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

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Abstract

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.

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

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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, 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 elaborate and the process is completed within the following weeks, just before birth [16,17]. However, little is known about the *in utero* or postnatal timing of human VAT [18,19]. Collectively, studies from both rodents and humans indicate that WAT organogenesis unfolds in a systematic and developmentally timed manner and that embryonic specification may denote the function and requirement of adipose tissue during development.

Developmental Origin

The subcutaneous embryonic and visceral postnatal organogenesis may reflect different developmental origins. Cell marking studies performed in mice indicate that SAT depots emerge from a field of cells marked by the homeobox gene *Prx1*. However, some VAT depots seem to originate from a field of cells marked by Wilms Tumor 1 (WT1), but the contribution seems to vary depending on the VAT depots [20,21]. Guertin and colleagues performed several elegant studies using Myf5-Cre-driven indelible reporters. They found that Myf5-Cre marked a subset of progenitor cells within PSCW SAT but not IGW SAT or PGW VAT, potentially uncovering key aspects of adipose organogenic mechanisms [22–24]. All SAT and VAT depots originate from cells that express platelet-derived growth factor receptor alpha (PDGFRα), consistent with the broad expression of PDGFRα throughout early and mid-embryogenesis [25,26]. However, it seems that PDGFRα has less of a role in adult adipose tissue homeostasis based on the lack of adipocyte labeling, except under HFD conditions. In general, it appears that a variety of mesodermal genetic tools mark WAT and BAT depots, but it will be beneficial to identify more specific markers to track and manipulate adipose tissue development, if such adipose-specific markers exist (Table 1).

Developmental APCs

Current evidence suggests that WAT development relies on one or several developmental or organogenic progenitors to pattern and form the SAT and VAT depots. To identify such a developmental cell, one group used direct *in vivo* examination, cell marking, and *in vitro* testing to identify that developmental APCs express perilipin and adiponectin. Importantly, these cells were capable of replication. Moreover, the authors noted that these proliferating perilipin+ cells appeared in clusters located along the growing vasculature within WAT [27]. In agreement, Jiang et al. showed that developmental APCs also reside juxtaposed to blood vessels within developing WAT [13]. To more restrictively probe the WAT developmental stem/progenitor compartment, Rodeheffer and colleagues used a leptin-luciferase reporter mouse to track adipose tissue development [15]. Exploiting this model, they found that leptin-luciferase activity could be detected as early as E16.5 and its activity progressively increased until birth. Genetic analysis of leptin-luciferase+ cells revealed a unique genetic signature as WAT developed. This genetic signature also appeared to demonstrate some differences to the classical NIH3T3-L1 adipocyte cell culture model used to study adipogenesis [15] (Box 3). These genes provide potential clues about the WAT developmental program; however, how this genetic network controls or initiates WAT development remains unanswered. Along the same lines, researchers have begun to identify genes that regulate WAT development versus homeostasis [6,28]. For example, both C/EBPα and AKT2 are involved in maintaining WAT homeostasis and expansion, but not WAT development [6,28].

Collectively, these seminal findings spanning WAT organogenesis to the embryonic cellular origins of WAT to identifying primitive developmental adipose stem cells have set the foundation for the next step in WAT developmental studies. For example, studies that try to identify the molecular underpinnings, such as the transcriptional and signaling networks that control developmental APCs, could unearth basic developmental questions. Additionally,

identifying key genes that control adipose tissue development may allow for the engineering of unique genetic tools to more restrictively mark and track developmental APCs.

