



HAL
open science

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

Geneviève Marcelin, Karine Clément

► **To cite this version:**

Geneviève Marcelin, Karine Clément. The multifaceted progenitor fates in healthy or unhealthy adipose tissue during obesity. *Reviews in Endocrine and Metabolic Disorders*, 2021, 10.1007/s11154-021-09662-0 . hal-03260162

HAL Id: hal-03260162

<https://hal.sorbonne-universite.fr/hal-03260162v1>

Submitted on 14 Jun 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Dear Author,

Here are the proofs of your article.

- You can submit your corrections **online**, via **e-mail** or by **fax**.
- For **online** submission please insert your corrections in the online correction form. Always indicate the line number to which the correction refers.
- You can also insert your corrections in the proof PDF and **email** the annotated PDF.
- For fax submission, please ensure that your corrections are clearly legible. Use a fine black pen and write the correction in the margin, not too close to the edge of the page.
- Remember to note the **journal title**, **article number**, and **your name** when sending your response via e-mail or fax.
- **Check** the metadata sheet to make sure that the header information, especially author names and the corresponding affiliations are correctly shown.
- **Check** the questions that may have arisen during copy editing and insert your answers/ corrections.
- **Check** that the text is complete and that all figures, tables and their legends are included. Also check the accuracy of special characters, equations, and electronic supplementary material if applicable. If necessary refer to the *Edited manuscript*.
- The publication of inaccurate data such as dosages and units can have serious consequences. Please take particular care that all such details are correct.
- Please **do not** make changes that involve only matters of style. We have generally introduced forms that follow the journal's style. Substantial changes in content, e.g., new results, corrected values, title and authorship are not allowed without the approval of the responsible editor. In such a case, please contact the Editorial Office and return his/her consent together with the proof.
- If we do not receive your corrections **within 48 hours**, we will send you a reminder.
- Your article will be published **Online First** approximately one week after receipt of your corrected proofs. This is the **official first publication** citable with the DOI. **Further changes are, therefore, not possible.**
- The **printed version** will follow in a forthcoming issue.

Please note

After online publication, subscribers (personal/institutional) to this journal will have access to the complete article via the DOI using the URL: [http://dx.doi.org/\[DOI\]](http://dx.doi.org/[DOI]).

If you would like to know when your article has been published online, take advantage of our free alert service. For registration and further information go to: <http://www.link.springer.com>.

Due to the electronic nature of the procedure, the manuscript and the original figures will only be returned to you on special request. When you return your corrections, please inform us if you would like to have these documents returned.

Metadata of the article that will be visualized in OnlineFirst

ArticleTitle	The multifaceted progenitor fates in healthy or unhealthy adipose tissue during obesity	
Article Sub-Title		
Article CopyRight	The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature (This will be the copyright line in the final PDF)	
Journal Name	Reviews in Endocrine and Metabolic Disorders	
Corresponding Author	FamilyName	Clément
	Particle	
	Given Name	Karine
	Suffix	
	Division	Nutrition and Obesities : Systemic Approaches (NutriOmics, UMRS U1269)
	Organization	Sorbonne Universités, INSERM
	Address	Paris, France
	Division	Nutrition department
	Organization	Assistance Publique Hôpitaux de Paris (AP-HP), Hôpital Pitié-Salpêtrière, CRNH Ile de France
	Address	75013, Paris, France
	Phone	
	Fax	
	Email	karine.clement@inserm.fr
	URL	
	ORCID	http://orcid.org/0000-0002-2489-3355
Author	FamilyName	Marcelin
	Particle	
	Given Name	Geneviève
	Suffix	
	Division	Nutrition and Obesities : Systemic Approaches (NutriOmics, UMRS U1269)
	Organization	Sorbonne Universités, INSERM
	Address	Paris, France
	Phone	
	Fax	
	Email	genevieve.marcelin@inserm.fr
	URL	
	ORCID	
Schedule	Received	
	Revised	
	Accepted	1 Jun 2021
Abstract	<p>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.</p>	

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

Footnote Information



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

3 Geneviève Marcelin¹ · Karine Clément^{1,2}

4 Accepted: 1 June 2021

5 © The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2021

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.
10 Obesity drives inflammatory leucocyte infiltration in adipose tissue and fibrotic transformation of the fat depots. Both fea-
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

31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55

A1 ✉ Karine Clément
A2 karine.clement@inserm.fr

A3 Geneviève Marcelin
A4 genevieve.marcelin@inserm.fr

A5 ¹ Nutrition and Obesity : Systemic Approaches (NutriOmics,
A6 UMRS U1269), Sorbonne Universités, INSERM, Paris,
A7 France

A8 ² Nutrition department, Assistance Publique Hôpitaux de Paris
A9 (AP-HP), Hôpital Pitié-Salpêtrière, CRNH Ile de France,
A10 75013 Paris, France

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.

