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The expanding problem of adipose depot remodeling and postnatal adipocyte progenitor recruitment

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ABSTRACT

The rising incidence of obesity and associated metabolic diseases has increased the urgency in understanding all aspects of adipose tissue biology. This includes the function of adipocytes, how adipose tissue expands in obesity, and how expanded adipose tissues in adults can impact physiology. Here, we highlight the growing appreciation for the importance of *de novo* adipocyte differentiation to adipose tissue expansion in adult humans and animals. We detail recent efforts to identify adipose precursor populations that contribute to the physiological postnatal recruitment of white, brown, and beige adipocytes in mice, and summarize new data that reveal the complexity of adipose tissue development *in vivo*.

1. Function of adipocytes in adult physiology

1.1. White adipocytes

Eukaryotes stores excess energy in the form of intracellular triglycerides. Triglyceride storage in vertebrates is largely confined to specialized, dedicated cells, called white adipocytes (fat cells). The white adipocyte is characterized by the presence of a large unilocular lipid droplet that functions as a safe storage compartment for triglycerides. During times of caloric excess, white adipocytes sequester free fatty acids (FFAs) from the circulation and store them as triglycerides. When there is a demand for energy, such as during a prolonged fast, triglycerides are hydrolyzed into glycerol and FFAs that are released into the circulation and subsequently utilized as fuel.

White adipose tissue (WAT) can be found throughout the body but is invariably organized into anatomically distinct "depots" (Fig. 1). In general, white adipose appears in subcutaneous regions, or within the intra-abdominal area (Shen et al., 2003). Several subcutaneous white adipose depots serve a mechanical function in providing support and cushioning to surrounding organs. In the heel pad, adipocytes are embedded in a dense network of collagen fibers for mechanical support. The orbital fat is a semifluid adipose layer that lines the bony orbit to cushion the eyeball. The subcutaneous fat directly below the skin serves as a layer of thermal insulation. Moreover, *bona fide* adipose tissue in various intra-abdominal regions juxtaposes several organs such as the kidney, heart, and intestine.

Fetal development of white adipose tissue begins with a dense mass of blood vessels surrounded by mesenchymal stem cells (Poissonnet et al., 1984). Human adipose tissue appears during the 14th–17th week of gestation as a cluster of fat lobules first in the head and neck, then the trunk, and later in the limbs (Poissonnet et al., 1984). The precise developmental origin of WAT during fetal development is still unclear; however, lineage tracing in mice indicates that subcutaneous and intra-abdominal depots emanate from distinct lineages (Chau et al., 2014). The specific origin may vary from depot to depot. For instance, in mice, craniofacial, but not peripheral, subcutaneous WAT depots originate from neuroectoderm rather than mesodermal structures (Billon and Dani, 2012). Fat mass in humans expands during the first year of birth through an expansion of cell size and number (Knittle et al., 1979; Spalding et al., 2008). Later in adulthood, adipocytes turnover at a rate of 10% per year and adipocyte number remains relatively stable regardless of BMI or weight loss (Spalding et al., 2008).

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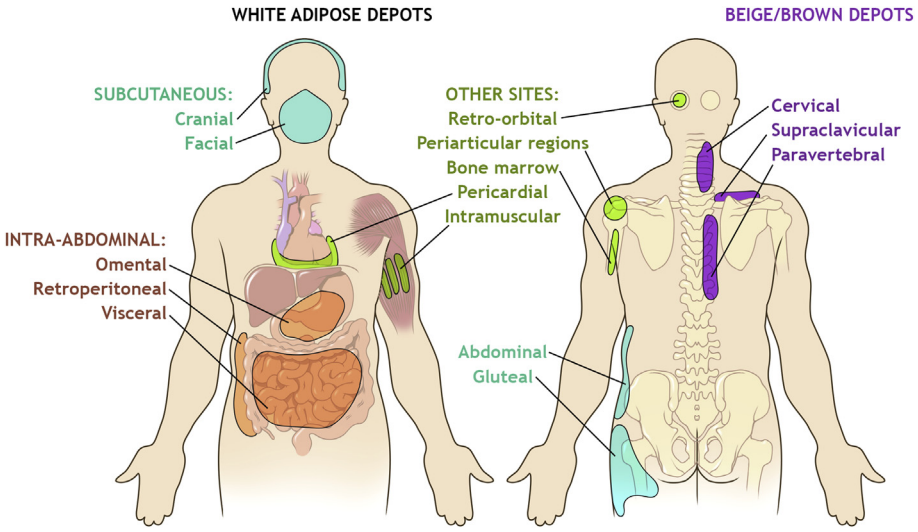

Fig. 1. Distribution of White and Brown/Beige Adipose Tissue in Adults. White adipose tissue (WAT) is organized into distinct depots, classified by location as subcutaneous or intra-abdominal. The major subcutaneous WAT includes the abdominal, gluteal, and femoral depots. Other white subcutaneous depots include the cranial and facial adipose tissue. Intra-abdominal adipose tissue is located within the peritoneum and includes the omental, retroperitoneal, and visceral (mesenteric) fat. White adipocytes also accumulate in other locations, including behind the eye (retro-orbital), around joints (periarticular), in bone marrow, surrounding the heart (pericardial), and within the skeletal muscle (intramuscular). Brown adipose tissue (BAT) in adults exists as a heterogeneous tissue, containing brown and beige adipocytes interspersed with white adipocytes. BAT depots are located in the cervical, supraclavicular, and paravertebral regions in adults.