WAT Homeostasis

The Adult APCs

Adipocyte turnover and ultrastructural studies suggest that APCs continually supply the tissue with new adipocytes throughout the lifespan of the organism [29,30]. Indeed, through the use of flow cytometric studies and genetic modeling, scientists have begun to uncover adult APCs in both rodents and humans [31–33]. However, multiple origins have been suggested for APCs (reviewed in [34]). A commonality from several independent research groups is the notion that adult APCs reside in the **stromal vascular fraction** (SVF) of WAT [31,32] (Box 2). Adipose tissue can be separated into two compartments based upon buoyant density: a floated fraction that contains lipid-laden white adipocytes and the SVF [35]. Within the SVF are cells that, when cultured in adipogenic medium, can form cells that contain lipid droplets, have some resemblance to adipocytes, and express adipocyte markers [36]. Using flow cytometry-based techniques, a population of cells from the SVF has been identified that express several cell surface markers and stem cell genes, such as Sca1+, CD24+, CD29+, CD34+ and PDFGRα+, and that can adipogenesis ectopically [31,32]. Additional studies have begun to generate a lineage progression framework from more stem-like CD24+ cells that can give rise to CD24– cells, which seem to be more committed to adipocyte differentiation [25]. PDGFRα also marks both populations of APCs [25].Overall, it appears that APCs may exist in various stages of adipocyte lineage commitment and that not all APCs are equal.

Notably, a similar population of murine SVF cells has been identified that have adipogenic potential but, surprisingly, these APCs express PPARγ, a nuclear hormone receptor and master regulator of adipocyte differentiation [32,37,38] (Box 3). Using genetic-tracing methodologies, it was found that PPARg-expressing APCs are critical for adipocyte formation *in vitro* and *in vivo* [13,32]. *In vivo* tracking of PPARγ+ cells indicated that these cells reside within the blood vessel walls of WAT [13,32] (Figure 2). In line with a vascular residency, these APCs resemble mural cells (aka: pericytes and vascular smooth muscle cells) because they express several mural cell markers, such as PDGFRβ and alpha smooth muscle actin (SMA) [13]. Importantly, these cells fate mapped into mature adipocytes under normal chow homeostatic conditions with an estimate of 10–20% of new adipocytes forming per month depending on the WAT depots [13]. Likewise, human studies based upon radioactive isotopic decay suggested that adipocytes are also continually turned over and replenished, with estimates of approximately 9% per year [30]. However, does this appreciable rate of adipocyte formation in murine models have an effect on adipose tissue homeostasis and systemic metabolism? Indeed, deletion of PPARγ in SMA+ cells demonstrated that these cells are required for new adipocyte formation. The inability to form new mature white adipocytes under normal homeostatic conditions resulted in blocked adipose tissue expansion and decreased glucose sensitivity [13]. These studies support the notion that APCs are used to maintain WAT and that, if WAT homeostasis is disrupted, metabolic dysfunction ensues.

Similarly, Gupta and colleagues identified a perivascular cell that expresses zinc finger protein 423 (ZFP423) and also PPARγ and other mural markers, such as PDGFRβ and SMA [39–41]. However, PDGFRβ/ZFP423+ cells only fate mapped into mature adipocytes under HFD conditions [42]. The difference in fate-mapping potential between PDGFRβ/ZFP423+ and SMA PPARγ+ cells needs further investigation. Correspondingly, PDGFRα+ cells have been identified as a progenitor source for white adipocytes, but only appear to contribute to VAT expansion [26]. These PDGFRα+ cells reside in the blood vessel adventitial region and resemble fibroblast-like cells [26]. These cells express neither mural cell markers nor PPARγ and fate mapped into perigonadal adipocytes under HFD conditions [26]. What might account for the discrepancies in adipocyte generation in different rodent models? Several reasons may exist: (i) specificity of genetic tools used to mark the APC and adipocyte compartment; (ii) the mouse: age, gender, and strain; (iii) the type of WAT depot under investigation; (iv) the location analyzed within the WAT depot; and (v) the reliance on the notion that APCs must divide (BrdU fate mapping: see ‘WAT Expansion’). What is clear from these studies is that some APCs do reside in adipose tissues. A future goal would be to tease apart the lineage and cellular differences and similarities among these various cell types. That is, does one cell type beget the other, or are they independent? In addition, are different cell types utilized under different dietary conditions? Answers to these lineage relation questions may be able to provide clues into when, why, and how APCs are engaged to differentiate into mature adipocytes under different cues.