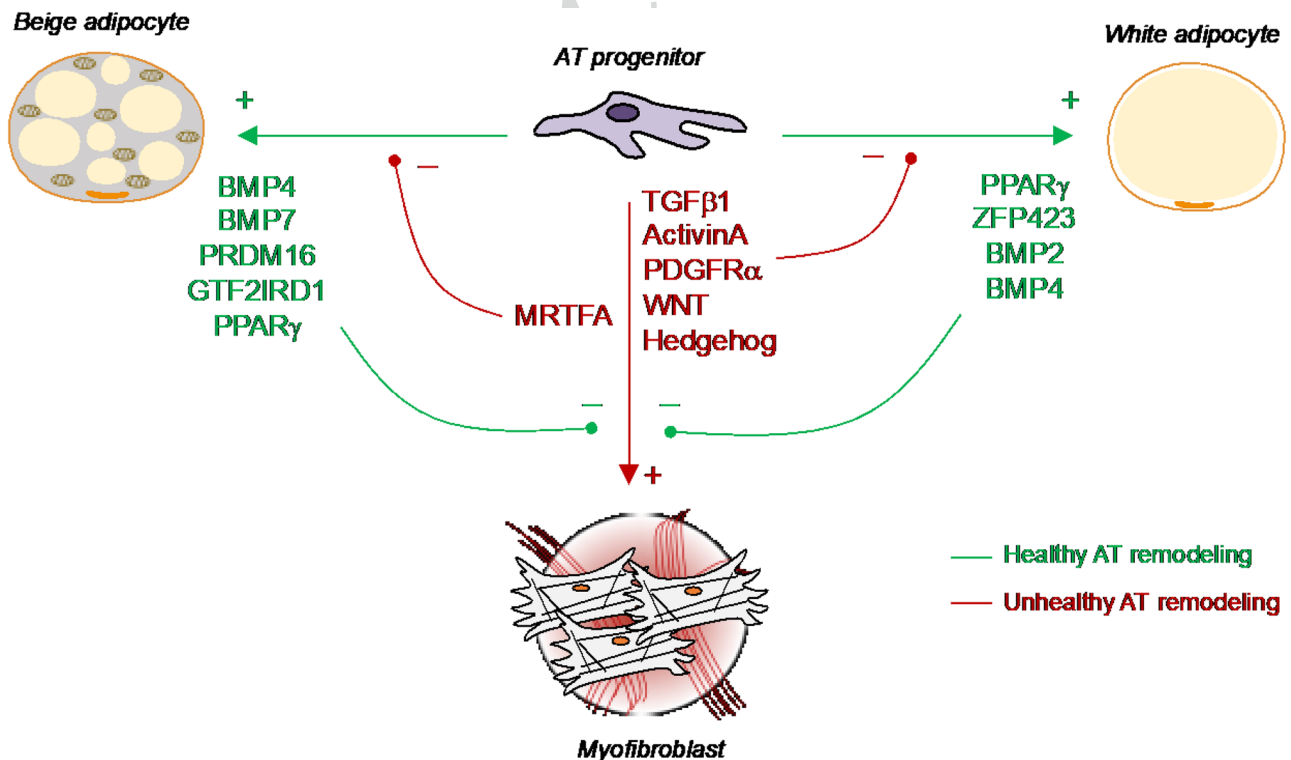


Fig. 1 The interplay between Adipogenic and fibrogenic pathways to shape progenitor fate in adipose tissue. Various signals and transcription factors found to promote beige or white adipogenesis can also limit fibrogenic pathways, and conversely

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-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],

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.

Acknowledgments We acknowledge supports from the Fondation pour
 la Recherche Medicale (“équipe FRM”), the French National Agency
 of Research (Adipofib and Captor programs), the research programs
 CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Supe-
 rior) / COFECUB (Comité Français d’Évaluation de la Coopération
 Universitaire et Scientifique avec le Brésil), the french clinical pro-
 gram (CRC-fibroTA), the European Foundation for the Study of Dia-
 betes (EFSD), the SFN (Société Française de Nutrition), the AFERO
 (Association Française d’Etude et de Recherche sur l’Obésité) and the
 Benjamin Delessert institute.

