Seminars in Immunology 27 (2015) 315–321

Contents lists available at ScienceDirect

Seminars in Immunology

journal homepage: www.elsevier.com/locate/ysmim

Review

Immunological contributions to adipose tissue homeostasis

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ARTICLE INFO

Article history:
Received 23 October 2015
Accepted 26 October 2015
Available online 24 November 2015

Keywords:
Adipocyte
Immunocyte
Obesity
Hyperplasia
Hypertrophy

ABSTRACT

Adipose tissue is composed of many functionally and developmentally distinct cell types, the metabolic core of which is the adipocyte. The classification of "adipocyte" encompasses three primary types – white, brown, and beige – with distinct origins, anatomic distributions, and homeostatic functions. The ability of adipocytes to store and release lipids, respond to insulin, and perform their endocrine functions (via secretion of adipokines) is heavily influenced by the immune system. Various cell populations of the innate and adaptive arms of the immune system can resist or exacerbate the development of the chronic, low-grade inflammation associated with obesity and metabolic dysfunction. Here, we discuss these interactions, with a focus on their consequences for adipocyte and adipose tissue function in the setting of chronic overnutrition. In addition, we will review the effects of diet composition on adipose tissue inflammation and recent evidence suggesting that diet-driven disruption of the gut microbiota can trigger pathologic inflammation of adipose tissue.

1. Introduction

Adipose tissue (AT) has multiple roles in orchestrating systemic adaptation to changes in nutrient availability. For a long time, it was considered almost exclusively as an energy storage depot that responded to energy deficits by catabolizing its lipid droplets to provide fatty acids as a fuel source for other tissues. The last several decades of obesity research have revealed additional roles for, and complexity of, adipose tissue. Most notably, it (1) acts as an endocrine organ that not only receives input from other metabolic tissues (brain, muscle, liver), but transmits soluble signals in the form of "adipokines" that act locally and systemically to regulate nutrient balance and (2) is infiltrated by, and crosstalks extensively with, cells of the innate and adaptive arms of the immune system. Both adipokine secretion and adipocyte–immunocyte interactions can become dysregulated during weight gain and subsequent obesity. Here, we review developments in our understanding of how fundamental adipocyte behaviors are influenced by immunocytes, and how these interactions are modulated by changes in energy balance (primarily chronic weight gain). We will also discuss the influence of the gut microbiome on metabolic inflammation and point out questions that have arisen from the exciting intersection of immunity and metabolism.

2. Immunocyte influences on metabolic functions of adipocytes

2.1. Adipocyte cell populations and anatomic distribution of adipose tissue

AT is composed of adipocytes and the "stromal vascular fraction" (SVF)—a heterogeneous mixture of mesenchymal, endothelial, and hematopoietic cell types. Adipocytes themselves are not monolithic, but rather consist of subsets with distinct developmental origins and metabolic functions. Classically, adipocytes were divided into white and brown subtypes. White adipocytes store lipid as triglycerides within unilocular droplets —a lipogenic pathway that is responsive to various stimuli, most notably insulin [1]. During times of energy deficit, other signaling pathways stimulate lipolysis of these triglyceride stores and release of free fatty acids (FFA) into the circulation. Notably, FFA released by white adipocytes can be utilized by brown adipocytes to fuel heat production via mitochondrial uncoupling, the major metabolic function of brown adipose tissue (BAT) [2]. Brown adipocytes store lipid

Abbreviations: AT, Adipose tissue; SVF, Stromal vascular fraction; WAT, White adipose tissue; BAT, Brown adipose tissue; DIO, Diet-induced obesity; FFA, Free fatty acid; Treg, Regulatory T cell; ILC, Innate lymphoid cell; SFA, Saturated fatty acids; PUFA, Polyunsaturated fatty acids; DHA, Docosahexaenoic acid; EPA, Eicosapentaenoic acid.

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http://dx.doi.org/10.1016/j.smim.2015.10.005
1044-5323/

Table 1

Adipocyte type	Primary function(s)	Lipid droplet morphology	Depot types/locations *(studied most frequently in mice)*	Lineage relationship
White	Lipid storage	Unilocular	Subcutaneous *(Inguinal)* Visceral *(Epididymal)*	Controversial, can derive from mesenchymal stem cells
Beige/brite	Lipid storage and mitochondrial uncoupling	Multilocular	Scattered within white adipose tissue depots Subcutaneous > visceral *(Inguinal)*	Closely related to smooth muscle?
Brown	Mitochondrial uncoupling	Multilocular	Interscapular Neck *(Interscapular through adulthood)*	Closely related to skeletal muscle

White and brown were the only known adipocyte types prior to the recent discovery of beige (also known as brite (brown-in-white)), which can function more like a white adipocyte or more like a brown adipocyte, depending on environmental stimuli. Cold temperatures and β-adrenergic signaling are two strong stimuli of the mitochondrial-uncoupling, energy-dissipating activity of both beige and brown adipocytes. The interscapular BAT depot of humans is most prominent in infants, while adults have uncoupling-competent adipocyte clusters in the neck region. Whether these depots are true brown, true beige, or some mix of the two, remains to be determined. Each adipocyte type appears to have a distinct progenitor, and one recent report suggests that beige adipocytes may be closely related to smooth muscle [7]. However, the precise developmental ancestry of each lineage is still unclear and is a matter of intense investigation [6,9].

in small, multilocular droplets that are quickly catabolized for fuel when the tissue is stimulated. Excitingly, the brown/white paradigm has been revised by the discovery of beige (also known as brite) adipocytes dispersed within WAT depots [3,4]. When rodents are exposed to cold temperatures, or, notably, after prolonged high fat diet (HFD) feeding, beige adipocytes can dissipate heat in a manner similar to classical brown adipocytes [5]. Importantly, despite their lipogenic abilities, white, brown, and beige adipocytes likely have distinct lineage ancestries [6,7] (Table 1).