Adding further to the progenitor fray is the observation that adult perivascular APCs have embryonic origins [13,43]. Current evidence suggests that adult APCs emanate from a small group of cells present in the E10.5 embryo [13,43]. These E10.5 cells express PPARγ and Pref-1, two genes that are also expressed postnatally in bone fide APCs [13,43]. PPARγ E10.5 fate-mapping studies showed that these cells lineage traced into adult, but not developing, WAT (SAT and VAT) [13]. Notably, E10.5 adult APCs do not reside in WAT before or during WAT development [13]. After WAT development, PPARγ+ E10.5 adult progenitor cells in ltrate the WAT depots and occupy vascular residency (Figure 2). Moreover, deleting PPARγ in these E10.5 cells resulted in abnormal WAT homeostasis (decreased adiposity and glucose sensitivity) but did not alter adipose tissue development [13]. Another study using Pref-1 labeling found similar results: Pref-1 marked a field of cells at E10.5 located in the dorsal mesenteric region that produced adipocytes [43]. However, the Pref-1 studies did not distinguish the temporal relation of specification between the developmental and adult pools. Recent studies suggest that retinoic acid upregulates Pref-1, but does this important embryonic hormone regulate Pref-1 under this biological setting [44]? Other questions relating to downstream pathways and genes that regulate and/or are regulated by Pref-1 and PPARγ could provide key insights into lineage specification and tissue development and homeostasis. Such insights might highlight how adult adipose tissues are developed and subsequently maintained throughout the lifespan of the organism.

Other Adipocyte Progenitor Cell Sources

Even though several studies have suggested WAT-resident APCs, others have suggested auxiliary sources, such as multipotent hematopoietic progenitors [45]. Through the use of imaging and bone marrow transplantation studies, researchers have identified multipotent

hematopoietic cells that are able to populate and contribute to adipocyte formation [46]. However, several transplant and genetic mouse studies are at odds, which has led to a heated debate as to whether bone marrow progenitors can differentiate into white adipocytes [47,48]. Recently, an elegant and sophisticated study was performed to address whether human bone marrow cells could produce SAT adipocytes. These researchers utilized genomic differences between donor and recipient cells to find that human bone marrow progenitors contributed to approximately 10% of SAT adipocyte number over the entire lifespan of the recipient [49]. This study corroborates that bone marrow progenitors can give rise to adipocytes, but raises the interesting notion that other lineages can serve as a reservoir for adipocytes under various conditions. Additionally, what is the relation between the identified perivascular sources and the multipotent hematopoietic stem cells? It will be exciting to distinguish the temporal relation(s) or difference(s) between these alternative sources and lineages of WAT homeostasis and expansion.

WAT Expansion: Plumped Up

Both WAT **hypertrophy** and **hyperplasia** are key responses to a HFD or Western diet [14]. However, it has been difficult to assess the relative contribution of hypertrophy and hyperplasia. To measure hyperplasia, scientists have relied on methods to measure DNA synthesis (BrdU) of the SVF compartment and to monitor the ability of SV cells to transition from the progenitor to adipocyte compartment. Studies examining the rodent APC compartment have proposed that 4.8% of progenitors are dividing at a given time and that the APC pool is continually replenished [50]. However, these DNA synthesis studies may not accurately reflect the overall contribution of the adipocyte progenitor compartment to adipocyte differentiation. Furthermore, this model also relies on the notion that APCs must proliferate before adipocyte differentiation. To overcome this, new genetic tools have been developed to access the overall contribution of hypertrophy and hyperplasia to WAT expansion. These recent efforts have shown that new adipocytes form in response to HFD but primarily in VAT depots [14]. In rodents, the generation of new adipocytes in response to a HFD appears to depend on the age of the animal. For example, juvenile mice fed HFD showed robust adipogenesis, whereas adult mice showed lower adipogenic potential [51]. Aging, in general, also appears to decrease the progenitor compartment activity (proliferation and differentiation) and this may be a component of metabolic failure that is triggered by dysfunctional adipocytes as we age [52].

Not only are new adipocytes formed under caloric excess, but the APC compartment also appears to be active. To begin to tease apart when and where APCs might proliferate under HFD conditions, Rodeheffer and colleagues found that, soon after HFD administration, APCs are prompted to enter the cell cycle [6]. The propagatory phase is relatively short lived. Yet, the burst of proliferation leads to a marked increase in the number of progenitors, potentially held as a reserve. Indeed, the newly formed progenitor cells are not immediately utilized to make adipocytes; instead, they are used after several weeks of HFD to generate new white fat cells [6]. However, the identity of signals and factors that govern this response remains unknown. Collectively, although it appears that new adipocytes are generated under HFD conditions, other factors, such as age, duration, and gender, should be taken into consideration when studying these events.

