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The multifaceted progenitor fates in healthy or unhealthy adipose tissue during obesity

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Abstract
While obesity is defined as an excessive fat accumulation conferring a risk to metabolic health, increased adipose mass by itself does not fully explain obesity's propensity to promote metabolic alterations. Adipose tissue regulates multiple processes critical for energy homeostasis and its dysfunction favors the development and perpetuation of metabolic diseases. Obesity drives inflammatory leucocyte infiltration in adipose tissue and fibrotic transformation of the fat depots. Both features associate with metabolic alterations such as impaired glucose control and resistance to fat mass loss. In this context, adipose progenitors, an heterogenous resident population of mesenchymal stromal cells, display functions important to shape healthy or unhealthy adipose tissue expansion. We, here, outline the current understanding of adipose progenitor biology in the context of obesity-induced adipose tissue remodeling.

Keywords Adipose tissue · Fibrosis · Progenitors

1 Introduction

Adipose tissue (AT) regulates numerous physiological processes and its dysfunction favors development and perpetuation of metabolic diseases. As a consequence, AT has been extensively studied since acting on this tissue may provide novel therapeutic opportunities. Two morphologically and functionally different types of AT can be distinguished: brown/beige adipose tissue and white adipose tissue (WAT). The brown adipose tissue (BAT) is found subcutaneously in specific locations mostly in newborns and in smaller amounts in adults. Moreover, BAT primarily functions as a thermogenic organ owing to the presence of multilocular adipocytes enriched with mitochondria and uncoupling protein 1 (UCP1) [1–3]. The overall morphology of beige adipocytes is similar to the brown adipocytes but beige cells infiltrate diffuse areas within the WAT depot. Beige adipogenesis, considered as a healthy remodeling process in the AT, significantly increases in response to thermogenic stimuli such as decreased temperature [4–6], β3-adrenergic receptor activation [7–9] or response to some metabolites [10, 11]. With obesity development, both brown and beige fat depots are reduced [12–14].

By contrast to brown/beige adipocytes, the white adipocytes display low mitochondrial abundance, are unilocular and function in storing calories from triglycerides rather than dissipating energy in the form of heat. In rodents or in humans, WAT displays functional differences according to their subcutaneous or visceral location. With obesity, both depots can expand and a high deposition of visceral WAT is generally associated with increased risk of developing cardiometabolic diseases. On the contrary predominant subcutaneous WAT storage may reduce the risk for comorbidities in some individuals [15–17]. Sex hormones and genetic determinants both influence fat distribution [18, 19]. Despite major progresses in physio-pathological understanding in this field, how depot-specific expansion of fat mass is controlled still remains elusive. In addition to adipose tissue growth, obesity is a chronic condition associated with AT histological alterations, depicting a maladaptive expansion of AT. This pathological remodeling includes

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adipocyte hypertrophy, inflammatory leucocyte infiltration and perturbed immunity, and eventually fibrosis deposition. These features generally associate with altered AT functions suggested to link obesity to obesity-related metabolic dysregulation [20]. By contrast, healthy adipose tissue growth, uncoupled to these pathological features, can dampen the consequences of obesity on whole-body metabolism [21, 22]. In this context, we here review the current understanding of the progenitor contributions in shaping healthy or unhealthy AT expansion during obesity.

2 Obesity induces fibrosis in white adipose tissue

WAT has the unique capacity to massively expand or shrink in response to nutritional or even temperature challenges. This remarkable plasticity relies on a dynamic and versatile metabolism which is responsive to energy demand. Overfeeding without adapted increased energy expenditure results in fat accretion, a physiological response necessary to prevent the toxic lipid deposition in other organs, such as in the skeletal muscle, liver or the heart. This remarkable ability is closely associated with preserved systemic metabolism. As a consequence, the lack of AT exerts important deleterious effects as exemplified in lipodystrophic condition. Lipodystrophy is indeed an extreme form of adipose tissue depletion that associates with ectopic lipid deposition leading to fatty liver and lipid accumulation in the muscle which result in severe insulin resistance. Interestingly, this phenomenon can be reversed with AT implantation in animal models (see below and [23, 24]).

