Chapter 2
Adipose Stem Cells and Adipogenesis

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Key Points

- Although most development occurs during prenatal and early postnatal life, white adipose tissue retains the ability to expand during adult life, especially to accommodate energy surplus. Adipose tissue expansion occurs by increase of existing adipocytes' size or by recruiting new fat cells. Evidence in human subjects suggests that obesity complications result from the inability of subcutaneous adipose tissue to expand and safely store lipids, which leads to ectopic deposition in other tissues and insulin resistance due to lipotoxicity. This impaired expandability is due to the limited ability of adipose tissue progenitor cells to supply new adipocytes through their differentiation into specialized cells (adipogenesis). Therefore, understanding the mechanisms regulating adipogenesis is important not only for gaining insight into the pathogenesis of metabolic diseases but also for identifying targets for pharmacological interventions.
- Mature adipocytes develop from committed preadipocytes through a process termed terminal differentiation. The molecular regulation of white adipocyte terminal differentiation is extensively characterized via utilization of cell lines. However, the preceding process involves commitment of adipose stem cells (ASCs) to the adipocyte lineage with the loss of capacity to differentiate into other cell types, known as determination. Little information is known about the mechanisms that regulate the adipocyte commitment phase. Current investigations are focused on elucidating this poorly characterized step in adipocyte development. This chapter summarizes recent findings regarding the role of ASCs in adipogenesis.
- Convincing evidence for distinct depot-dependent populations of ASC pools is emerging, as adipocyte progenitors may contribute to regional variation in white adipose tissue function and development. Thus, a summary of depot-dependent differences in the gene expression patterns and cellular dynamic properties of adipocyte progenitor cells is presented.
- Finally, new lines of evidence analyzing how obesity impacts ASC abundance and functional potential are included.

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Abbreviations

ASCs	Adipose stem cells or adipose-derived stem cells
WAT	White adipose tissue
MSCs	Mesenchymal stem cells
SVF	Stromovascular fraction
ESCs	Embryonic stem cells
iPSC	Induced pluripotent stem cells
hMADS	Human multipotent adipose-derived stem
APCs	Adipocyte precursor cells
VAT	Visceral adipose tissue
SAT	Subcutaneous adipose tissue
Pref-1	Preadipocyte factor 1
COL6A2	Type VI collagen alpha 2 chain
FRP2/SFRP2	Frizzled-related protein 2
DIPA	Delta-interacting protein A
Zfp423	Zinc-finger protein 423
LXRα	Liver X receptor alpha
BMP(s)	Bone morphogenetic proteins
IGF-1	Insulin-like growth factor-1
FGF	Fibroblast growth factors
Lox	Lysyl oxidase
Gpc4	Glypican 4
Nr2f1	Nuclear receptor subfamily 2 group F member
Shox2	Short stature homeobox 2
En1	Engrailed 1
PBX1	Pre-B-cell leukemia transcription factor

Introduction

Adipocytes are highly specialized cells that form and store fat in adipose tissue and play a major role in energy homeostasis in vertebrate organisms. Obesity results from an energy surplus and is characterized by an increased storage of lipid and expansion of adipose tissue. Obesity modifies the endocrine and metabolic functions of adipocytes and is a risk factor for many other metabolic diseases, including type II diabetes, cardiovascular ischemic disease, atherosclerosis, and hypertension.

Although most development occurs during prenatal and early postnatal life (reviewed in [1]), white adipose tissue (WAT) retains the ability to expand during adult life, especially to accommodate energy surplus. Adipose tissue expansion occurs in two ways—by increase of existing adipocytes' size (hypertrophy) or by recruiting new fat cells (hyperplasia). Accumulating evidence in human subjects suggests that obesity complications result from the inability of subcutaneous adipose tissue to expand and safely store lipids, which leads to ectopic deposition in other tissues and insulin resistance due to lipotoxicity. This impaired expandability is due to the limited ability of adipose tissue progenitor cells to supply new adipocytes through their differentiation into specialized cells (adipogenesis) (reviewed in [2]) [3–6]. Hence, in order to support expansion of adipose tissue mass and to maintain adipose dynamics in adults, proliferative adipocyte precursor cells (APCs) must exist to accommodate metabolic demands. Furthermore, recent studies by Spalding et al. suggest that approximately 10 % of the body's adipocytes

are regenerated each year [7]. In addition, adipocyte number can increase during the development of obesity, despite a higher rate of apoptosis [8]. Therefore, an adipocyte precursor pool is thought to remain present in adipose tissue during adult life and contribute to the renewal of new, mature adipocytes. Very few data is available regarding the nature of APCs, including commitment to the preadipocyte, as well as the processes that control adipose conversion and formation of new adipocytes in human adult adipose tissue. Understanding the origin of adipocyte precursors, as well as adipocyte differentiation, is relevant not only for gaining insight into the pathogenesis of metabolic diseases but also for identifying proteins or pathways which might be appropriate targets for pharmacological interventions. It is important to note that the developmental origin of white and brown fat is distinct, and different precursor cells are involved in the generation of these different types of adipose tissue (reviewed in [9]) [10].