Beige/Brite Adipocyte Lineage: Beige/Brite Is the New Black

Brown adipose tissue (BAT) generates heat rather than energy (ATP) [53]. It does so, in part, by expressing the mitochondrial protein uncoupling protein 1 (UCP1), which uncouples the electron transport chain [53]. In addition to UCP1, there may be other unique energy expenditure features of BAT, such as arginine/creatine metabolism, that assist in thermogenic activity [54]. This key thermogenesis feature of BAT has been shown to be essential for hibernating animals, which require heat to increase their core body temperature after a long bout of torpor [55]. During the 1980s, it was realized that rodents exposed to cold induced the formation of brown-like adipocytes within WAT [56]. Successive studies showed that β-adrenergic agonists stimulated a related phenomenon, identifying the sympathetic nervous system as a regulator of endothermia [57]. In rodents, it was thought that these brown-like adipocytes induced by cold or β-adrenergic stimuli within WAT depots, were related to classical interscapular brown adipocytes. However, recent efforts have begun to distinguish them into a third type of adipocyte, termed beige or brite (brown-in white adipose tissues) [58,59]. **Beige/brite adipocytes** are inducible, multilocular, can express UCP1, and are thermogenic [58]. Even though both brown and beige/brite adipocytes express a core of common thermogenic genes, they differentially express other genes, such as *CD137* and *TMEM26*, which are highly enriched in beige/brite adipocytes [58]. However, further characterization is needed to fully identify whether beige/brite adipocytes are analogs to, or distinct from, brown adipocytes [60].

Recent technological (imaging) and methodological (monitoring *in vivo* BAT activity) advances have led to the identification and revitalization of brown and cold-inducible BAT as a potential therapy for metabolic dysfunction for humans [61–65]. This renewal has been spearheaded due to human research that demonstrates the presence of brown and/or beige/brite adipocytes [62,63,66–69]. Biopsies of human supraclavicular WAT after cold exposure demonstrated the presence of inducible thermogenic brown-like adipocytes [70]. Molecular profiling studies indicate that the thermogenic adipocytes that appear in humans are more like rodent beige/brite adipocytes rather than the classical rodent brown adipocytes [58,59]. Thus, the ability to manipulate the formation or function of each adipocyte lineage could be a component in the diabesity pharmacopeia. However, whether beige/brite adipocytes are therapeutically relevant in the fight against human metabolic dysfunction remains controversial, although we favor a therapeutic role.

Since the discovery of beige/brite adipocytes, the cellular lineage that generates these cellular furnaces has troubled scientists and has remained murky [53]. An early popular notion was that beige/brite adipocytes derive from the *trans*-differentiation of mature white adipocytes [71]. This notion has been rekindled by genetic studies examining adipocyte cell marking, which have suggested that white adipocytes could convert from white to inducible beige/brite adipocytes [72]. However, another adipocyte fate-mapping study (AdipoChaser) is at odds with the white to beige/brite conversion possibility [14]. This may be related, in part, to the type of genetic tools and drugs used to induce labeling recombination [73]. In agreement with the interconversion hypothesis, another study identified that, after cold exposure in mice, beige/brite adipocytes are not eliminated, but convert to white adipocytes [74]. However, upon additional cold exposure, these phenotypic white, once