In chronic obesity, whereas the AT expands, it is generally coupled to pathological remodeling of AT with local inflammation and subsequently fibrosis deposition in the latter stages of the disease. These processes result in AT dysfunctions. The local inflammation relies on the infiltration of leucocytes (CD45 expressing cells, $CD45^{+}$) in which macrophages represent a large population. Local hypoxia due to suboptimal angiogenesis was proposed as an originating event [25–29]. AT macrophages accumulation coincides with the observation of adipocytes surrounding by macrophages (named crown like structure, CLS) on histological Sects. [30]. Adipocytes engaged in CLS display loss of perilipin expression (lipid droplet protein) and ultrastructural features of stressed cells suggestive of dying adipocytes [31, 32]. In mice, macrophages critically control AT inflammation and favor the onset of insulin resistance, however the kinetic of events in human and their relationships with metabolic deterioration still need understanding [33–36]. Inflammatory pathway activated by the local production of many cytokines including TNFα, IL1β or IL6, can interact with insulin signaling pathway in adipocytes to precipitate insulin resistance [37]. Beside leucocyte infiltration, adipose tissue remodeling is also characterized with senescence contributing to the altered adipose tissue secretory profile and to the local inflammation status [38, 39].

However, while chronic inflammation and the obesity associated metabolic alterations are closely related, studies have suggested a paradoxical beneficial effect of inflammation on adipose tissue in the context of obesity. The use of transgenic mouse models harboring anti-inflammatory construction showed that constitutive inhibition of inflammation was also damaging for adipose tissue expansion [40]. Similarly, the lack of *Il6* in myeloid lineage has detrimental consequences for metabolic fitness [41]. Thus, the remained ability to produce balanced inflammation appears necessary for AT homeostasis.

By contrast, the persistence of inflammatory stress in tissues is often associated with altered remodeling in a number of pathological states that can progress to fibrosis, as also observed in AT [42, 43].

Fibrosis is a dysfunctional process characterized by excessive extracellular matrix (ECM) component deposition. The ECM is composed of two main classes of macromolecules: the extremely hydrophilic proteoglycans and the fibrous proteins including collagens, elastins, fibronectins and laminins [44]. Collagen is the most abundant fibrous protein of the ECM, and in the physiological context, the ECM provides tensile strength, regulates cell adhesion, supports chemotaxis and migration, and guides tissue development [44, 45]. In pathological context, continuous ECM synthesis with enhanced ECM crosslinking by lysyl oxidase (LOX) enzymes promote the formation of collagen bundles that stiffen the tissue [46]. In human AT, fibrosis forms collagen bundles traversing the parenchyma and also surrounding the adipocytes [47]. Several evidences support that AT fibrosis is an aggravating factor for metabolic condition [20, 48]. Various studies indeed link AT fibrosis to the loss of glycemic control, insulin resistance and liver disease in mouse models but also in human [49–51]. Moreover, increased AT fibrosis accumulation in subcutaneous depot is associated with a decreased fat mass loss induced by bariatric surgery in subjects with severe obesity [48]. Thus, targeting AT fibrosis with the aim of maintaining or rescuing AT plasticity could be of interest in the treatment of obesity associated metabolic alterations. In this setting, pathways are being identified to efficiently brake AT fibrosis progression (see sections below) [43, 52]. However, the cellular and molecular mechanisms of AT fibrosis resolution remained to be elucidated. While fibrosis resolution can be observed in various models following the cessation of the profibrotic stimuli [53, 54], AT fibrosis could be an irreversible condition, especially in advanced stages and chronic conditions. In mouse and human, even when the obesogenic trigger (i.e. dietary intervention or bariatric surgery) is abrogated and,

despite the metabolic improvement induced by weight loss, there is no evidence of fibrosis resolution as collagen accumulation is maintained in the long term [55, 56].

