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Keywords (separated by '-') Adipose tissue - Fibrosis - Progenitors

Footnote Information



1 The multifaceted progenitor fates in healthy or unhealthy adipose 2 tissue during obesity

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6 Abstract

7 While obesity is defined as an excessive fat accumulation conferring a risk to metabolic health, increased adipose mass by
8 itself does not fully explain obesity's propensity to promote metabolic alterations. Adipose tissue regulates multiple pro-
9 cesses critical for energy homeostasis and its dysfunction favors the development and perpetuation of metabolic diseases.
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11 tures associate with metabolic alterations such as impaired glucose control and resistance to fat mass loss. In this context,
12 adipose progenitors, an heterogenous resident population of mesenchymal stromal cells, display functions important to shape
13 healthy or unhealthy adipose tissue expansion. We, here, outline the current understanding of adipose progenitor biology in
14 the context of obesity-induced adipose tissue remodeling.

15 **Keywords** Adipose tissue · Fibrosis · Progenitors

16 1 Introduction

17 Adipose tissue (AT) regulates numerous physiological pro-
18 cesses and its dysfunction favors development and perpetu-
19 ation of metabolic diseases. As a consequence, AT has been
20 extensively studied since acting on this tissue may provide
21 novel therapeutic opportunities. Two morphologically and
22 functionally different types of AT can be distinguished:
23 brown/beige adipose tissue and white adipose tissue (WAT).
24 The brown adipose tissue (BAT) is found subcutaneously
25 in specific locations mostly in newborns and in smaller
26 amounts in adults. Moreover, BAT primarily functions as
27 a thermogenic organ owing to the presence of multilocu-
28 lar adipocytes enriched with mitochondria and uncoupling
29 protein 1 (UCP1) [1–3]. The overall morphology of beige
30

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], β 3-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 adipo-
cytes 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 devel-
oping cardiometabolic diseases. On the contrary predomi-
nant 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 associ-
ated with AT histological alterations, depicting a maladapt-
ive 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 TNF α , IL1 β 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,

159 despite the metabolic improvement induced by weight loss,
160 there is no evidence of fibrosis resolution as collagen accu-
161 mulation is maintained in the long term [55, 56].

162 **3 Molecular alterations linking fibrosis** 163 **to adipose tissue dysfunction**

164 The fibrotic transformation of AT is generally associated
165 with loss of function and, some of the adipocyte failures
166 were attributed to the perturbation of ECM stiffness. Actu-
167 ally, the potential involvement of mechano-sensing path-
168 ways, was first suggested following the evaluation of tissue
169 rigidity with a non-invasive prototypic tool [57]. The anal-
170 ysis of human obese abdominal subcutaneous AT (scAT)
171 revealed increased stiffness in scAT with high fibrosis con-
172 tent [57]. Furthermore, modeling the physical constrains
173 applied to adipocytes in ex vivo systems showed that the
174 mechanical compression can lead to increased production
175 and secretion of inflammatory molecules as well as dysreg-
176 ulated lipolysis, adipokine secretion and perturbed insulin
177 responsiveness in adipocytes [58, 59]. The mechanosensitive
178 Integrin $\beta 1$, FAK and Caveolin activation were proposed to
179 regulate those effects in adipocytes [58].

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

194 Sustained fibrosis and modified ECM composition may
195 probably promote pathways that amplify alterations of tis-
196 sue structure and functions. For instance, the soluble cleav-
197 age product of collagen VI chain, referred as endotrophin,
198 seems to play an important role in obesity induced systemic
199 insulin resistance by stimulating inflammation and fibrosis
200 in AT [52, 65]. Similar pathological effects were suggested
201 for osteopontin [66]. This matricellular protein is known
202 to mediate diverse biological functions through interactions
203 with integrins [66]. In obesity, AT macrophages express
204 high levels of osteopontin [67] and osteopontin neutraliza-
205 tion partially decreases obesity-associated inflammation in
206 AT and, reverses signal transduction related to insulin resist-
207 ance [8, 68]. Furthermore, increased circulating osteopon-
208 tin, 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 recep-
tors, 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 extracel-
lular 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 multipotential-
ity 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 adi-
pogenic potential with surface epitope including CD44,
CD34, CD29, PDGFR α and PDGFR β expression. In
C3H mice prone to AT fibrosis development [43, 74],
PDGFR α^+ 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 α SMA forming cel-
lular stress fibers, high amount of ECM proteins together
with autocrine growth factor maintaining cell prolifera-
tion and survival [74]. In fibrotic AT, PDGFR α^+ 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
PDGFR α^+ progenitors are not homogeneous populations
and, although they need better investigation in AT, line-
age tracing experiments suggested that only a subset of
the PDGFR α^+ 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 tet-
raspanin CD9 among PDGFR α^+ progenitor populations.
PDGFR α^+ CD9^{high} cells were driven toward a myofi-
broblastic phenotype, whereas PDGFR α^+ CD9^{low} cells
were committed to adipogenesis [74]. In the fibrotic AT,
PDGFR α^+ CD9^{high} progenitor population expands while
their PDGFR α^+ CD9^{low} counterparts were rapidly lost.
In human AT, CD9^{high} and CD9^{low} PDGFR α^+ progenitors