The white–beige–brown adipocyte continuum informs our understanding of the anatomical distribution and functional distinctions of mammalian AT depots. White adipose tissue (WAT) is classified as subcutaneous or visceral. Subcutaneous depots are found throughout the body underneath the skin and humans have prominent elastic depots in the abdomen and legs. Major sites of human visceral adipose tissue (VAT) are the abdominal mesenteric and omental depots [8]. The omental fat pad comprises a much larger fraction of total body fat in humans than in rodents, though the rodent epididymal depot in males (which is often sampled as the representative visceral WAT depot) may be functionally equivalent to human omental fat [8]. Other VAT depots studied in rodents include the mesenteric and retroperitoneal. BAT is located in rodent and human interscapular regions perinatally but regresses and is not found there in human adults. Rather, we possess BAT-like thermogenic cells in the neck and supraclavicular regions [9]. Functionally, AT depots differ in progenitor proliferation rates, lipogenic and lipolytic capacity, and adipokine secretion profiles [10]. The tendency of visceral depots to become more inflamed in the setting of diet-induced obesity (DIO) is especially germane to the topics covered in this review.

2.2. Immunocyte populations infiltrating white adipose tissue

Infiltration of AT by macrophages was discovered in 2003, and for several years studies of this myeloid cell population dominated the field of immunometabolism [11,12]. Twelve years later, the roll call of immunocyte populations found as resident within, or diet-driven to, AT depots reads like a census of almost all known myeloid and lymphoid subsets [13]. A useful framework for discussing these populations is to distinguish cell types associated with maintaining metabolic health in the lean state and in early stages of DIO from those believed to initiate and/or exacerbate the chronic inflammation that contributes to adipocyte dysfunction in obesity.

In lean humans and rodents, AT macrophages may promote tissue remodeling and temper inflammation by secreting anti-inflammatory cytokines [14]. Eosinophils and Type 2 innate lymphoid cells (ILCs) are thought to have a similar role, especially given their ability to produce the Type 2 cytokines IL-4 and IL-13 that sustain anti-inflammatory macrophages [15,16]. Importantly, gain- and loss-of-function studies have shown that Type 2 ILCs and eosinophils limit weight gain during HFD feeding and also promote glucose tolerance and insulin sensitivity, likely due in part to their effects on body weight [15,16]. Macrophages, mast cells, and neutrophils are three pro-inflammatory populations that accumulate in AT during DIO, with neutrophil influx observed after only a few days of HFD feeding [17,18]. Contrary to results for the anti-inflammatory cell populations, genetic and/or pharmacological inhibition of mast cells and neutrophils improves metabolic indices, with the latter doing so independently of differences in body weight vis-à-vis wild-type control mice [17,18]. In many tissues, macrophages can adopt a spectrum of phenotypes, and AT is likely no exception. An early model proposed that the anti-inflammatory macrophages in the WAT of lean individuals undergo a "phenotypic switch" to a pro-inflammatory phenotype closely related to classically LPS and IFNγ-activated M1 macrophages, during DIO [19]. Several studies have refined this model [20,21], including the recent description of "metabolically activated" macrophages that accumulate in AT during DIO and can be induced by a cocktail of metabolic stimuli (insulin, glucose, and the saturated fatty acid palmitate). This population secretes pro-inflammatory cytokines but is distinguished from classical M1 macrophages by expression of genes regulating lipid metabolism [22].

B and T lymphocyte subsets can similarly be segregated based on their associations with limiting or exacerbating the pro-inflammatory tone of AT. A population of regulatory B cells, notable for their constitutive production of IL-10, is abundant in the AT of lean mice. B cell-derived IL-10 restrains the HFD-induced accumulation of pro-inflammatory macrophages and CD8+ T cells in VAT [23]. The AT-resident B cell population in lean mice may be heterogeneous, as a second, distinct population of IL-10 producing anti-inflammatory B cells has been found in VAT [24]. Prior to the description of AT-resident regulatory B cells, a population of CD4+ and Foxp3+ regulatory T cells (Tregs) was discovered in the visceral, and (to a lesser extent) subcutaneous, AT of lean individuals. The fractional representation of Tregs within the CD4+ T cell compartment is far higher in VAT than in lymphoid tissues, and their numbers decline specifically in VAT with diet-induced or genetic obesity [25–27]. Importantly, systemic and AT-specific ablation of Tregs exacerbates diet-induced AT inflammation and metabolic dysfunction [25,28,29]. VAT Treg maintenance in AT may be supported by a resident population of invariant natural killer T (iNKT) cells that produces IL-2. These anti-inflammatory iNKT cells also produce IL-10 and may act in concert with VAT Tregs and Bregs to maintain metabolic homeostasis [30]. On the pro-inflammatory side are IFNγ-producing CD4+ T cells that resemble classic Th1 cells and IFNγ-producing CD8+ T cells. Genetic ablation or antibody-mediated depletion of CD8+ T cells ameliorates AT inflammation during DIO [31,32]. B cells also have a pro-inflammatory,