The initial phase of white adipocyte differentiation is known as determination and involves the commitment of mesenchymal stem cells (MSCs) to the adipocyte lineage [11]. Determination results in the conversion of MSCs to preadipocytes, with the loss of capacity to differentiate into other cell types. Current investigations are focused on elucidating this poorly characterized step in adipocyte development. The second phase of adipogenesis is terminal differentiation, whereby preadipocytes assume the characteristics of mature adipocytes. Conversely, the molecular regulation of white adipocyte terminal differentiation is more extensively characterized via utilization of cell lines.

In recent years, much effort has been given to identify, isolate, and analyze APCs. Several laboratories have identified a source of multipotent stem cells, known as adipose-derived stem cells (ASCs) that are capable of proliferation and differentiation into multiple lineages in vitro and in vivo, including adipocytes, osteoblasts, chondrocytes, and myocytes [12–20]. ASCs have been defined by a variety of other terms, including the following: processed lipoaspirate cells, adipose-derived stromal cells, adipose-derived mesenchymal progenitor cells, and stromovascular fraction (SVF) (reviewed in [21]). Isolated ASCs have been shown to confer multiple lineages; however, the ability of ASCs to form tissues in vivo under specific experimental conditions may not accurately reflect their multilineage capacity in physiological contexts. Hence, it remains to be determined whether native ASCs within WAT behave in the same manner. In this chapter, we will review recent findings highlighting the role of ASCs in adipogenesis with a focus on the adipocyte commitment phase. We will also evaluate the influence of regional adipose tissue distribution as well as obesity on ASC biology.

Research Tools to Study Adipogenesis

Interestingly, the majority of studies that have identified molecular pathways and transcriptional regulators involved in adipogenesis have been performed in vitro using well-characterized cellular models. These studies have been primarily conducted in the 3T3-L1 or 3T3-F442A murine preadipocyte cell lines that were originally generated in the laboratory of Dr. Howard Green at Harvard University [22, 23]. In the last 37 years, these cells lines have been used by thousands of investigators worldwide. These clonal cell lines possess the properties of adipocytes in vivo and are homogeneous in regards to cellular population and differentiation stage, which allows a uniform response to treatments. In addition, these cells can be passaged indefinitely. The preadipocyte cell lines developed by Dr. Green have been extremely useful model systems for adipocyte biologists, and the data obtained in these cells have been validated from less mechanistic in vivo studies in the last decade.

Though cell culture systems have been useful to investigate adipogenesis, there are limitations of in vitro cellular models. In vivo adipocytes do not exist as a monolayer of identical cells, but in a complex environment comprised of various other cell types and influential factors within an extracellular matrix. In addition, cell lines are already committed to the preadipocyte lineage, and therefore cannot be

utilized to examine preadipocyte commitment phases. Despite substantial progress in defining adipogenic transcriptional control mechanisms, there is little in vivo information regarding the processes that regulate the commitment of adipose tissue-derived stem cells to a defined adipocyte lineage or the development of adipocyte progenitors into adipocytes.

An alternative approach for analyzing adipocyte commitment is the use of embryonic stem cells (ESCs) derived from the inner cell mass of mouse blastocysts. ESCs are able to differentiate into various lineages; therefore, pretreatment with retinoic acid (RA) is necessary to facilitate commitment to the adipose lineage and subsequent differentiation into adipocytes with adipogenic hormones [24]. Though ethical issues in extracting ESCs from human subjects limit their use in a clinical context, many laboratories utilize rodent ESCs to acquire valuable information regarding adipocyte development. Conversely, novel ESC-like pluripotent cells, termed induced pluripotent stem cells (iPSC), were generated from human skin fibroblasts by introducing various transcription factors (Oct3/4, Sox2, Klf4, and c-Myc) [25–27]. Hence, the generation of iPSC offers a method of analyzing human precursor cells by overcoming the immunological and ethical problems associated with ESCs. Although iPSC were shown to undergo adipogenesis [28], these induced cells are not a homogeneous adipocyte precursor population and have low adipogenic potential compared to other human adipose tissue-derived cells.

Additional stem cell lines have yielded valuable information regarding adipocyte development. The multipotent cell line of C3H/10T1/2 fibroblasts represents another good model to study adipocyte commitment, as in vitro exposure to 5-azacytidine, an inhibitor of methyltransferases, followed by adipogenic, chondrogenic, or myogenic stimuli can initiate differentiation into the respective mesenchymal cell type [29, 30]. Likewise, human multipotent adipose-derived stem (hMADS) cells are also a unique cell model to analyze adipocyte development [31], as they are isolated from the adipose tissue of young donors. These hMADS cells exhibit the characteristics of MSCs, i.e., the capacity to self-renew, as cells can be expanded in vitro for more than 160 population doublings (i.e., around 30 passages) while maintaining a normal diploid karyotype and multipotency at clonal level. These cells also have the capacity to differentiate into cells of the adipogenic, osteogenic, and myogenic lineages [19].