260 were equally observed. However, PDGFR α + CD9^{high}
 261 cell frequency positively correlated with the degree of
 262 fibrosis, and with the deterioration of the glycemic control
 263 in patients with obesity. Indeed, significant positive
 264 associations were observed between the amount of
 265 PDGFR α ⁺ CD9^{high} cells in AT and glycated hemoglobin,
 266 fasting glycemia and insulinemia and HOMA-IR, a surrogate
 267 of insulin resistance. Thus, an imbalance favoring
 268 WAT CD9^{high} over CD9^{low} PDGFR α ⁺ progenitors
 269 appears to promote AT fibrotic transformation associated
 270 with altered glucose control [74]. More recently,
 271 unbiased analysis using single cell RNA sequencing of
 272 progenitors from visceral fat depot narrowed the definition
 273 of the profibrotic and proinflammatory progenitors
 274 (FIP) as CD9^{high} LY6C⁺ progenitors in mice [77]. In addition
 275 to their ability for fibrosis production, the FIP exert
 276 strong inhibitory effects on adipogenesis. Such regulatory
 277 activity was also described for the progenitor subsets
 278 defined by CD142 expression in subcutaneous WAT with
 279 adipogenesis-regulatory properties [78]. Furthermore, FIP
 280 display important proinflammatory activity as illustrated
 281 by their contribution to chemokines and cytokines production
 282 in obese AT [74, 77, 79, 80]. Thus, in obesity, the
 283 cell progenitors harbor functions that can be highly detrimental
 284 for AT homeostasis. Importantly, the interplay

285 between adipogenic and fibrogenic pathways regulate
 286 progenitor fates during obesity (Fig. 1). Profibrotic signaling,
 287 indeed, also acts as anti-adipogenic pathway as
 288 shown with PDGFR α signaling that drives AT fibrosis
 289 by limiting progenitor cell adipogenic capacity [74, 81,
 290 82]. Accordingly, PPAR γ activity is pivotal in progenitor
 291 fate and the bidirectional manipulation of PPAR γ expression
 292 induced reciprocal changes in driving adipogenic or
 293 myofibroblastic fate decision [83].