483 Declarations

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

486 References

1. Cannon B, Nedergaard J. Brown Adipose Tissue: Function and Physiological Significance. *Physiol Rev.* 2004;84(1):277–359. 487
2. Chouchani ET, Kajimura S. Metabolic adaptation and maladaptation in adipose tissue. *Nat Metab.* 2019;1(2):189–200. 488
3. Wu J, Cohen P, Spiegelman BM. Adaptive thermogenesis in adipocytes: Is beige the new brown? *Genes Dev.* 2013;27(3):234–50. 489
4. Vishvanath L, et al. Pdgfr β + Mural Preadipocytes Contribute to Adipocyte Hyperplasia Induced by High-Fat-Diet Feeding and Prolonged Cold Exposure in Adult Mice. *Cell Metab.* 2016;23(2):350–9. 490
5. Wang QA, Scherer PE. The AdipoChaser mouse. *Adipocyte.* 2014;3(2):146–50. 491
6. Wang QA, Tao C, Gupta RK, Scherer PE. Tracking adipogenesis during white adipose tissue development, expansion and regeneration. *Nat Med.* 2013;19(10):1338–44. 492
7. Lee Y-H, Petkova AP, Mottillo EP, Granneman JG. In vivo identification of bipotential adipocyte progenitors recruited by β 3-adrenoceptor activation and high-fat feeding. *Cell Metab.* 2012;15(4):480–91. 493
8. Lee Y-H, Petkova AP, Granneman JG. Identification of an adipogenic niche for adipose tissue remodeling and restoration. *Cell Metab.* 2013;18(3):355–67. 494
9. Burl RB, et al. Deconstructing Adipogenesis Induced by β 3-Adrenergic Receptor Activation with Single-Cell Expression Profiling. *Cell Metab.* 2018;28(2):300–309.e4. 495
10. Carrière A, et al. Browning of White Adipose Cells by Intermediate Metabolites: An Adaptive Mechanism to Alleviate Redox Pressure. *Diabetes.* 2014;63(10):3253–65. 496