Primary preadipocytes, isolated and cultured from the SVF of adult adipose tissue explants, are able to proliferate and differentiate into mature adipocytes under appropriate adipogenic stimuli and can also be utilized for in vitro analysis of adipocyte development (reviewed in [32]) [33–36]. However, primary culture has disadvantages in that large amounts of adipose tissue are required, as preadipocytes comprise a small percentage of total fat tissue. Furthermore, preadipocytes are difficult to isolate from other fibroblast-like cells, and once isolated, have a limited life-span. Primary cultures also undergo a dramatic decrease in their ability to differentiate, and replicative senescence occurs with repeated subculturing. Nevertheless, primary preadipocyte cultures may more accurately represent adipose tissue function in vivo, as these cells are derived from an environment where various cell types and the natural milieu may influence differentiation and responsiveness. For instance, the proliferation and differentiation of both human and rodent primary preadipocytes have been shown to be influenced by the anatomic location of the depot as well as aging and gender [5, 33, 37–46].

Interestingly, several studies have demonstrated that mature adipocytes derived from adipose tissue have the ability to dedifferentiate in vitro into fibroblast-like stem cells by utilizing the ceiling culture technique [47–52]. Though dedifferentiated fat cells are a homogeneous mixture of adipocyte progenitors, it is unknown whether the level of dedifferentiation reaches that of native adipocyte progenitors or stem cells. Nevertheless, dedifferentiated fat cells can proliferate and differentiate into mature adipocytes both in vitro and in vivo [52] and, hence, can be a useful tool for studying in vivo adipogenesis.

The Characterization of Adipose Stem Cells

Characterization of ASCs has yielded conflicting findings, partially due to differences in isolation and culture techniques [53]. Notably, one cannot distinguish between ASCs and committed preadipocytes in culture, due to the lack of bona fide markers. Therefore, one of the greatest issues limiting the progression of ASC clinical research is the lack of consistency among research groups in defining the term "ASC." Likewise, many laboratories use the crude SVF, which is a mixture of all cells comprising the adipose tissue, such as endothelial cells, smooth muscle cells, various immune cell types (neutrophils, mast cells, and macrophages), and adipocyte progenitor cells. Yet, researchers classify these cells as ASCs. Conversely, others utilize the expanded and passaged adherent cell population derived from the SVF, which are enriched with adipocyte progenitor cells. Hence, the crude SVF cells, genuine ASCs, and committed preadipocytes may all exhibit different features and properties. Overall, a standardized ASC characterization will allow direct comparison of scientific results and clarify the potential clinical applications of ASCs.

Flow cytometry has been the most valuable in recent progress toward characterizing the cell populations of ASCs, and several laboratories have proposed cell surface marker expression profiles for ASCs (reviewed in [54]). More recently, cell surface markers have been identified to define adipocyte progenitor cell populations of ASCs that differentiate into adipocytes and form functional adipose tissue. Based on numerous observations, the surface marker expression pattern of adipocyte progenitor cells is believed to be Lin−, Sca-1+, CD34+, CD31−, CD45−, CD105−, CD24+, CD29+ [55–59]. Notably, CD34+ cells are distinct with regard to adipogenic progenitors and distinguish between different subgroups of ASCs, as they are more adipogenic than CD34− populations in vitro [55, 57, 59, 60]. One compelling study revealed that exclusion of CD34+ cells in human skeletal muscle studies inhibits ectopic adipose tissue formation in vitro and in vivo [61]. Recent work by Maumus et al. supports previous evidence that native ASCs are contained in the CD34+ cell population of WAT [62]. Additional markers have offered valuable information regarding preadipocyte commitment. Preadipocyte factor 1 (Pref-1) is an accepted marker of preadipocytes [63] but is also expressed in other cell types. Other preadipocyte markers include the type VI collagen alpha 2 chain (COL6A2) [64] and a secretory protein FRP2/SFRP2 [65]. All of these factors are highly expressed in undifferentiated preadipocytes and reduced in mature adipocytes; however, none are adipose tissue specific. Overall, the use of inconsistent surface markers for different experiments has made it difficult to compare results and draw definitive conclusions. Notably, some analyses of ASCs vary in the detection of CD133, a marker that is characteristic of stemness [3, 18]. Based on these data, it is suggested that identifying ASCs by the expression of a widely used set of cell surface markers will likely not be sufficient and proposed that identity should be established by physiological properties and function [66]. Therefore, ASCs have been characterized through functional assays, in which isolated cellular fractions are tested for proliferation and differentiation capacity in both in vitro cell culture and in vivo transplantation experiments. The limitation of these methods is that ASCs are removed from their natural cellular environment, which may alter their normal function.