3 Molecular alterations linking fibrosis to adipose tissue dysfunction

The fibrotic transformation of AT is generally associated with loss of function and, some of the adipocyte failures were attributed to the perturbation of ECM stiffness. Actually, the potential involvement of mechano-sensing pathways, was first suggested following the evaluation of tissue rigidity with a non-invasive prototypic tool [57]. The analysis of human obese abdominal subcutaneous AT (scAT) revealed increased stiffness in scAT with high fibrosis content [57]. Furthermore, modeling the physical constrains applied to adipocytes in ex vivo systems showed that the mechanical compression can lead to increased production and secretion of inflammatory molecules as well as dysregulated lipolysis, adipokine secretion and perturbed insulin responsiveness in adipocytes [58, 59]. The mechanosensitive Integrin β1, FAK and Caveolin activation were proposed to regulate those effects in adipocytes [58].

In addition, some evidences suggest that fibrosis deposition also compromises the adapted expansion capacity of AT. The use of static compression to mirror the fibrosis effects alters adipocyte differentiation as well as lipid accumulation [60, 61]. By contrast, the reduced adipose tensile strength in Collagen VI-knockout mice is associated with abnormally large but healthy adipocytes [62]. Thus, AT fibrosis appears to impede fat expandability in limiting both adipogenesis and adipocyte hypertrophy, suggesting that fatty acids can more easily spill over into ectopic sites. In line with this assumption, increased subcutaneous AT fibrosis was shown to be associated to visceral fat accretion in a cohort of Chinese American men and women [63] or to fatty liver in women [49, 64].

Sustained fibrosis and modified ECM composition may probably promote pathways that amplify alterations of tissue structure and functions. For instance, the soluble cleavage product of collagen VI chain, referred as endotrophin, seems to play an important role in obesity induced systemic insulin resistance by stimulating inflammation and fibrosis in AT [52, 65]. Similar pathological effects were suggested for osteopontin [66]. This matricellular protein is known to mediate diverse biological functions through interactions with integrins [66]. In obesity, AT macrophages express high levels of osteopontin [67] and osteopontin neutralization partially decreases obesity-associated inflammation in AT and, reverses signal transduction related to insulin resistance [8, 68]. Furthermore, increased circulating osteopontin, related to visceral fat production, was shown to mediate cardiac aging in mice [69]. Likewise, Tenascin C (TNC), an ECM glycoprotein, was also recently highlighted for its role in amplifying fibrosis pathway [70]. TNC can interact with several extracellular matrix molecules and cell receptors, including Toll-like receptor 4 (TLR4). The expression levels of TNC are increased in the visceral AT from obese subjects with normal glycemia or type 2 diabetes with non-alcoholic steatohepatitis [57]. Similarly, expression levels of TNC in epididymal AT was increased in obese mice [71], and fibrosis is attenuated in TNC deficient mice [70]. Thus, TNC is suggested to be a relevant mediator of AT fibrosis via a TLR4-dependent activation of fibroblasts.

