remodeling in regulating the expandability and functional integrity of this tissue. In obesity, the macrophages are recruited, surrounding dead adipocytes and polarized toward an inflammatory phenotype. The number of dead adipocytes is closely associated with the pathophysiological consequences of obesity, including insulin resistance and hepatic steatosis. Further, there are substantial depot-, sex- and species differences in the extent of remodeling.

Summary—Adipose tissue undergoes a continuous remodeling process 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.

Keywords

Remodeling; obesity; adipose tissue; extracellular matrix; inflammation

Introduction

Adipose tissue (AT) includes lipid-filled adipocytes, endothelial cells (form an extensive vasculature), pericytes (have the potential to become adipocytes), fibroblasts (provide structural support), preadipocytes (partially committed to an adipocyte fate), mast cells (influence angiogenesis and remodeling), and immune cells (resident macrophages and T-cells). Each of these cells likely contributes to the synthesis and turnover of extracellular matrix (ECM) components that collectively create unique microenvironments within different anatomical adipose depots. The concept of AT remodeling refers to the turnover of cells within AT and the renovation of the ECM in response to requirements for growth and expansion, changes in hormonal milieu, aging, or pathologies such as cancer cachexia or lipodystrophies.

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Adipose tissue remodeling: a dynamic process

The idea that mature, terminally differentiated adipocytes never died was well accepted in the literature until recently. This notion was based on the stability of ^3H -thymidine incorporated into adipocyte DNA in epididymal fat pad of lean male rats that were followed for only 7 months of a possible 2+ year lifespan [1]. Although apoptotic adipocytes had been reported in AT of individuals with cancer cachexia [2], until recently few researchers searched for evidence of adipocyte turnover in other situations. A seminal paper by Cinti and collaborators first showed the existence of significant numbers of so-called ‘crown-like structures (CLS)’, consisting of macrophages surrounding dead adipocytes, in obese rodents and humans [3].

Adipose tissue remodeling and adipocyte death

High fat (HF) diets (60% of calories as lard) provoke a nearly complete remodeling of the epididymal fat depot of male mice [4]. After 16 weeks of HF, the epididymal fat is invaded by numerous macrophages, many of which are found in CLS surrounding dead adipocytes (identifiable by the lack of perilipin staining [3]). Whether the macrophages respond to or directly contribute to adipocyte death is not clear. With time, the macrophages phagocytose the lipid and other cellular constituents. These molecules may activate toll like receptors on the macrophages and neighboring adipocytes, inducing proinflammatory cytokine and chemokine releases. Crosstalk among adipocytes, macrophages and other cells promotes inflammation and ECM remodeling, as described later. The macrophages eventually assume the appearance of lipid-laden foam cells. Within weeks, the lipid and other cellular debris disappear from the AT and new, apparently healthy adipocytes populate the tissue. The time course of tissue remodeling coincides with the development and amelioration of insulin resistance (IR) (Figure 1), suggesting the remodeling process has a metabolic consequence at the organism level [4].

Depot and sex differences in remodeling

The remarkable, nearly complete remodeling of the epididymal fat does not occur in the sc (inguinal) AT of the male mouse in diet-induced obesity [4]. Adipocyte death in inguinal depot is detectable but much lower (3% compared to 80% in epididymal at 16 week on HF [4]). Similar depot differences are observed in genetic obese models [5*]. The mechanisms underlying depot differences in rates of remodeling are poorly understood. The anatomy and growth characteristics and the composition of the ECM differ substantially among adipose depots. While the sc depot grows in response to a HF diet mainly by increasing the number of adipocytes, the hyperplastic capacity of the visceral depot is far lower [6]. The limited adipocyte precursor pool and hence the limited capacity for hyperplasia in visceral depots may contribute to the stress on the existing adipocytes.