Comprehensive gene expression studies have been carried out by various groups and reveal distinct genetic profiles for ASCs compared to other stem cell populations of different origins. Interestingly, ASCs and bone marrow-derived MSCs share many gene expression patterns and may be closely related [18, 67]. Likewise, a comprehensive proteomic analyses of the ASC secretome determined that cytokine secretory profiles are similar to that of bone marrow-derived MSCs (reviewed in [68]). Epigeneomic analyses of ASCs have been also performed during the last decade and have revealed that DNA methylation and posttranslational histone modifications greatly influence gene activity (reviewed in [69–72]). Epigenetic studies of human ASCs have located a large number of transcriptionally repressed hypermethylated gene promoters, primarily of genes encoding proteins involved in signaling and developmental functions pertaining to early fetal development.

However, promoter methylation changes after adipogenesis of ASCs are specific but did not correlate with their differentiation, suggesting that the adipose-tissue specific combinatorial changes of the DNA methylation and the histone code may contribute to the transcriptional regulation of genes involved in adipogenesis. Notably, many of these hypermethylated promoters are also found in stem cells from other tissues, supporting the view of common ontogeny of MSCs.

An interesting novel approach that characterizes the electrophysiological properties of the ion channels of ASC using a whole-cell voltage clamp technique has been recently established [73–76]. These studies detect high levels of mRNAs of various ion channel subunits and also identify Ca^{2+}-activated K^+ outward currents, characterized by rapid or slow activation, with an insignificant contribution from inward currents. Importantly, they demonstrate that these functional ion channels may contribute to the regulation of proliferation and differentiation. In addition, the depot-dependent differences in the membrane potential and electrophysiological properties of ASCs reflect their adipogenic potential and could thus be used as markers of adipogenesis [74]. Additional studies have shown that the activity of the large conductance K^+ channels in smooth muscle cells is modulated by phosphorylation via specific receptor-mediated signaling cascades [77], suggesting the possibility that the ion channels in ASCs could be effectors of receptor-dependent pathways of adipogenesis regulatory factors. The molecular mechanisms that underlie the link between ion conductance and ASCs require further analysis. Lastly, it is also hypothesized that ASC mechanical biomarkers can be used to identify cell types as well as predict tissue-specific lineage differentiation potential for ASCs [78].

Development of ASCs into the Adipocyte Lineage

Though controversy surrounds the developmental origin of ASCs and their association with adipocyte development, numerous studies have shown that ASCs can undergo adipogenesis in vitro and form adipose tissue in vivo, following culturing and adipogenic induction in vitro [79–81]. Novel data by both Rodeheffer et al. and Tang et al. highlight the detection and origin of white ASCs. Using cell surface markers (flow cytometry) or lineage tracing, they identified and isolated a population of murine undifferentiated APCs resident within the adipose tissue SVF cells that is capable of in vitro adipogenesis as well as proliferating and differentiating into a functional adipose tissue depot in vivo in rodents [57, 58]. This was evidence that WAT contains adipocyte precursors.

Significant advances toward understanding the regulatory processes involved in adipogenesis have largely been made by the identification of transcription factors and pathways that contribute to the adipogenic process (reviewed in [9]). The adipogenic cascade centers on the expression and activation of PPARγ, the master transcriptional regulator of adipogenesis. Three members of the C/EBP family (α, β, δ) also play important roles in differentiation and act in a feedback loop to regulate PPARγ expression. In addition to these central players, Krox20 (also known as early growth response gene 2, or Egr2), several members of the KLF family, STAT5, and SREBP-1c have been reported to promote adipogenesis, while GATA2/3, ETO/MTG8, CHOP10, GILZ, Delta-interacting protein A (DIPA), KLF2, FoxO1, and TCF/LEF are inhibitory (reviewed in [82]). The expression and activity of these transcription factors play an important role in modulating a variety of target genes that are important in conferring lipid accumulation, insulin sensitivity, and endocrine properties in mature adipocytes.

Though poorly understood, novel transcriptional regulators and factors that modulate WAT preadipocyte commitment are being identified. Studies by the Spiegelman laboratory have identified two transcription factors, PPARγ and zinc-finger protein 423 (Zfp423), that are expressed in adipogenic fibroblast cells, as opposed to nonadipogenic cells [83]. This evidence supports previous studies that establish PPARγ as a marker of preadipocytes [58]. Conversely, this report identifies Zfp423 as a novel transcriptional regulator of preadipocyte commitment, as exogenous expression of Zfp423 in nonadipogenic cells is sufficient to increase PPARγ expression and their adipogenic potential and knockout or knockdown of this transcription factor inhibits in vitro adipogenesis [83].

Recent work characterizes Zfp467 as another potential transcriptional regulator of preadipocyte commitment [84]. Likewise, exogenous expression of Zfp467 enhances the cells' adipogenic potential and upregulates PPARγ, adiponectin, and C/EBPα, while knockdown of this transcription factor impairs adipogenesis.