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

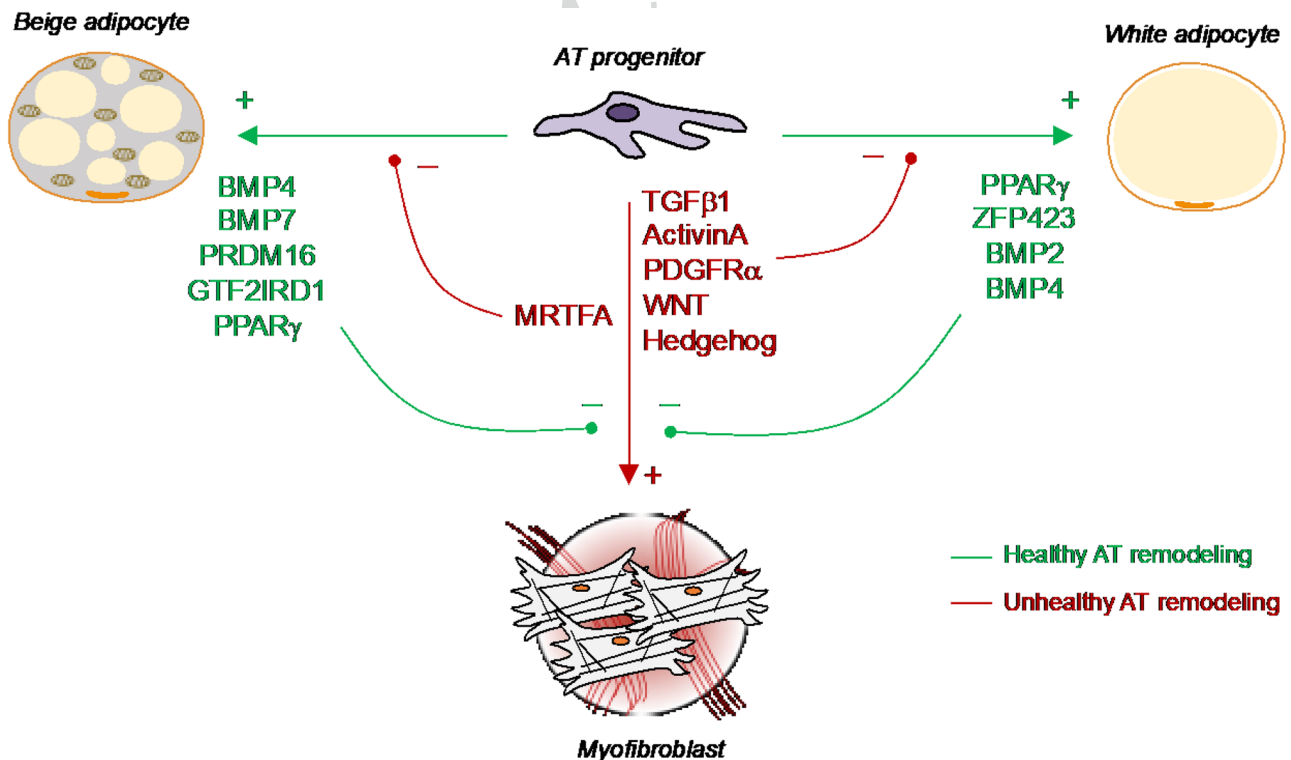


Fig. 1 The interplay between Adipogenic and fibrogenic pathways to shape progenitor fate in adipose tissue. Various signals and transcription factors found to promote beige or white adipogenesis can also limit fibrogenic pathways, and conversely

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 (TNF α), 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 PPAR γ (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 PDGFR α 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 PPAR γ 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, Pref1, -expressing progenitors as cells with high proliferative capacity, being early adipose cell precursors prior to cells with the expression of ZFP423 or PPAR γ . 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-beige 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],

411 but also potently represses AT fibrosis through its direct inter-
 412 action with GTF2IRD1 [103]. In addition, PRDM16 depend-
 413 ent metabolic signals arising from adipocytes regulates the
 414 progenitor fate blocking fibrosis together with enhancing beige
 415 adipogenesis [11]. In this reciprocal relationship between
 416 fibrogenesis and beige adipogenesis, the highly conserved
 417 canonical TGF- β /BMP (bone morphogenetic proteins) signal-
 418 ing cascade is of particular interest, since members have been
 419 shown to produce beige adipogenesis from AT progenitors.
 420 The BMP7-ROCK signaling axis regulates the formation of
 421 beige adipocytes via controlling the G-actin-regulated tran-
 422 scriptional coactivator myocardin related transcription factor
 423 A (MRTFA) [105]. WAT from mice deficient for MRTFA con-
 424 tains more multilocular adipocytes and expresses enhanced
 425 levels of UCPI [105]. Conversely, MRTFA was highlighted
 426 as an inducer of progenitor fibrotic fate [106]. Similarly, in
 427 AT, BMP4 signaling is known to induce commitment of pluri-
 428 potent stem cells to the adipocyte lineage by producing cells
 429 that possess the characteristics of preadipocytes. As such,
 430 the overexpression of a BMP4 transgene promotes a healthy
 431 WAT remodeling with reduced AT mass and white adipocyte
 432 size along with an increased number of beige, thermogenic
 433 adipocytes (i.e. adipocytes enriched with mitochondria and
 434 uncoupling protein 1) [107, 108]. Most interestingly, adding
 435 BMP in a profibrotic environment promotes the resolution
 436 of fibrosis driving myofibroblast dedifferentiation to regener-
 437 ate the adipocyte pool [109]. The transcriptional landscape of
 438 TGF- β /BMP family can be regulated by the progenitor in a
 439 cell autonomous dependent manner [110], as shown in mice
 440 harboring autophagy deficient progenitors. In these mice, the
 441 emergence of beige adipocyte features in the white fat depot
 442 was coincident with lower fibrosis expression (110).

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

455 7 Conclusions

456 AT progenitors are a highly heterogeneous population of stro-
 457 mal cells. Subsets are defined through not only their degree
 458 of commitment toward white or beige adipogenesis but
 459 also through their immunoregulatory or fibrogenic poten-
 460 tial. 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

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