4 Cellular origin of adipose tissue fibrosis

In fibrotic organs, the excessive deposition of extracellular matrix (ECM) starts with the local accumulation of cells producing high level of ECM components. In AT, the fibrosis producing cells originate from resident cells exhibiting features of mesenchymal progenitor cells. In the stroma-vascular fraction, these progenitors are non-hematopoietic cells and display multipotentiality allowing them to become adipocytes, chondrocytes or even osteoblasts among other cell lineages [72, 73]. In AT, they delineate a cell population with a strong adipogenic potential with surface epitope including CD44, CD34, CD29, PDGFRα and PDGFRβ expression. In C3H mice prone to AT fibrosis development [43, 74], PDGFRα$^+$ CD45$^-$ CD31$^-$ progenitors were isolated as a main contributors to ECM production [74]. In response to fibrogenic stimuli, these cells can differentiate into myofibroblast and start to express αSMA forming cellular stress fibers, high amount of ECM proteins together with autocrine growth factor maintaining cell proliferation and survival [74]. In fibrotic AT, PDGFRα$^+$ cells express the highest levels of the fibrosis markers, such as collagens, as compared to other predominant cells in AT (i.e. adipocytes, endothelial cells, macrophages) [74]. The PDGFRα$^+$ progenitors are not homogeneous populations and, although they need better investigation in AT, lineage tracing experiments suggested that only a subset of the PDGFRα$^+$ cell population originates the pro-fibrotic cells. These progenitors were identified as ADAM12 or GLI1 expressing cells in injured heart, kidney, lung, and liver [75, 76]. In the AT, our team identified the pro-fibrotic cells thanks to the expression level of the tetraspanin CD9 among PDGFRα$^+$ progenitor populations. PDGFRα$^+$ CD9^{high} cells were driven toward a myofibroblastic phenotype, whereas PDGFRα$^+$ CD9^{low} cells were committed to adipogenesis [74]. In the fibrotic AT, PDGFRα$^+$ CD9^{high} progenitor population expands while their PDGFRα$^+$ CD9^{low} counterparts were rapidly lost. In human AT, CD9^{high} and CD9^{low} PDGFRα$^+$ progenitors

were equally observed. However, PDGFRα + CD9^{high} cell frequency positively correlated with the degree of fibrosis, and with the deterioration of the glycemic control in patients with obesity. Indeed, significant positive associations were observed between the amount of PDGFRα^{+} CD9^{high} cells in AT and glycated hemoglobin, fasting glycemia and insulinemia and HOMA-IR, a surrogate of insulin resistance. Thus, an imbalance favoring WAT CD9^{high} over CD9^{low} PDGFRα^{+} progenitors appears to promote AT fibrotic transformation associated with altered glucose control [74]. More recently, unbiased analysis using single cell RNA sequencing of progenitors from visceral fat depot narrowed the definition of the profibrotic and proinflammatory progenitors (FIP) as CD9^{high} LY6C^{+} progenitors in mice [77]. In addition to their ability for fibrosis production, the FIP exert strong inhibitory effects on adipogenesis. Such regulatory activity was also described for the progenitor subsets defined by CD142 expression in subcutaneous WAT with adipogenesis-regulatory properties [78]. Furthermore, FIP display important proinflammatory activity as illustrated by their contribution to chemokines and cytokines production in obese AT [74, 77, 79, 80]. Thus, in obesity, the cell progenitors harbor functions that can be highly detrimental for AT homeostasis. Importantly, the interplay between adipogenic and fibrogenic pathways regulate progenitor fates during obesity (Fig. 1). Profibrotic signaling, indeed, also acts as anti-adipogenic pathway as shown with PDGFRα signaling that drives AT fibrosis by limiting progenitor cell adipogenic capacity [74, 81, 82]. Accordingly, PPARγ activity is pivotal in progenitor fate and the bidirectional manipulation of PPARγ expression induced reciprocal changes in driving adipogenic or myofibroblastic fate decision [83].

The interplay between the pro-adipogenic transcription factor ZFP423 (C2H2 zinc finger protein 423) and the TLR4 signaling in the progenitors also controls macrophage accumulation in the AT in response to high fat feeding. Mechanistically, ZFP423 suppresses the DNA-binding capacity of the p65 subunit of NF-κB activated through TLR4 signaling [80]. The immunoregulatory potential of the progenitors not only affects AT macrophage accumulation, but also other immune cells. For example, as a main producer of IL33 in AT [84], the IL33^{+} PDGFRα^{+} progenitor subset can control both the accumulation of the regulatory T cell and ILC2 in the AT [84, 85]. With obesity, IL33 is significantly downregulated while the administration of IL33 was associated with a healthy remodeling with increased AT expression of UCP1 [86]. Thus, the progenitors most probably exert critical regulatory functions that can either participate in healthy or unhealthy AT remodeling.