beige/brite, adipocytes revert to being beige/brite adipocytes. This study suggests that these 'interconverting adipocytes' have retained a beige/brite genetic memory that allows them to become reactivated when stimulated. Of note, after re-exposure to cold, new unlabeled beige/brite adipocytes were also generated that were not from the previously marked beige/brite adipocytes [74]. Thus, other cellular sources might exist. In agreement with this notion, several other studies have proposed a perivascular source for cold-induced beige/brite adipocytes, a resemblance to WAT progenitors. For example, smooth muscle genetic fate-mapping studies have suggested cells marked by Myh11, PDGFRβ, and SMA can generate beige/brite adipocytes in response to cold exposure [42,75,76]. In a recent fate-mapping study, SMA+ perivascular cells generated 50–70% of new beige/brite adipocytes after 1 week of cold exposure [76]. Conversely, other smooth muscle genetic fate-mapping tools, such as Myh11 and PDGFRβ, only label beige/brite adipocytes after 2 weeks of cold exposure [42,75]. What accounts for the differences between 1-week versus 2-weeks of cold exposure is not clear. Flow cytometric studies indicate that different populations of smooth muscle cells may exist that express one or multiple smooth muscle markers, which suggests that different cellular populations are used after different durations of cold exposure. Regardless of the contribution, two methodologies, blockade of adipocyte differentiation or a cell killing strategy, tested the ability of SMA+ cells to generate beige/brite adipocytes. Remarkably, blocking adipogenesis within SMA+ cells or ablating SMA+ cells led to the failure of cold-induced beige/brite adipocytes. The absence of beige/brite adipocytes also appeared to impair metabolism; mice were unable to either defend their temperature or lower plasma glucose [76]. This was not the case when adipogenesis was blocked in Myh11+ cells: mice formed beige/brite adipocytes, defended their body temperature, and reduced their plasma glucose after 2 weeks of cold exposure [76]. Further studies aimed at delineating the relation and/or differences between cellular sources may help unravel the molecular underpinnings and signals that govern beige/brite adipocyte formation during prolonged cold exposure.

Concluding Remarks and Future Perspectives

Here, we have pieced together the current understanding of how APCs regulate adipose tissue development, homeostasis, expansion, and thermogenesis. This is an emerging eld that is evolving rapidly (see Outstanding Questions). However, the adipose stem/progenitor field has lagged behind and is only now beginning to catch up with other advanced lineages, such as the hematopoietic and neuronal fields, to define and characterize the cells that generate adipocytes. Recent efforts have provided hints of several aspects of APCs, such as their lineage and/or anlagen, niche, and role in tissue development and homeostasis. In addition to these fundamental aspects of stem cells, recent *in vivo* studies have made inroads towards defining molecular attributes and signatures, such as transcriptional networks and signaling pathways that regulate adipocyte formation. However, reconciling current knowledge into an outline of how the APC lineage is established and how these progenitors control WAT biology is difficult. Many discrepancies exist within the published data, which could be attributed to transgenic mouse models, mouse gender, mouse age, mouse strain, WAT depot under investigation, position of analysis within the WAT depot, and specificity of cell sorting antibodies. Nevertheless, this is an exciting time for the field with many new discoveries

ahead that will begin to address these fundamental WAT questions. Such insights may begin to paint a picture of the APC lineage and its role in WAT development, homeostasis, expansion, and thermogenesis.

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Glossary

Beige/brite adipocytes
a cold and b3 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

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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].

Box 2.

The APC Niche: A Vascular Zip Code

The niche is a major regulator of stem cell biology [83]. It controls stem cell properties, such as proliferation, migration, paracrine and endocrine signaling, and quiescence and differentiation [83]. Elegant in vivo studies from the 1940s and electron microscope studies from the 1960s demonstrated that broblast-like cells reside on WAT blood vessels [81,84]. These electron microscope images showed vascular-residing cells peeling away from the blood vessel as they transitioned into lipid-filled cells, or adipocytes [84]. Recently, genetic fate-mapping studies have positioned APC to the vascular niche [13,42]. These progenitor cells reside in perivascular positions along blood vessels within the adipose tissue. These vascular-residing progenitor cells appear to resemble mural cells in that they express a multitude of not only mural cell markers, such as SMA, but also adipocyte lineage markers, such as PPARg, ZFP423, and Pref-1 [13,42]. Although the niche is a critical regulatory component of stem cell biology, it has been difficult to examine the adipose tissue niche. One such difficulty has been the inability to isolate and examine the intact niche. This could be addressed by using an organotypic culture procedure termed ‘stromal vascular particulates’ (SVPs), which maintain the native structure of the microenvironment. Isolation of SVPs showed APCs wrapped around the blood vessel. Upon adipogenic signals, these cells peel away from the SVP, becoming lipid-filled adipocytes loosely associated with the vascular unit [13,32]. Several other studies have implicated the blood vessel niche as the microenvironment that controls APC number and adipose tissue mass [85]. The relation between blood vessels and APCs appears to be reciprocal [86]. That is, APCs stimulate blood vessel formation and blood vessels stimulate APCs expansion and differentiation [1,87]. Taken together, these studies support the notion that the vasculature is the niche for APCs. Future studies aimed at examine the APC niche may highlight important regulators of adipose tissue biology

Box 3.