Over the past two decades, our understanding of adipose tissue has expanded dramatically. The adipose tissue was long considered as merely a storage reservoir; however, now, it is recognized as an active endocrine organ capable of regulating systemic nutrient balance and energy homeostasis (Neumann et al., 2016; Ouchi et al., 2011; Rosen and Spiegelman, 2014). Adipose tissue secretes hormones and cytokines, termed “adipokines,” that regulate systemic glucose homeostasis, lipid metabolism, inflammation, and many other physiological events (Deng and Scherer, 2010). The essential roles of adipose tissue in energy balance become increasingly apparent in individuals that lack functional adipose tissue (lipodystrophy) and in individuals that have excess fat cells (obesity). Both of these extremes lead to dyslipidemia, insulin resistance, and inflammation and are associated with an altered adipokine profile (Barroso et al., 1999; Haque et al., 2002).

1.2. Brown adipocytes

Eutherian mammals also contain “brown” adipocytes whose principle function beyond nutrient homeostasis is to convert chemical energy into heat. Brown adipocytes are characterized by their multilocular lipid droplet appearance and high mitochondrial content (Cannon and Nedergaard, 2004). The thermogenic function of brown adipocytes is mediated by the specific expression of uncoupling protein 1 (UCP1) (Klingenberg, 1999). UCP1 is a transport protein that sits within the inner membrane of mitochondria and facilitates a proton leak across the inner membrane (Fedorenko et al., 2012). This dissipates the electrochemical gradient that has been generated via the electron transport chain, thereby uncoupling oxidative metabolism from ATP synthesis. Heat production occurs as the biochemical reactions involved in mitochondrial fuel oxidation are subsequently accelerated. The activity of brown adipocytes is regulated by the sympathetic nervous system via β3-adrenergic signaling (Lowell and Flier, 1997). This pathway triggers the activation of UCP1 as well as a transcriptional program that leads to further UCP1 expression. Lineage tracing reveals that brown adipocytes, but not most white adipocytes, derive from a Myf5+/Pax7+ lineage, and thus share a common developmental origin with skeletal muscle (Seale et al., 2008).

Brown adipose tissue (BAT) plays an important role in lipid metabolism but likely evolved as a mechanism for mammals to defend against hypothermia (Cannon and Nedergaard, 2004). As such, rodents housed in standard conditions have copious amounts of BAT at the time of birth and maintain these depots throughout life. The most prominent BAT depot in mice is found in the interscapular region. This depot is also present in human infants but largely involutes with age (Aherne and Hull, 1966; Lidell et al., 2013). Initially, it was widely believed that adult BAT was limited to individuals with pheochromocytoma, an adrenal tumor characterized by excess catecholamine secretion, and in outdoor workers in Northern Europe with chronic exposure to cold temperatures (Huttunen et al., 1981; Ricquier et al., 1982). A series of studies published in 2008 showed that this was not the case. ^{8}F-fluoro-2-deoxy-d-glucose positron emission tomography computed tomography (^{18}F-FDG-PET) imaging verified the existence of BAT as an active, energy-consuming organ in most non-obese adults (Cypess et al., 2009; Virtanen et al., 2009). In adults, thermogenic BAT is located in the supraclavicular, cervical, paravertebral, and perirenal regions and the amount of BAT is higher in lean verses obese individuals (Fig. 1) (van Marken Lichtenbelt et al., 2009). Importantly, human supraclavicular BAT can be activated in response to chronic cold exposure and contributes to nutrient homeostasis (Chondronikola et al., 2014, 2016).

1.3. Beige adipocytes

It has long been recognized that WAT depots of cold exposed rodents can undergo extensive remodeling and adopt a thermogenic phenotype, elicited by the emergence of “brown-like” energy-burning adipocytes (Loncar, 1991). However, lineage-tracing reveals that most UCP1^{+} cells within WAT depots are not derived from a Myf5^{+} lineage, suggesting a developmental origin distinct from the brown adipocytes formed during the fetal period (Sanchez-Gurmaches and Guertin, 2014; Seale et al., 2008). These cells activate UCP1 upon cold exposure and exhibit a multilocular lipid droplet phenotype (Long et al., 2014); however, they appear to