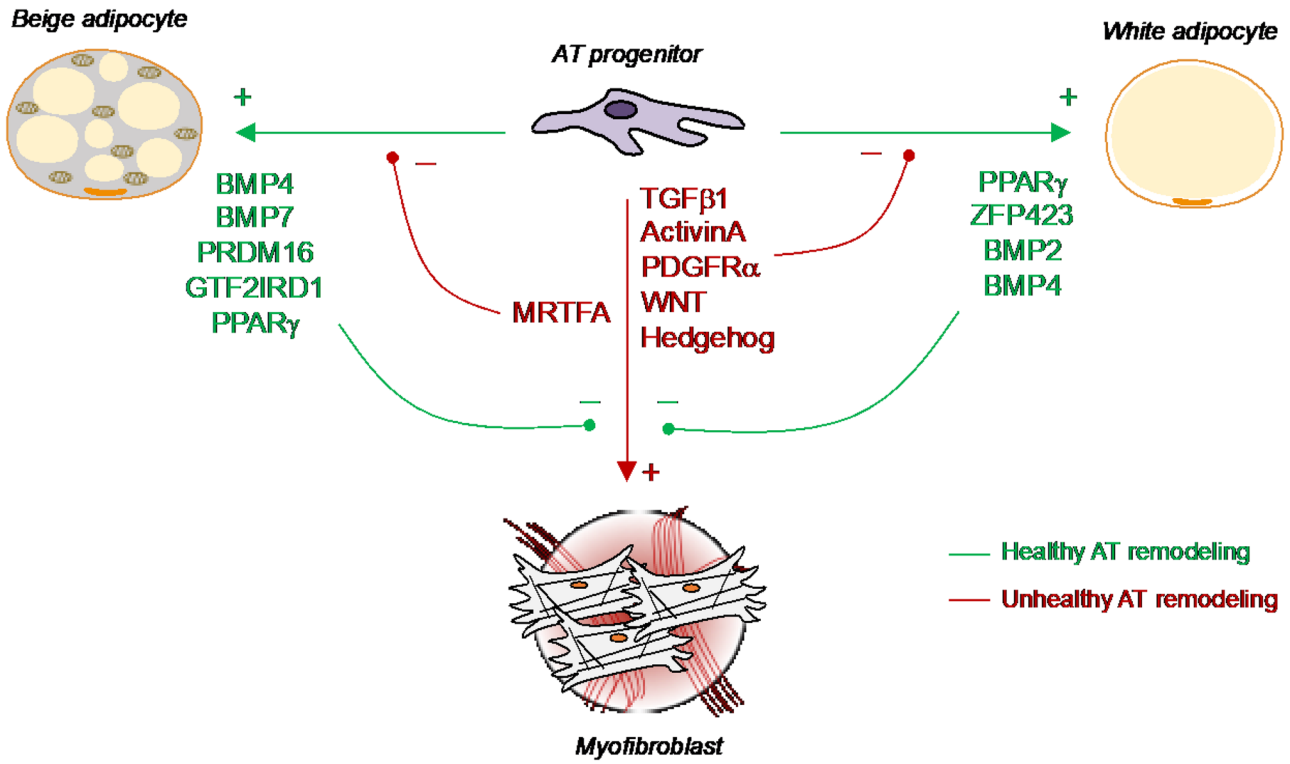

Fig. 1 The interplay between Adipogenic and fibrogenic pathways to shape progenitor fate in adipose tissue. Various signals and transcription factors found to promote beige or white adipogenesis can also limit fibrogenic pathways, and conversely