Adipogenesis: How to Make a Fat Cell

Decades of elegant adipocyte research has focused on *in vitro* cell culture modeling, studying what has been coined ‘adipogenesis’ [88]. Adipogenesis was first described to demonstrate the transition of cultured and confluent NIH-3T3-L1 fibroblast cells to individual lipid-laden mature adipocytes. Fibroblast-like cells were incubated with a powerful recipe comprising thought-to-be adipogenic ‘inducers’: cAMP inducers, glucocorticoid agonists, and insulin or insulin-like growth factor (IGF) [89]. These pioneering studies paved the way for understanding adipocyte differentiation. For decades, researchers have teased apart various transcriptional components that regulate this complex differentiation process [88]. Advances derived from the NIH-3T3-L1 cellular system have been the identification of relevant molecules expressed during fat accumulation, particularly the transcriptional regulatory program. Among these, PPARγ, a nuclear hormone receptor, is necessary and sufficient for adipocyte formation. Several regulators of the differentiation program converge upon PPARγ to influence the conversion of progenitor cells to mature adipocytes [90]. In addition to transcriptional regulators, multiple signaling molecules, such as insulin, thyroid hormone, and TGFβ superfamily members, have been elucidated, and appear to initiate the adipogenic cascade (reviewed in [91]). Once adipogenic signals have been induced, a transcriptional cascade occurs, leading to the activation of multiple factors, such as Kruppel-like factor 4 (KLF4), SMAD1/5/8, CREB, glucocorticoid receptor, C/EBPβ, and C/EBPδ. Other transcription factors, such as thyroid receptor, C/EBPα, and LXR, are involved in adipocyte maturation and fat storage [91]. The appearance of a unilocular lipid droplet and the expression of lipid storage proteins characterize terminal differentiation [91]. Many signaling molecules, hormones, vitamins, and transcriptional factors positively regulate adipocyte differentiation, but just as many block or inhibit adipocyte maturation, such as WNT signaling, hedgehog, and retinoic acid [92,93]. *In vitro* adipogenesis has led the way for the basic biological understanding of adipogenesis; however, many aspects of in vitro adipocyte formation may not be conserved *in vivo*; thus, a potential challenge for adipose tissue biologists is to determine whether these molecules and their signaling control adipose tissue formation *in vivo*.

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.

Outstanding Questions

How do APCs pattern, organize, and form both the developmental and adult adipose tissues? What are the transcriptional and signaling networks involved in both of these phases? Are these same phases and networks observed in human adipose organogenesis and homeostasis?

What is the role of PPARγ in the adipose lineage? Does PPARγ regulate stem cell attributes, niche interaction, or only adipocyte differentiation?

How do other proposed cellular sources of WAT relate to the identified perivascular adipose progenitors? Are these other sources required for adipose tissue development or homeostasis?

What function do dermal and bone marrow adipocytes perform: functional, metabolic, niche, or other?

How does a HFD alter adipose progenitor cell dynamics (proliferation, migration, niche positioning, and differentiation)? Are different progenitor cells used in response to a HFD compared with a normal diet or homeostatic conditions?

What factors regulate adult APC niche interactions? What are the consequences when these signals are disrupted genetically, pharmacologically, or via diet? What is the niche for developmental APCs?

Are beige and white adipocytes generated from the same SMA+ progenitors or from a different SMA pool? What is the lineage relation between SMA, Myh11, and PDGFRb with regards to generating cold-induced beige adipocytes after 1 week versus 2 weeks of cold exposure? What are the relative contributions from other cellular sources to beiging?

Are there differences between cold-induced and b-adrenergic-induced beige adipocytes?