Adipose tissues of female mice are far less susceptible to HF diet-induced adipocyte death and AT remodeling. This sex difference is dramatic in the gonadal (parametrial vs. epididymal), but also holds for sc inguinal fat depots [7**]. Compared to the gonadal depots, the sc fat showed less macrophage infiltration and the fewest number of CLS representing dead adipocytes [4;7**]. While ovariectomy increased the numbers of CLS in both depots, the numbers were still lower [7**], suggesting the sex difference in adipose remodeling is not entirely due to sex steroids.

Are rates of adipocyte turnover similar in human and rodent adipose tissues?

No studies have directly assessed the lifespan of adipocytes in rodents. But based on the time course studies [4], under the stress of very HF diets/obesity, almost 80% of the adipocytes in the epididymal AT died and were replaced within a few weeks. Even in the omentum of severe obese subjects, the number of CLS is much lower (absent or maximum estimate of ~3% adipocytes calculated from the data in Figure 1D of [8] with an assumption of 4 macrophages in one CLS), but these values are not dissimilar to the numbers in the sc of mice fed regular chow or low fat diets.

Recent studies estimate that the lifespan of a sc adipocyte in humans is ~2–3 [9] or 10 years [10*]. Methodological issues likely account for the disparate estimates, most likely due to variable contamination with non-adipocytes including macrophages in isolated adipocyte fractions [11]. Interestingly, according to the estimates resulting from a natural experiment made possible by the labeling of DNA by radioactive fallout, BMI and weight loss do not alter the adipocyte turnover rates [10*]. This finding implies that adipocyte number is tightly regulated, static during adulthood and the relative rates of adipocyte death are equal between lean and obese. However, because obese individuals have more adipocytes, the absolute number of dead or dying adipocytes at any time point is higher and could contribute to the chronic inflammatory state. It is conceivable however, that under extreme circumstances (massive or prolonged weight loss or lipoatrophy), the rate of adipocyte loss could exceed the rate at which they are replaced, decreasing the average cell half life and leading to net loss of mature adipocytes, but experimental evidence is lacking. Due to the cross-sectional nature of this study, periods of more rapid turnover during overfeeding could also have been missed.

Potential diet effects on adipose remodeling

Many rodent studies used saturated fat as a major component of energy intake. Saturated and unsaturated fatty acids have differential effects on AT production of chemotactic factors [12]. n-3 poly-unsaturated fat has been shown to prevent HF diet-induced AT inflammation and remodeling [13;14]. Thus, dietary factors are important modulators of inflammatory events and potentially rates of adipocyte death and tissue remodeling. Whether dietary factors contribute to the apparent species differences in rates of adipocyte turnover observed merits further study.

What factors instigate AT remodeling and what mechanisms are involved?

Excessive stiffness of the ECM can limit adipocyte size [15**]. ECM remodeling is required during adipocyte hypertrophy. It is mediated by fibrinolytic plasminogen and plasmin, matrix metalloproteinase (MMP), a disintegrin and metalloprotease (ADAM), and tissue inhibitors of MMP (TIMP) systems. Plasminogen activator inhibitor-1 is highly expressed in obese AT [16]. MMPs are over-expressed in AT of obesity with increases matrix degradation (increased plasticity) [17–19]. Cathepsins may also contribute to the remodeling process through their proteolytic activity toward extracellular elastins and collagens. Expression of adipose cathepsin K and S is increased in obesity [20;21*] and decreases after weight loss [21*;22]. Interestingly, MMP2, cathepsin K, and L null mice exhibit reduced adiposity [19;23–25], while ADAM-12 transgenic are overweight or obese [26], supporting the critical roles of these molecules in AT development. Genetic variations in the activities of these proteolytic enzymes is likely to contribute to inter-individual variations in the capacity for AT expansion, allowing for the safe storage of lipid in adipocytes in the face of a positive energy balance in some individuals. The improved insulin sensitivity despite

increased fat mass of collagen VI knockout mouse [15**] provides a clear example of this concept.