5 Adipogenesis in white adipose tissue and metabolic health

When tipped into storage mode, fat pad growth is driven by both adipocyte hypertrophy (enlarged adipocytes) and hyperplasia (increased cell number). Evidences support that the maintenance of metabolic health involves the increased number of white adipocytes rather than enlargement of adipocytes knowing that bigger cells are more dysfunctional [83, 87]. Oversized adipocytes indeed experience hypoxia and higher mechanical stress that promote a reoriented secretome associated with increased inflammation which promotes insulin resistance. These enlarged adipocytes indeed display induced secretion of tumor necrosis factor α (TNFα), interleukin (IL)-6, IL-8, monocyte chemoattractant protein-1 (MCP-1) and acute-phase serum amyloid A proteins amongst others [88], thus sustaining low grade inflammation in AT. In addition, lower adiponectin secretion and elevated basal lipolysis by adipocytes [89, 90], also favor inflammation [91]. Overall, unaltered adipogenic capacity per se may accompany healthy AT. As such, better understanding of in vivo adipogenesis in human may lead to strategies to uncouple obesity from metabolic diseases.

The generation of new adipocytes requires the proliferation and differentiation of progenitors that reside within the AT stromal cell reservoir. Most of the current knowledge about adipocyte differentiation derived from in vitro study examining heterogenous cell populations including 3T3-L1 cell line, mouse embryonic fibroblast (MEF) and plastic adherent stroma vascular cell fraction of AT. Although very informative, it remained to elucidate how the associated molecular pathways are relevant to in vivo progenitor biology.

The use of markers allowing the specific tracking of these progenitors within the AT combined to single cell RNA sequencing highlight a high diversity of progenitors. Initially, the tracing of PPARγ (peroxisome proliferator-activated receptor gamma)-expressing cells revealed an adipocyte lineage tightly associated with the adipose vasculature [92]. Concomitantly, with multiparameter flow cytometry the use of various antibodies targeting cell surface epitopes, previously reported as mesenchymal stem cells antigens Sca1, CD34, CD29 and PDGFRα delineate a cell population with a strong adipogenic potential [93, 94]. CD24 expressing precursors exhibit stem cell-like properties, which play a role in the maintenance or the growth of local adipocyte precursors [19, 93]. Indeed, sorted $CD24^+$ cells, but not the $CD24^-$ cells, transplanted in the residual fat depot of lipodystrophic mice, provided a favorable adipogenic microenvironment enabling the generation of a functional WAT depot. Interestingly, this transplantation led to major metabolic improvement with the rescue of a diabetic phenotype that develops in lipodystrophic animals [93]. In many models of obesity, the activation of the precursors is dependent on the phosphoinositide 3-kinase (PI3K)-AKT2 pathway [19]. Moreover, the coexpression of the pro-adipogenic transcription factors PPARγ and ZFP423 defined a sub-set of progenitors with a strong commitment in the adipocyte lineage [95, 96].

Other studies also identified a preadipocyte factor 1, Pref-1,-expressing progenitors as cells with high proliferative capacity, being early adipose cell precursors prior to cells with the expression of ZFP423 or PPARγ. Upon high-fat feeding stimulation, $Pref1^+$ cells are engaged in adipogenesis. However, upon adipogenesis, Pref1 (also called Dlk1/FA1) expression is downregulated as it prevents adipocyte differentiation to maintain progenitor stemness [97].

Interestingly, Merrick et al. examined the progenitor cell hierarchy in subcutaneous inguinal WAT [98]. The analysis of cellular trajectory in the adipogenic fate pointed out dipeptidyl peptidase–4 (DPP4 +) cells as multipotent progenitors giving rise to both CD54 + and CD142 + cells, which further differentiate into differentiated adipocytes. In this work, the adipogenesis-regulatory properties of $CD142^+$ subset is however not recapitulated. In obesity, the depletion of $DPP4^+$ progenitors leads to reduced precursor differentiation that may contribute to pathological remodeling and metabolic disease progression [98]. Overall, single cell RNA sequencing studies evidenced that progenitor subsets, that may delineate functional differences, are rearranged with AT remodeling [99, 100]. Further investigations are still needed to appreciate subcutaneous versus visceral depot peculiarities. In addition, it remains to clarify whether progenitor clusters represent distinct states of adipogenic differentiation or whether they are independent cell subsets in AT.

