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Review

Emerging Roles of Adipose Progenitor Cells in Tissue Development, Homeostasis, Expansion and Thermogenesis

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Stem or progenitor cells are an essential component for the development, homeostasis, expansion, and regeneration of many tissues. Within white adipose tissue (WAT) reside vascular-resident adipose progenitor cells (APCs) that can proliferate and differentiate into either white or beige/brite adipocytes, which may control adiposity. Recent studies have begun to show that APCs can be manipulated to control adiposity and counteract 'diabesity'. However, much remains unknown about the identity of APCs and how they may control adiposity in response to homeostatic and external cues. Here, we discuss recent advances in our understanding of adipose progenitors and cover a range of topics, including the stem cell/progenitor lineage, their niche, their developmental and adult roles, and their role in cold-induced beige/brite adipocyte formation.

Trends

Subcutaneous and visceral white adipose depots have different embryonic and postnatal development from different adipose progenitor sources.

APCs contribute to adipocyte formation under both homeostatic and environmental cues.

White APCs reside in a perivascular niche resembling a subset of mural cells.

Beige APCs reside in a perivascular niche and, upon cold exposure, form beige adipocytes, a potential therapy to combat excess fat.

Evidence for Adipose Progenitor Cells

Adipose tissues are widely distributed in stereotypic positions throughout the body [1]. This distribution can specify function, spanning diverse roles such as protection against trauma, cold, and starvation [2]. Yet, the ability of adipose tissue to expand in response to caloric excess can lead to obesity and its associated metabolic disorders (diabetes, hypertension, cardiovascular disease, atherosclerosis, cancer, etc.), which can have profound physiological, psychological, sociological, and economical ramifications [3,4]. While controlled caloric intake and increased fitness can address the obesity pandemic, it may also be addressed by identifying therapies that can manipulate adipose tissue formation, mass, and function. However, such a metabolic 'silver bullet' remains elusive. Targeting adipocytes themselves has proved to be only modestly or temporarily effective. For example, although liposuction and abdominoplasty remove unwanted adipose tissue, the adipose tissue compensates by regenerating its mass [5]. This reconstitution suggests that APCs are involved in the responses to injury or trauma and, conceivably, that stem/progenitor cells may also regulate tissue homeostasis and expansion. The possibility of a stem compartment is also supported by other findings. For instance, high fat diet (HFD) and exercise appear to regulate the adipose stem compartment to produce the number of cells (stem and adipocytes) necessary to meet metabolic demand [6–9]. The adipose stem compartment also seems subject to pharmacological manipulation; for example, the antidiabetes drug thiazolidinedione (TZD) has been shown to drive APC commitment to adipocytes [10]. Thus, the adipose stem compartment may be a modulatory nexus to counteract adiposity and metabolic dysfunction. Although our understanding of adipose stem biology is in its infancy, recent efforts to characterize APCs,

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their niche, and how they control adiposity and metabolic dysfunctions have begun to bear fruit. In this review, we delineate these findings and discuss unresolved questions.

WAT Development, Homeostasis and Expansion

Three phases of **WAT** (see Glossary) biology exist: (i) the development of adipose tissue (organogenesis); (ii) the homeostasis or maintenance of adipose tissue; and (iii) the expansion of adipose tissue to external stimuli, such as caloric excess and cold exposure. Recent studies into these three facets have begun to make inroads into this relatively poorly understood area of adipose tissue biology, and the findings indicate that progenitor/stem cells contribute to each phase. In this review, we discuss the role of APCs in adipose tissue development, homeostasis, and expansion, and in thermogenic responses.