Recently, a study identified a novel transcription factor *Ets2*, a member of the ETS transcription factor family, which coordinately regulates expression of genes altered during different time points of pre- and postnatal adipose tissue development in mice [85]. Experiments in differentiating 3T3-L1 preadipocytes show that *Ets2* stimulates mitotic clonal expansion during the adipocyte commitment phase [85]. Interestingly, another member of the ETS domain-containing transcription factors from the PEA3 subgroup, ETV4, has been reported as one of the mediators of the adipogenic effect of a small molecule phenamil, which acts as an upstream inducer of the PPARγ expression [86].

Additional candidates that could be involved in adipocyte commitment have been identified using a comprehensive transcriptional analysis of in vitro differentiating hMADs [87]. A computational analysis of transcription binding sites in their promoters identifies a potential role for regulation by the nuclear hormone receptors, including liver X receptor alpha (LXRα), PPARγ, and COUP-TF1, an orphan nuclear receptor acting predominantly as a transcriptional repressor. In addition, several laboratories have investigated other potential transcriptional and paracrine regulators of preadipocyte commitment utilizing gene expression profiling of both adipogenic and nonadipogenic cells [58, 83], such as Gsc, Twist2, Mmp3, Egfr, Fgf10, Efemp1, Lgals3, Igfbp4, and Lpl.

Multiple signaling factors have been shown to influence the development of ASCs into adipocytes by an autocrine and/or paracrine mechanism, such as bone morphogenetic proteins (BMPs) [88], transforming growth factor β (TGFβ) (reviewed in [89]), insulin-like growth factor-1 (IGF-1) (reviewed in [90]), fibroblast growth factors (FGF) 1 and 2 [91, 92], and activin [93]. Various studies have also revealed negative regulators of adipocyte development, such as Hedgehog signaling [94] and WNT signaling, whose suppression in both in vitro and in vivo adipocyte development is essential for adipogenesis (reviewed in [95]). Additional intracellular signaling pathways have also been implicated in the adipogenic cascade, whose functions are continuously revealed (reviewed in [96]). Limited studies have shown that cell shape as well as extracellular matrix components may also influence adipocyte lineage commitment (reviewed in [97, 98]).

Members of the TGF-β superfamily, notably BMP-2 and BMP-4, have been shown to stimulate commitment toward the white adipocyte lineage [88, 99–101]. Specifically, BMP-4 upregulates PPARγ expression and enhances adipogenesis both in vitro and in vivo after implantation into mice [101]. Moreover, BMPs have been shown to exert their proadipogenic effects through the intracellular proteins Smads, which may also be important for preadipocyte commitment. Notably, both Zfp423 and Schnurri-2 are BMP-dependent transcriptional coactivators of Smad proteins [102], which confer their proadipogenic effects [83, 103]. Likewise, expression of BMP-4, BMP-4 receptors, and Smads is elevated in a cell line of MSCs that have increased adipogenic potential [100]. Lysyl oxidase (Lox) is another BMP-dependent transcriptional target of Smad 1/4 that is important for preadipocyte commitment; as knockdown of Lox impairs the commitment of MSCs to the adipocyte lineage and inhibits the adipogenesis of murine fibroblasts [88]. Collectively, these studies highlight the importance of BMP-2/4, Smads 1/4/5/8, and Lox as positive regulators of white preadipocyte commitment in rodents.

In recent years, activins, which are secreted proteins of the TGFβ family, have emerged as regulators of the ASC pool as well as the function of mature adipocytes (reviewed in [104]). They represent dimers composed of various combinations of four inhibin β subunits, βA, βB, βC, and βE. Adipocytes and ASCs express homodimers of βA and βB, named activin A and activin B respectively, as well as the heterodimer βA and βB named activin AB. Activin A is highly expressed in human ASCs and displays proliferative and antiadipogenic effects via the Smad 2 pathway. In contrast, activins B and AB are highly expressed in mature adipocytes, particularly in obesity, and contribute to their insulin resistant and inflammatory state. The activity of activins is controlled by a binding protein follistatin, which is decreased in obesity. Thus, the ratio of the follistatin/activin complex appears to be an important regulator of the ASC pool and adipocyte function that requires further investigation.

Studies have also identified FGFs as positive regulators of preadipocyte commitment. Exposure of cultured rat MSCs or human ASCs to FGF2 leads to increased expression of PPARγ and enhanced adipogenesis [105, 106]. Likewise, exogenous FGF2 confers in vivo WAT formation via isolated human SVF cells [107]. FGF-10 is expressed primarily in WAT preadipocytes and facilitates increased proliferation, but does not affect their differentiation [108]. FGF-1 has been shown to enhance the adipogenesis of human preadipocytes [109].