6 Interplay between beige adipogenic and fibrogenic pathways

Upon thermogenic or some metabolic stimuli, beige adipocytes can arise in specific regions inside the WAT depot. Depending on the stimulus, beige adipocytes can emerge from preexisting white adipocytes or from AT progenitors [4, 6, 7, 101, 102]. From a metabolic point of view, in obesogenic environment, activating beige adipocytes display therapeutic potential due to their ability to improve glucose and lipid homeostasis [2]. Those beneficial effects were initially attributed to energy burning capacity achieved through non-shivering thermogenesis, during which these cells dissipate chemical energy as heat notably by increasing UCP1 activity. However, recent evidences highlight that pro-beigeing pathways potently repress AT fibrosis (Fig. 1), independently of UCP1 uncoupling function [103]. As such, the PRDM16 transcriptional complex not only activates brown/beige fat development [104],

but also potently represses AT fibrosis through its direct interaction with GTF2IRD1 [103]. In addition, PRDM16 dependent metabolic signals arising from adipocytes regulates the progenitor fate blocking fibrosis together with enhancing beige adipogenesis [11]. In this reciprocal relationship between fibrogenesis and beige adipogenesis, the highly conserved canonical TGF-β/BMP (bone morphogenetic proteins) signaling cascade is of particular interest, since members have been shown to produce beige adipogenesis from AT progenitors. The BMP7-ROCK signaling axis regulates the formation of beige adipocytes via controlling the G-actin-regulated transcriptional coactivator myocardin related transcription factor A (MRTFA) [105]. WAT from mice deficient for MRTFA contains more multilocular adipocytes and expresses enhanced levels of UCP1 [105]. Conversely, MRTFA was highlighted as an inducer of progenitor fibrotic fate [106]. Similarly, in AT, BMP4 signaling is known to induce commitment of pluripotent stem cells to the adipocyte lineage by producing cells that possess the characteristics of preadipocytes. As such, the overexpression of a BMP4 transgene promotes a healthy WAT remodeling with reduced AT mass and white adipocyte size along with an increased number of beige, thermogenic adipocytes (i.e. adipocytes enriched with mitochondria and uncoupling protein 1) [107, 108]. Most interestingly, adding BMP in a profibrotic environmental promotes the resolution of fibrosis driving myofibroblast dedifferentiation to regenerate the adipocyte pool [109]. The transcriptional landscape of TGF-β/BMP family can be regulated by the progenitor in a cell autonomous dependent manner [110], as shown in mice harboring autophagy deficient progenitors. In these mice, the emergence of beige adipocyte features in the white fat depot was coincident with lower fibrosis expression (110).

In human, the ability to develop beige adipocytes is observed in limited situations such as burn trauma victims and pheochromocytoma patients [111, 112]. However, in vitro experimentation revealed that progenitors isolated from human AT can undergo beige adipogenesis [113]. Interestingly, progenitors defined with high or low expression of CD34 appeared to have similar adipogenic properties but are characterized by unique molecular profiles with different potential for adaptive thermogenesis [114]. However, the development of a pro-inflammatory microenvironment in the obese WAT seems to restrict the beige adipogenic potential of the progenitors [113].

7 Conclusions

AT progenitors are a highly heterogenous population of stromal cells. Subsets are defined through not only their degree of commitment toward white or beige adipogenesis but also through their immunoregulatory or fibrogenic potential. The AT exhibits a complex lobular architecture that is suggested to provide a local environment influencing the progenitor phenotype and functionality [115]. Therefore, the functional heterogeneity of the progenitor can also be explained by a spatial and temporal heterogeneity in addition to specific depot microenvironments [116]. Given the pivotal role of progenitors in maintaining AT homeostasis, a better understanding of their biology is certainly of interest in a therapeutic perspective. Future studies will aim to identify molecular and surface markers allowing the discrimination of the various progenitor sub-populations to understand how they crosstalk with adipocytes and other stromal cells in the adipose tissue.

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Declarations

Conflict of interest No conflict of interest to declare for this present work.

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