Role of AT macrophages (ATMs)

Macrophages normally reside in lean AT where they participate in normal remodeling. In obesity, as mentioned previously, macrophages are often found in CLS surrounding dead adipocytes during periods of tissue remodeling [3]. With development of obesity, ATMs are polarized to an M1 inflammatory phenotype and both the number of adipose M1 and the M1/M2 ratio are associated with systemic inflammation and the induction of IR [27;28**] (Figure 1). M2 macrophages, which normally reside within AT, express anti-inflammatory genes (IL-10) and are involved in tissue remodeling. Other work suggests the situation may be more complex. Human ATMs have M2-like surface markers but can produce excessive amount of pro-inflammatory cytokines [29] and mixed expression of both pro-inflammatory and anti-inflammatory characteristics [30*]. A coincident M2 and M1 phenotype of ATMs was also observed during HF diet induced AT remodeling in mice [31*]. These data suggest that ATMs that accumulate within obese AT acquire particular remodeling phenotypes.

Recently recognized role of T cells in adipose remodeling

The importance of T cells in AT inflammation and remodeling was demonstrated recently, although a nature of details remain controversial [32*;33**]. Obese AT is characterized with decreased numbers of regulatory T cells (CD4⁺Foxp3⁺; Treg) and increased numbers of CD8⁺ T cells [32*;34**]. Selective increases in Treg improve whole-body insulin sensitivity [35**]. CD8⁺ T cell infiltration may precede macrophage accumulation and may be involved in macrophage differentiation and activation [33**]. Mast cells may also be important regulators of angiogenesis, T cell recruitment and remodeling events in obese adipose tissue [36*].

Role of blood flow and hypoxia

During development, angiogenesis and adipogenesis are temporally and spatially coupled [37]. Classic studies of blood flow showed a constant blood supply per adipocyte as rats grew spontaneously more obese [38]. However, blood flow per unit adipocyte surface declines with obesity, raising the possibility that oxygen and nutrient delivery to the adipocyte becomes suboptimal. In vivo imaging studies show that AT blood flow is discontinuous and leukocyte adhesion, which is increased in obesity, appears to perturb the flow [5*]. The vasculature of obese AT may also exhibit abnormal responses to vasodilators (e.g. NO) or increased permeability [5*;39;40*]. Direct measurements of oxygenation document lower AT oxygen tension (pO₂) with lower capillary density in obese. Further, pO₂ was inversely correlated with proinflammatory markers, suggesting that lower AT pO₂ could drive AT inflammation in obesity, consistent with a causal role of the low vascularity for hypoxia, fibrosis, and adipocyte dysfunction [41]. Inhibition of angiogenesis reduces AT mass [42;43] and targeting angiogenesis in hypoxia may improve AT function in obesity. However, the result may be healthy, but more obese individuals.

Adipocyte dysfunction may contribute to the cycle of accelerated AT remodeling in obesity. Of the two major adipokines, leptin has potent pro-angiogenic effects [44] and adiponectin may also be pro-angiogenic [45]. The ability of the adipocyte to upregulate and respond to these hormones, as well as vascular endothelial growth factor, likely determines whether the tissue can maintain normal function in the face of expansion and the stress of hypoxia. Other adipocyte secretory products (metabolites and adipokines) also affect immunocyte recruitment and activation. Increased FFA, leptin and serum amyloid A (SAA) with reduced adiponectin characterize adipocytes in obese. SAA has been shown to increase migration of monocytes and neutrophils [46] and T lymphocyte migration and adhesion [47]. SAA

expression highly correlates with adipocyte size [48] and thus, SAA may be a casual link between the hypertrophy of adipocytes and immunocytes accumulation in obesity. Other secretory and cell adhesion molecules may also play a role in recruitment and activation of immune cells into AT of obese.

Mechanisms regulating adipose remodeling and its consequences appear to vary among depots. Omental AT is known to secrete angiogenic compounds and to add wound healing [49]. Although expression of numerous proinflammatory cytokines is higher in omental AT, the adipocytes themselves are not especially insulin resistant. GLUT4 expression and the insulin stimulation of glucose transport as well as rates of triglyceride turnover are in fact higher in visceral [50;51] than sc AT. Thus, depot specific local factors may protect adipocytes from inflammatory stress [52], and the higher number of CLS in omental vs. sc may not necessarily reflect adipocyte dysfunction or hypoxia.