The Origin of Adipocyte Progenitors

Adipocytes are generally thought to arise from mesodermal stem cells residing in the adipose tissue stroma; however, previous work has postulated that adipocyte precursors may exist in the adipose vasculature, embedded in the walls of blood vessels in WAT [58, 59]. Additional studies have also shown that preadipocytes may derive from mural cell origin, as adipocytes and pericytes may share a common origin [17, 55, 57, 110, 111]. Committed preadipocytes have been shown to express pericyte markers, notably SMA, NG2, and PDGFRB [58], which is characteristic of mural cells and required for their formation (reviewed in [112]. Hence, committed preadipocytes may constitute a subset of mural cells (i.e., pericytes) in WAT. These findings support earlier studies indicating that angiogenesis and adipogenesis are tightly correlated (reviewed in [113]) and [114, 115]. Consequently, other evidence suggests that proliferating progenitor cells are located in the stromal fraction of human adipose tissue [62]. Interestingly, recent analysis of intact human WAT revealed that ASCs were found scattered in the adipose tissue stroma, and these ASCs did not express pericytic markers *in situ,* as previously reported [62]. Though it has been widely accepted that adipocytes arise entirely from the mesoderm, evidence has also shown that neuroepithelial cells derived from mouse ESCs can undergo adipogenesis in vitro [116, 117]. Hence, the neuroectoderm could be a source of adipocytes. Though Billon et al. were able to show that adipocytes in vivo arise from the neural crest, only a subset of adipocytes in specific depots, notably the cephalic region, may be of neuroectoderm origin.

Interestingly, evidence suggests that nonadipose tissue-resident progenitors are able to migrate to adipose tissue, undergo adipogenesis, and contribute to the white adipocyte pool. Hong et al. demonstrated that circulating fibrocytes (peripheral blood mononuclear cells) can undergo adipogenesis in vitro as well as form adipocytes in vivo after implantation into SCID mice [118]. It was also reported by several studies in rodents that adipocytes may derive from circulating bone marrow cells [119–121]. However, an additional study found the opposite and suggests that bone marrow-derived cells do not differentiate into adipocytes or contribute to adipose tissue development [122]. Additional bone marrow reconstitution studies demonstrate that bone marrow progenitor-derived adipocytes and adipocyte progenitors do indeed derive from hematopoietic cells via the myeloid lineage [123]. Yet, the adipocytes developed from these progenitors were different from traditional white adipocytes, in that they had increased expression of inflammatory cytokines and decreased expression of leptin and other genes involved in mitochondrial biogenesis and lipid oxidation, supporting previous conclusions that contribution of bone marrow-derived progenitors to functional WAT may be negligible [120, 122]. Of consideration, these bone marrow progenitor-derived adipocytes accumulated more in VAT depots compared to SAT and were more plentiful in women compared to men; therefore, accumulation of adipocytes from bone marrow origin may contribute to adipose tissue depot heterogeneity.

Overall, evidence to support the origin of adipocytes from areas outside the mesoderm is controversial, and whether the adipocyte precursor population is resident within the adipose tissue and/or originates from the recruitment of circulating progenitor cells remains to be determined. Lack of specific cell surface markers to identify human adipocyte origins precludes the accurate isolation of human APCs and analysis of the adipogenic cascade. Though resident pools of APCs have been identified in rodents, these cells are not fully identified in humans; hence, the exact nature of human preadipocytes still remains unclear.

Effects of Obesity on ASC Pool

Due to the inability to analyze the varying degrees of cell turnover in humans, few data are available concerning human adipocyte precursor renewal within adipose tissue; although this process is essential to maintain a preadipocyte pool to be available during WAT expansion. The development, availability, and response of the adipocyte progenitor pool define an individual's capacity for adipose tissue expandability. Hence, characterizing factors that regulate the size and differentiation of adipocyte progenitor pools may denote novel therapeutic strategies to control the deposition of lipid due to excess energy surplus. Likewise, new lines of evidence are analyzing how obesity impacts ASC biology. Detrimental consequences of adipose tissue remodeling, resulting from adipocyte hypertrophy, hypoxia, and local inflammation [124], include enhanced proliferation of preadipocytes [125, 126], with concurrent inhibition of preadipocyte differentiation [127–130] and increased preadipocyte apoptosis [131]. Therefore, phases of adipocyte hyperplasia would be achieved with increased requirements for proliferation coupled with successive less efficient adipogenesis. Frequent cycling will thus promote replicative senescence of adipocyte progenitor cells with gradual impairment of adipocyte function and viability. Overall, obesity would promote accelerated exhaustion of the adipocyte progenitor pool, decreased capacity for preadipocyte self-renewal, and extensive adipose tissue remodeling, all leading to impaired expandability of subcutaneous adipose tissue, ectopic lipid accumulation, and obesity-related metabolic perturbations (insulin resistance). Isakson et al. demonstrated impaired differentiation of preadipocytes from the stromal fraction of subcutaneous abdominal adipose tissue from obese versus lean individuals [3]. Early studies using thymidine incorporation into fat cell DNA reported increased preadipocyte proliferation in high fat diet-fed rats [132]. More recent reports demonstrate that human subcutaneous abdominal adipose tissue has increased proliferation of adipocyte precursors in increasing obese conditions [126]. Yet, other studies indicate that preadipocyte numbers in the SVF were lower in obese women as compared to lean [4]. However, the aforementioned observations could be attributed to greater recruitment of preadipocytes to adipogenesis or greater preadipocyte apoptosis. Recent evidence suggests that adipocyte precursor/preadipocyte number may depend on the degree of obesity; as humans with morbid obesity, with corresponding excessive AT development, had decreased ASCs (heterogeneous fraction), compared to individuals with moderate obesity [62]. This decrease was accompanied by smaller mean adipocyte diameter and a marked increase in the expression of adipogenic markers, suggesting increased proliferation of preadipocytes and/or increased differentiation of new preadipocytes. Indeed, recent compelling data reported decreased replicative potential, premature cellular senescence, and loss of the multilineage differentiation potential of omental ASCs from patients with morbid obesity compared to lean individuals [133]. In addition, recent findings have also shown that chronic thiazolidinedione treatment decreases the adipogenic potential of ASCs, exhausting the pool of committed preadipocytes in WAT [134].