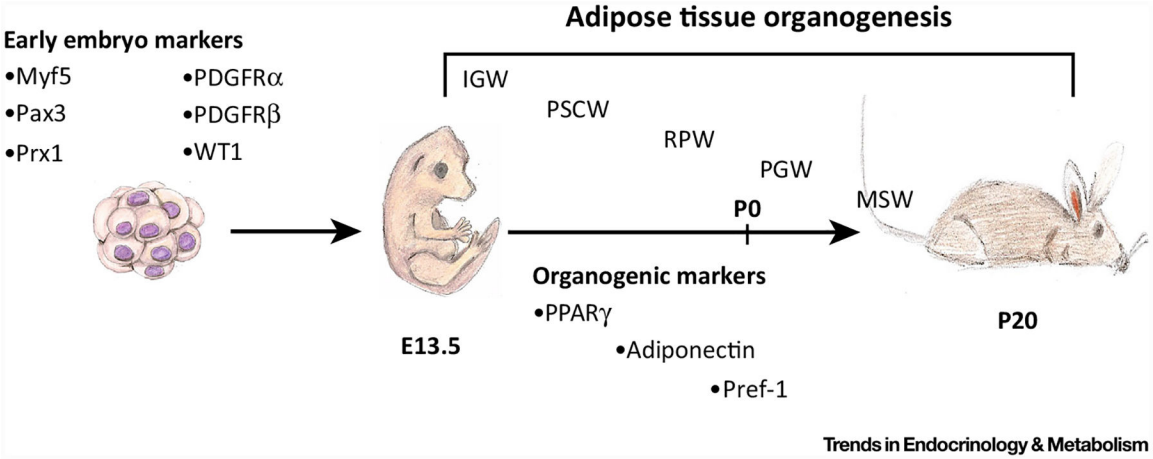

Figure 1. Adipose Tissue Organogenesis.

White adipose tissues are formed embryonically and postnatally. A variety of tools have been used to broadly identify early embryonic markers of adipose tissue, such as Myf5, Pax3, and Prx1. Around embryonic day (E)13.5, subcutaneous inguinal and periscapular adipose tissues are specified, patterned, and formed by more restrictive adipose lineage markers, such as PPARγ, adiponectin, and Pref-1. As embryogenesis continues (E18.5), the retroperitoneal adipose depot becomes specified, patterned, and formed. Both the perigonadal and mesenteric white adipose tissues are specified postnatally, beginning at postnatal day 2 (P)2 and ending near P20. Within the first month of life, all adipose depots are specified, formed, lipid filled, and functional. Designation of white adipose depots: IGW, Inguinal; MSW, mesenteric; PGW, perigonadal; PSCW, periscapular; RPW, retroperitoneal.