Thiazolidinediones induce a healthy remodeling of adipose tissue

The TZDs are antidiabetic drugs that were developed as insulin-sensitizing drugs. TZDs activate PPAR γ , increase adipogenesis, and may also cause apoptosis of hypertrophied adipocytes [53], although it is unclear whether the latter is a direct action. The appearance of the new, smaller and more insulin sensitive adipocytes after TZDs treatment leads to AT expansion but improvements in systemic insulin action. TZDs also increase angiogenesis which is required for AT growth [54] and promote infiltration of M2 into AT [55]. These data suggest endogenous PPAR γ ligands may regulate processes that promote the normal, healthy remodeling of AT.

Associations of adipocyte death with metabolic dysfunction in humans

Like the situation in rodents, CLS are also more numerous in visceral (omental) than sc of women and men [3;8;56], but systematic comparisons between the sexes have not been carried out to date. The number of CLS decreases after massive weight loss [57]. Intriguingly, the number of CLS correlates with the level of inflammation (assessed by expression levels of inflammatory genes), a HOMA-IR as a rough reflection of systemic insulin sensitivity, as well as systemic vascular endothelial dysfunction, independent of the level of obesity [56;58]. Additionally, the numbers of CLS in omental AT correlate with the severity of hepatic fibroinflammatory lesions [56] and liver fat content [59]. These data suggest macrophage infiltration in AT contributes to the complications of obesity. Studies are needed to carefully assess how the number of CLS is related to obesity-, sex-, and depot differences in adipocyte function, and whether there is a functional link to metabolic dysfunction or it is simply a marker for the metabolic syndrome.

Summary and Conclusion

The normal growth and expansion of adipocyte size may have no negative consequences if accompanied by flexible ECM and a proportional increase in blood flow and hence oxygenation. However, with overnutrition, if adipocyte hyperplasia does not keep pace with the need to store lipid, excessive adipocyte hypertrophy combined with a limited vasculature expansion may lead to metabolic or hypoxic stress, inflammation and the recruitment and activation of macrophages. Considering the apparently much lower rates of adipocyte death in humans compared to mice, and clear depot and sex differences, the importance of this process as a major driver of AT inflammation and remodeling in human AT, and hence the metabolic complications of obesity remains uncertain.

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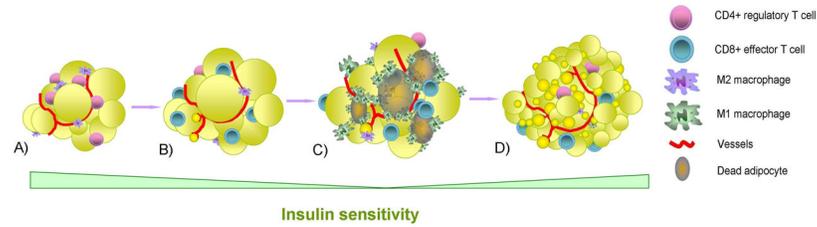


Figure 1. The process of remodeling in obese mice

A) In well vascularized healthy adipose tissue, resident regulatory CD4+ T cells and M2 macrophages are present and remodel the tissue, restricting inflammation and improving insulin sensitivity.

B) With increasing adipocyte hypertrophy, the ratio of CD8+/CD4+ T cells increases and this may help recruit macrophages.

C) With the further expansion of adipose tissue, more macrophages acquire a proinflammatory, M1 phenotype, especially those in CLS around dead or dying adipocytes. Coincidentally, restrictions of blood flow and hypoxia stimulate inflammatory cytokine production and worsen adipocyte dysfunction.

D) With time, macrophages clear out the dead adipocytes which are replaced by the newly-differentiated, insulin sensitive adipocytes.