- 515 11. Wang W, et al. A PRDM16-Driven Metabolic Signal from Adipo-
516 cytes Regulates Precursor Cell Fate. *Cell Metab.* 2019;30(1):174-
517 189.e5. 581
- 518 12. Kajimura S, Spiegelman BM, Seale P. Brown and beige fat:
519 Physiological roles beyond heat-generation. *Cell Metab.*
520 2015;22(4):546–59. 582
- 521 13. Wang W, Seale P. Control of brown and beige fat development.
522 *Nat Rev Mol Cell Biol.* 2016;17(11):691–702. 583
- 523 14. Leitner BP, et al. Mapping of human brown adipose tis-
524 sue in lean and obese young men. *Proc Natl Acad Sci U S A.*
525 2017;114(32):8649–54. 584
- 526 15. Kissebah AH, Krakower GR. Regional adiposity and morbidity.
527 *Physiol Rev.* 1994;74(4):761–811. 585
- 528 16. Wajchenberg BL. Subcutaneous and Visceral Adipose Tis-
529 sue: Their Relation to the Metabolic Syndrome. *Endocr Rev.*
530 2000;21(6):697–738. 586
- 531 17. Ibrahim MM. Subcutaneous and visceral adipose tissue: struc-
532 tural and functional differences. *Obes Rev.* 2010;11(1):11–8. 587
- 533 18. Schleinitz D, Böttcher Y, Blüher M, Kovacs P. The genetics of
534 fat distribution. *Diabetologia.* 2014;57(7):1276–86. 588
- 535 19. Jeffery E, et al. The Adipose Tissue Microenvironment Regu-
536 lates Depot-Specific Adipogenesis in Obesity. *Cell Metab.*
537 2016;24(1):142–50. 589
- 538 20. Marcelin G, Silveira ALM, Martins LB, Ferreira AVM, Clément
539 K. Deciphering the cellular interplays underlying obesity-induced
540 adipose tissue fibrosis. *J Clin Invest.* 2019;129(10):4032–40. 590
- 541 21. Kim J-Y, et al. Obesity-associated improvements in metabolic
542 profile through expansion of adipose tissue. *J Clin Invest.*
543 2007;117(9):2621–37. 591
- 544 22. Kusminski CM, Bickel PE, Scherer PE. Targeting adipose tissue
545 in the treatment of obesity-associated diabetes. *Nat Rev Drug*
546 *Discovery.* 2016;15(9):639–60. 592
- 547 23. Gao H et al. Lipoatrophy and metabolic disturbance in mice
548 with adipose-specific deletion of kindlin-2 [Internet]. *JCI Insight*
549 4(13). <https://doi.org/10.1172/jci.insight.128405> 593
- 550 24. Gavrilova O, et al. Surgical implantation of adipose tis-
551 sue reverses diabetes in lipoatrophic mice. *J Clin Invest.*
552 2000;105(3):271–8. 594
- 553 25. Sung H-K, et al. Adipose vascular endothelial growth factor regu-
554 lates metabolic homeostasis through angiogenesis. *Cell Metab.*
555 2013;17(1):61–72. 595
- 556 26. An YA et al. Angiopoietin-2 in white adipose tissue improves
557 metabolic homeostasis through enhanced angiogenesis. *Elife*
558 2017;6. <https://doi.org/10.7554/eLife.24071> 596
- 559 27. Robciuc MR, et al. VEGFB/VEGFR1-Induced Expansion of
560 Adipose Vasculature Counteracts Obesity and Related Metabolic
561 Complications. *Cell Metab.* 2016;23(4):712–24. 597
- 562 28. Wree A, et al. Adipokine expression in brown and white
563 adipocytes in response to hypoxia. *J Endocrinol Invest.*
564 2012;35(5):522–7. 598
- 565 29. Michailidou Z, et al. Increased angiogenesis protects against
566 adipose hypoxia and fibrosis in metabolic disease-resistant
567 11 β -hydroxysteroid dehydrogenase type 1 (HSD1)-deficient
568 mice. *J Biol Chem.* 2012;287(6):4188–97. 599
- 569 30. Hill DA, et al. Distinct macrophage populations direct inflam-
570 matory versus physiological changes in adipose tissue. *Proc Natl*
571 *Acad Sci USA.* 2018;115(22):E5096–105. 600
- 572 31. Giordano A, et al. Obese adipocytes show ultrastructural
573 features of stressed cells and die of pyroptosis. *J Lipid Res.*
574 2013;54(9):2423–36. 601
- 575 32. Cinti S, et al. Adipocyte death defines macrophage localization
576 and function in adipose tissue of obese mice and humans. *J Lipid*
577 *Res.* 2005;46(11):2347–55. 602
- 578 33. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expres-
579 sion of tumor necrosis factor-alpha: direct role in obesity-linked
580 insulin resistance. *Science.* 1993;259(5091):87–91. 603
34. Ferrante AW. The immune cells in adipose tissue. *Diabetes*