Depot Differences of ASC Pool

It is well documented that differences in regional fat distribution affect metabolic parameters in humans, presumably due to intrinsic differences in function of the adipose tissue [135–139]. The two types of WAT, visceral (VAT) and subcutaneous (SAT), are defined by location, and the mechanisms and developmental signals that account for each depot's unique characteristics are steadily emerging. Studies have revealed that subcutaneous upper body depots and visceral depots both correlate with an increased susceptibility for metabolic perturbations [140, 141], while lower-body fat is protective [138, 142–144] (reviewed in [145]). In addition, evidence suggests that VAT expands predominantly by adipocyte hypertrophy, while SAT by adipocyte hyperplasia with nutritional overload [146]. While numerous studies have investigated regional differences in adipose tissue metabolism [147–150],

few have examined depot-specific differences in adipocyte progenitor development. Subsequently, convincing evidence for distinct depot-dependent populations of ASC pools is emerging, as adipocyte progenitors may contribute to regional variation in WAT function and development. Early studies from the Kirkland laboratory revealed that abdominal subcutaneous preadipocytes derived from adipose stromal cells accumulated more lipids and had higher differentiation capacity and levels of adipocyte markers compared to visceral preadipocytes from obese subjects [151]. Studies performed in primary cultures also showed that the proliferation and differentiation capacity of ASCs from subcutaneous precursor cells was higher than in omental cells in obese individuals [148]. Flow cytometric analysis supported previous data by validating that the number of $CD34^{+}/CD31^{-}$ SVF cells from gluteal SAT positively correlated with increasing BMI of overweight individuals [152]. Additional lines of evidence indicate that SAT adipocyte precursors in rodents are more abundant and have increased proliferation as compared to VAT adipocyte progenitors in response to high-fat diet [146]. Notably, recent studies by Macotela et al. that highlight the intrinsic differences of VAT versus SAT preadipocyte pools in rodents reveal that visceral APCs display less differentiation capacity, and VAT has a decreased percentage of APCs following high-fat diet, with subsequent increase in other SVF cells (i.e., macrophages). They also demonstrate that visceral APCs highly express antiadipogenic factors, as opposed to subcutaneous APCs, which show higher expression of proadipogenic genes [153]. Overall, the reduced differentiation capacity of visceral preadipocytes may account for the increased hypertropy of existent adipocytes and the metabolic abnormalities associated with visceral adipose tissue. Hence, depot-specific differences in adipocyte progenitor abundance and proliferation influence whether a fat depot expands by hypertrophy or hyperplasia, and thus may have important implications on the development of metabolic disease.

Though the aforementioned data collectively indicate that subcutaneous depots contain a greater number of functional adipose progenitors as compared to visceral depots, these findings are controversial. Other investigations indicate that preadipocytes from upper body (abdominal) SAT of obese women differentiate less readily and are more susceptible to apoptosis as compared to the lower body (femoral) depot [4]. These results support previous reports in primary cultures showing that subcutaneous abdominal preadipocyte differentiation inversely correlates with increased obesity and central adiposity [154]. Thus, the SVF of subcutaneous abdominal fat tissue from centrally obese individuals might contain more preadipocytes with impaired differentiation potential than tissue from lean individuals. This provides evidence that abdominal VAT and abdominal SAT may share similar properties, as previously shown [74]. Overall, these studies are complicated due to the lack of distinct markers of ASCs and preadipocytes and the complexity in defining precisely where in the commitment and differentiation phase a given cell may be.