WAT Development

Developmental Timing

Many organ systems require a specialized developmental cell, which coordinates the development, pattern, and formation of the tissue [11–13]. Recent studies suggest that adipose tissues require a specialized developmental cell type that patterns and forms the depots. Studies directed at murine adipose tissue organogenesis have indicated that **subcutaneous** and **visceral adipose depots** (SAT and VAT, respectively; Box 1) form in an ordered and timed manner throughout embryogenesis and within the first few weeks of birth [13–15]. SAT depots begin to develop during embryogenesis and the progenitor compartment is established for all SAT depots before the first few days of life. For example, the SAT depots, inguinal WAT (IGW) and periscapular WAT (PSCW), are specified between embryonic days E13.5 and E18.5 [13–15]. VAT depots principally form postnatally: the perigonadal (PGW) lineage forms approximately between postnatal day 3 (P3) and the second week of life. The mesenteric (MSW) VAT adipose compartment completes its organogenesis lineage establishment between the second and third weeks of life [13,14]. The retroperitoneal (RPW) VAT depot is formed in-between these pre- and postnatal stages, and has a morphogenesis, texture, and histology that also seems intermediate [13] (Figure 1). Early-to-mid embryonic establishment of SAT progenitors and tissues also occurs in humans. Human APCs begin to accumulate lipid during the second trimester of embryogenesis [16]. As embryogenesis continues, adipose depots and progenitors

Box 1. Adipose Tissue: Back to Basics

Lessons from Histology

Histological studies from the first half of the 20th century suggested that WAT comprises specialized cells termed 'adipocytes' that store lipid, rather than comprising connective tissue intercalated with lipid droplets [77]. WAT is not only specialized in lipid storage, but also acts as an endocrine organ by maintaining systemic metabolism, such as insulin sensitivity and lipid homeostasis. Decades of additional research has uncovered key roles for adipose tissue in physiology and metabolism, such as appetite, sexual reproduction, and thermogenic regulation [78]. The classic histological efforts delineated two types of adipose tissue: WAT [2] and brown adipose tissue (BAT). Fatty energy stores are liberated from WAT into the bloodstream upon demand and are brought to the appropriate cells, organs, and tissues for utilization [2]. BAT has a unique interscapular location, distinguished histology, and markedly different function due to the expression of mitochondrial uncoupling protein 1 (UCP1) [53], which functions to uncouple the electron transport chain to produce heat [53]. This thermogenic capability of BAT is essential for hibernating animals, which require heat to increase their core body temperature after a long bout of torpor [53].

Anatomy and Types

WAT is anatomically separated into two broad adipose compartments: subcutaneous (SAT), just below the dermis, and visceral (VAT), within the body cavity [1]. The SAT and VAT compartments themselves contain several distinct adipose depots. For example, murine SAT includes periscapular and inguinal depots; VAT includes perirenal, perigonadal, and mesenteric depots [1,18]. SAT and VAT have defined anatomical locations and distinctive developmental timing, texture, vascularity, adipocyte size, and gene expression [18,19]. These traits may confer body-fat distribution, body mass index, and insulin and glucose sensitivity, and have important functional attributes. For example, several studies indicate that humans with increased VAT have a higher prevalence of metabolic dysfunction than those with increased SAT [20,21].

Glossary

Beige/brite adipocytes: a cold and β3 adrenergic-inducible multilocular adipocyte that can express UCP1 and has thermogenic capacity.
Brown adipose tissue (BAT): multilocular, mitochondria-rich adipocytes with thermogenic function. They express uncoupling protein 1 (UCP1), which uncouples the electron transport chain to generate heat rather than chemical energy (ATP).
Hypertrophy: the enlargement of pre-existing adipocytes, which can expand to accommodate excess dietary nutrients, storing them as triglycerides,
Hyperplasia: the proliferation and expansion of the APC and stromal vascular compartment within adipose depots in response to caloric excess.
Subcutaneous adipose tissue (SAT): white adipose tissues that form just below the dermis. Inguinal (posterior) and periscapular (anterior) are distinct depots of SAT.
Stromal vascular fraction (SVF): the numerous cell types that comprise the nonadipocyte compartment of adipose depots. Cell types include: endothelial cells, mural/smooth muscle cells, fibroblasts, neuronal cells, inflammatory cells, and APCs
Visceral adipose tissue (VAT): white adipose tissues that form within the body cavity. Perigonadal, retroperitoneal, and mesenteric are distinct depots of VAT.
White adipose tissue (WAT): lipid-storing unilocular adipocytes that store energy in the form of triglycerides