581 *Obes Metab.* 2013;15(Suppl 3):34–8. 582
35. Weisberg SP, et al. Obesity is associated with macrophage accu-
583 mulation in adipose tissue. *J Clin Invest.* 2003;112(12):1796–808. 584
36. Cancellor R, et al. Increased infiltration of macrophages in omen-
585 tal adipose tissue is associated with marked hepatic lesions in
586 morbid human obesity. *Diabetes.* 2006;55(6):1554–61. 587
37. de Luca C, Olefsky JM. Inflammation and Insulin Resistance.
588 *FEBS Lett.* 2008;582(1):97–105. 589
38. Villaret A, et al. Adipose Tissue Endothelial Cells From Obese
590 Human Subjects: Differences Among Depots in Angiogenic,
591 Metabolic, and Inflammatory Gene Expression and Cellular
592 Senescence. *Diabetes.* 2010;59(11):2755–63. 593
39. Rouault C, et al. Senescence-associated β -galactosidase in
594 subcutaneous adipose tissue associates with altered glycaem-
595 ic status and truncal fat in severe obesity. *Diabetologia.*
596 2021;64(1):240–54. 597
40. Wernstedt Asterholm I, et al. Adipocyte inflammation is essential
598 for healthy adipose tissue expansion and remodeling. *Cell Metab.*
599 2014;20(1):103–18. 600
41. Mauer J et al. Signaling by IL-6 promotes alternative activa-
601 tion of macrophages to limit endotoxemia and obesity-associated
602 resistance to insulin. *Nature immunology* 2014;15(5):11. 603
42. Wynn TA, Ramalingam TR. Mechanisms of fibrosis: therapeutic
604 translation for fibrotic disease. *Nat Med.* 2012;18(7):1028–40. 605
43. Vila IK, et al. Immune cell Toll-like receptor 4 mediates the
606 development of obesity- and endotoxemia-associated adipose
607 tissue fibrosis. *Cell Rep.* 2014;7(4):1116–29. 608
44. Frantz C, Stewart KM, Weaver VM. The extracellular matrix at
609 a glance. *J Cell Sci.* 2010;123(Pt 24):4195–200. 610
45. Datta R, Podolsky MJ, Atabai K. Fat fibrosis: friend or foe?
611 [Internet]. *JCI Insight* 2018;3(19). <https://doi.org/10.1172/jci.insight.122289> 612
46. Tschumperlin DJ, Ligresti G, Hilscher MB, Shah VH. Mechano-
613 sensing and fibrosis. *J Clin Invest.* 2018;128(1):74–84. 614
47. Divoux A. Fibrosis in human adipose tissue: composition, dis-
615 tribution, and link with lipid metabolism and fat mass loss. -
616 *PubMed - NCBI* [Internet]2010;[https://www.ncbi.nlm.nih.gov/pubmed/?term=Divoux+A%2C+et+al.++\(2010\).+Diabetes+59\(11\)%3A2817-2825](https://www.ncbi.nlm.nih.gov/pubmed/?term=Divoux+A%2C+et+al.++(2010).+Diabetes+59(11)%3A2817-2825). cited September 26, 2018 617
48. Bel Lassen P, et al. The FAT Score, a Fibrosis Score of Adipose
618 Tissue: Predicting Weight-Loss Outcome After Gastric Bypass.
619 *J Clin Endocrinol Metab.* 2017;102(7):2443–53. 620
49. Abdennour M, et al. Association of adipose tissue and liver fibro-
621 sis with tissue stiffness in morbid obesity: links with diabetes
622 and BMI loss after gastric bypass. *J Clin Endocrinol Metab.*
623 2014;99(3):898–907. 624
50. Sun K, Tordjman J, Clément K, Scherer PE. Fibrosis and Adipose
625 Tissue Dysfunction. *Cell Metab.* 2013;18(4):470–7. 626
51. Guglielmi V et al. Omental adipose tissue fibrosis and insulin
627 resistance in severe obesity. *Nutr Diabetes* 2015;5:e175. 628
52. Sun K, et al. Endotrophin triggers adipose tissue fibrosis and
629 metabolic dysfunction. *Nat Commun.* 2014;5(1):3485. 629
53. Jun JI, Lau LF. Resolution of organ fibrosis. *J Clin Invest*
630 128(1):97–107. 630
54. Tacke F, Trautwein C. Mechanisms of liver fibrosis resolution. *J*
631 *Hepatol.* 2015;63(4):1038–9. 631
55. Liu Y, et al. Accumulation and Changes in Composition of Col-
632 lagens in Subcutaneous Adipose Tissue After Bariatric Surgery.
633 *J Clin Endocrinol Metab.* 2016;101(1):293–304. 632
56. Zamarron BF, et al. Macrophage Proliferation Sustains Adi-
634 pose Tissue Inflammation in Formerly Obese Mice. *Diabetes.*
635 2017;66(2):392–406. 633
57. Sasso M, et al. AdipoScan: A Novel Transient Elastography-
636 Based Tool Used to Non-Invasively Assess Subcutaneous
637 638 639 640 641 642 643 644 645