Transcriptional profiling has revealed limited yet valuable information about depot-specific differences in adipose tissue, as morphological and functional differences in developmental gene expression have been reported in rodents and humans [155–158]. Adipocytes from VAT express higher levels of *HoxA5*, *HoxA4*, *HoxC8*, *Glypican 4* (*Gpc4*), *Thbd*, and *Nr2f1* (*nuclear receptor subfamily 2 group F member 1*), whereas subcutaneous WAT has higher levels of *HoxA10*, *HoxC9*, *Tbx15*, *Shox2* (*Short stature homeobox 2*), *En1* (*Engrailed 1*), and *Sfpr2*, and most of these differences are observed in rodents and humans. Notably, depot-specific variations in gene expression were also observed in preadipocytes [147, 157]. In addition, select developmental genes, *Tbx15*, *Glyp4*, and *HoxA5*, demonstrate changes in expression that correlate with levels of obesity (body mass index) and fat distribution (waist-to-hip ratio) [157]. More extensive gene expression analyses reveal that additional genes that regulate early development, such as homeobox family members and pregnancy-associated factors, are distinct between fat cell progenitors of both rodent and human adipose tissue depots [147, 159, 160]. The observed differences in gene expression appear to be intrinsic and persist through in vitro culture and differentiation; hence, the microenvironment does not appear to be an influence. Furthermore, the results from the aforementioned experiments by Tchkonia et al. highlighting the differences in lipid

accumulation and differentiation capacity of SAT versus VAT preadipocytes [151] were associated with distinct patterns of gene expression and conserved over multiple cell generations [158]. Collectively, these data suggest that WAT depots originate from different precursor cells, whose function is presumably controlled by genes involved in development and pattern specification. Moreover, pre-B-cell leukemia transcription factor (PBX1), a family member of the homeodomain transcription factors, has been shown to be induced after commitment of mouse ESCs to the adipocyte lineage following treatment with RA [161]. A siRNA-mediated silencing of PBX1 expression in hMADs shows that PBX1 may play a role in human adipogenesis by maintaining the proliferation of ASCs and prevention of their commitment to adipocyte lineage [161]. Although the expression of PBX1 in different depots has not yet been explored, these data strongly suggest that the depot-specific differences in preadipocyte pools are established during development. Thus, the apparent differences in adipose tissue distribution in normal and obese individuals may be derived from distinct precursors in the different WAT depots.

Sex steroids are endogenous modulators of adipose tissue development, function, and distribution of SAT versus VAT depots [162], though little is known about the cellular and molecular mechanisms of this regulation. Men often have more adipose tissue distributed in the abdominal or visceral region ("android" or "apple" phenotype), which carries a much greater risk for metabolic disorders than does adipose tissue distributed subcutaneously (reviewed in [163]. In contrast, women, have more subcutaneous adipose tissue ("gynoid" or "pear" phenotype), and this distribution is predominantly sex hormone (estrogen)-dependent [164]. Likewise, in men and menopausal women, conditions in which estrogen levels are low, visceral adiposity increases. These distinct sex differences in patterns of fat distribution often develop during puberty; hence, sex steroids may potentially regulate fat distribution through epigenetic mechanisms involving adipose progenitors. Likewise, suboptimal maternal diet predisposes to visceral obesity and metabolic syndrome [165], further supporting the role of epigenetic mechanisms in the interaction between maternal nutrition and the regional fetal development of adipose tissue.

Complexity of Characterization and Analysis of ASCs

Though much progress has been made to elucidate the mechanisms that underlie the commitment of stem cells to the adipocyte lineage, many challenges remain in elucidating the function of ASCs in adipose tissue development. SVF subpopulations that contain committed preadipocytes can only confer WAT formation in vivo under certain inducible conditions that are conducive to alterations in adipose tissue expansion, such as HFD or lipodystrophy [57]. Other studies provide evidence that dietary stimulus can modulate the proliferation of adipogenic progenitors [146]. Hence, the ASC natural microenvironment is significant, but cannot be fully recapitulated in the realm of culture experiments. Consequently, to date, little is known about the capacity of these adipose "stem cells" to self-renew and produce new preadipocytes in humans or undergo adipogenesis. Of note, preadipocyte replication is often analyzed as an indicator of progenitor pool activity, yet this proliferation could be either a mechanism to replenish the local pool of immature progenitor cells of the expanding adipose tissue or also an index of adipocyte progenitor cell entry into adipogenesis. Frequently, the ASCs commonly utilized for experimentation are a heterogeneous cell population with the potential to commit to other lineages; so functional differences may exist between ASCs and committed preadipocytes in vivo. Though recent evidence suggests that ASCs are involved in the adipogenic process [62], additional studies are necessary to elucidate the contribution of ASCs to committed preadipocytes. More knowledge about the mechanisms that regulate ASCs is necessary in order to refine and standardize laboratory techniques to isolate, characterize, and manipulate ASCs.

Importantly, analyses to understand ASCs and adipocyte origins have clinical implications, as these findings may offer insight into diseases linked to adipose tissue. The identified novel transcriptional and auto/paracrine factors that regulate adipocyte development present potential therapeutic avenues to modulate the size and management of the ASC pools as well as the adipose cell turnover rate. Likewise, this would allow the manipulation of subcutaneous adipose tissue expandability, with subsequent prevention of metabolic abnormalities associated with ectopic fat deposition and improvement of insulin sensitivity in conditions of obesity as well as lipodystrophy. Hence, continued efforts to investigate the contribution of these pathways to the regulation of adipocyte progenitor pools in different depots may lead to the prevention of metabolically unfavorable fat distribution [166].

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