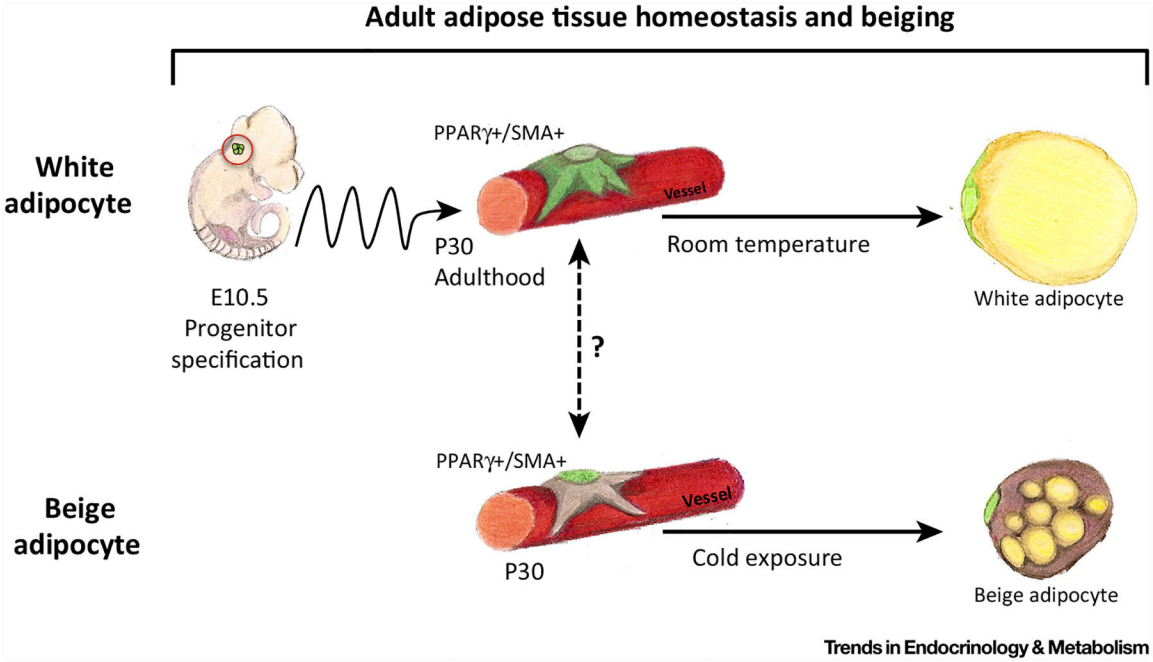

Figure 2. Adult Adipose Tissue Homeostasis and Beiging.

White adipocytes formation: adult white adipocyte progenitor cells (APCs) emanate from different lineages than do developmental APCs. However, adult APCs are specified at or near embryonic day (E)10.5; these cells then undergo a rostral–caudal migration throughout embryogenesis, eventually arriving at the adipose depots at approximately postnatal day (P)30. At P30, adult E10.5-specified APC then occupy vascular niche positioning and express mural cell and APC markers. Under homeostatic and adipogenic cues, these cells then transition from the blood vessel niche as they differentiate into mature unilocular white adipocytes. Beige/brite adipocyte formation: in cold-stimulated adult mice, vascular residing alpha smooth muscle actin (SMA)+ beige/brite progenitor cells leave their perivascular niche and differentiate into beige/brite adipocytes. The relation between adult vascular-residing white APC and vascular-residing beige/brite adipocyte progenitors is currently unknown, as is the embryonic specification of beige/brite progenitors.

Table 1.

Marking the Adipose Lineage

Lineage Marker	WAT Marked	Phase of Adipose Tissue Biology	Refs
aP2-Cre	All SAT and VAT	Development and homeostasis	[32,79]
Lysm-Cre	Bone marrow WAT	Undetermined[a]	[80]
Myf5-Cre	SAT, periscapular; VAT, retroperitoneal	Undetermined[a]	[24]
Pax3-Cre	SAT, periscapular; VAT, retroperitoneal	Undetermined[a]	[24]
PDGFRα/-Cre	All SAT and WAT	Undetermined[a]	[25]
PDGFRβ-Cre	SAT, inguinal; VAT, retroperitoneal	Undetermined[a]	[32]
Prx-1-Cre	SAT only, inguinal and periscapular	Undetermined[a]	[21]
SM22-Cre	SAT, inguinal; VAT, perigonadal	Thermogenic[b]; not developmental	[32,76]
Sox10-Cre	Head-neck WAT	Undetermined[a]	[81]
Ve-Cadherin-Cre	All SAT and VAT	Developmental and homeostasis[b]	[82]
Adiponectin-rtTA; AdipoChaser	All SAT and VAT	All phases	[14]
Myh11-Cre^{ERT2}	Undetermined	Thermogenic[b]	[75]
NG2-Cre^{ERT2}	SAT	Thermogenic[b]	[76]
PPARγ-tTA AdipoTrak	All SAT and VAT	All phases	[13,32,76]
PDGFRα/-Cre^{ERT2}	VAT	Expansion and thermogenic	[26]
PDGFRβ-rtTA MuralChaser	SAT, inguinal; VAT, perigonadal	Expansion and thermogenic	[42]
Pref-1-rtTA	All SAT and VAT	Developmental and homeostasis[b]	[43]
SMA-Cre^{ERT2}	All SAT and VAT	Homeostasis and thermogenic[b]; not developmental	[13,76]
WT1-Cre^{ERT2}	VAT	Developmental and homeostasis[b]	[20]

[a]These genetic models cannot decipher when (timing) and where (adipocyte or progenitor) the Cre driver is actively marking the adipose lineage.

[b]Other phases of adipose tissue biology have not been assessed.