- 646 Adipose Tissue Shear Wave Speed in Obesity. *Ultrasound Med*
647 *Biol.* 2016;42(10):2401–13.
- 648 58. Pellegrinelli V, et al. Human adipocyte function is impacted by
649 mechanical cues: Human adipocytes as mechanosensitive cells.
650 *J Pathol.* 2014;233(2):183–95.
- 651 59. Li Q, Hosaka T, Jambaldorj B, Nakaya Y, Funaki M. Extracel-
652 lular matrix with the rigidity of adipose tissue helps 3T3-L1 adi-
653 pocytes maintain insulin responsiveness. *J Medic Investigation*
654 2009;56(3,4):142–149.
- 655 60. Hossain MdG, et al. Compressive force inhibits adipogenesis
656 through COX-2-mediated down-regulation of PPAR γ 2 and C/
657 EBPA. *J Biosci Bioeng.* 2010;109(3):297–303.
- 658 61. Chun T-H, et al. A pericellular collagenase directs the 3-dimensional
659 development of white adipose tissue. *Cell.* 2006;125(3):577–91.
- 660 62. Khan T, et al. Metabolic Dysregulation and Adipose Tissue Fibro-
661 sis: Role of Collagen VI. *Mol Cell Biol.* 2009;29(6):1575–91.
- 662 63. Alba DL, et al. Subcutaneous Fat Fibrosis Links Obesity to Insu-
663 lin Resistance in Chinese Americans. *J Clin Endocrinol Metab.*
664 2018;103(9):3194–204.
- 665 64. Walker RW, et al. Macrophage accumulation and fibrosis in adipo-
666 se tissue is linked to liver damage and metabolic risk in obese
667 children. *Obesity (Silver Spring).* 2014;22(6):1512–9.
- 668 65. Park J, Morley TS, Scherer PE. Inhibition of endotrophin, a
669 cleavage product of collagen VI, confers cisplatin sensitivity to
670 tumours. *EMBO Mol Med.* 2013;5(6):935–48.
- 671 66. Denhardt DT, Noda M, O'Regan AW, Pavlin D, Berman JS. Osteo-
672 pontin as a means to cope with environmental insults: regula-
673 tion of inflammation, tissue remodeling, and cell survival. *J Clin*
674 *Invest.* 2001;107(9):1055–61.
- 675 67. Kiefer FW, et al. Osteopontin expression in human and murine
676 obesity: extensive local up-regulation in adipose tissue but minimal
677 systemic alterations. *Endocrinology.* 2008;149(3):1350–7.
- 678 68. Kiefer FW, et al. Neutralization of Osteopontin Inhibits Obe-
679 sity-Induced Inflammation and Insulin Resistance. *Diabetes.*
680 2010;59(4):935–46.
- 681 69. Sawaki D et al. Visceral Adipose Tissue Drives Cardiac Aging
682 Through Modulation of Fibroblast Senescence by Osteopontin
683 Production 51.
- 684 70. Bhattacharyya S, et al. Tenascin-C drives persistence of organ
685 fibrosis. *Nat Commun.* 2016;7(1):11703.
- 686 71. Catalán V, et al. Increased tenascin C and Toll-like receptor 4
687 levels in visceral adipose tissue as a link between inflammation
688 and extracellular matrix remodeling in obesity. *J Clin Endocrinol*
689 *Metab.* 2012;97(10):E1880-1889.
- 690 72. Farahani RM, Xaymardan M. Platelet-Derived Growth Fac-
691 tor Receptor Alpha as a Marker of Mesenchymal Stem Cells
692 in Development and Stem Cell Biology [Internet]. *Stem Cells*
693 *Intern* 2015;2015:e362753.
- 694 73. Santini MP, et al. Tissue-Resident PDGFR α + Progenitor Cells
695 Contribute to Fibrosis versus Healing in a Context- and Spatio-
696 temporally Dependent Manner. *Cell Rep.* 2020;30(2):555-570.
697 e7.
- 698 74. Marcelin G, et al. A PDGFR α -Mediated Switch toward
699 CD9(high) Adipocyte Progenitors Controls Obesity-Induced
700 Adipose Tissue Fibrosis. *Cell Metab.* 2017;25(3):673–85.
- 701 75. Dulauroy S, Di Carlo SE, Langa F, Eberl G, Peduto L. Line-
702 age tracing and genetic ablation of ADAM12⁺ perivascular cells
703 identify a major source of profibrotic cells during acute tissue
704 injury. *Nat Med.* 2012;18(8):1262–70.
- 705 76. Kramann R, et al. Perivascular Gli1+ Progenitors Are Key
706 Contributors to Injury-Induced Organ Fibrosis. *Cell Stem Cell.*
707 2015;16(1):51–66.
- 708 77. Hepler C et al. Identification of functionally distinct fibro-
709 inflammatory and adipogenic stromal subpopulations in visceral
710 adipose tissue of adult mice. *eLife* 2018;7:e39636.
- 711 78. Schwalie PC, et al. A stromal cell population that inhibits adipo-
712 genesis in mammalian fat depots. *Nature.* 2018;559(7712):103.
- 713 79. Kaplan JL, et al. Adipocyte progenitor cells initiate monocyte
714 chemoattractant protein-1-mediated macrophage accumulation
715 in visceral adipose tissue. *Mol Metab.* 2015;4(11):779–94.
- 716 80. Shan B et al. Perivascular mesenchymal cells control adipose-
717 tissue macrophage accrual in obesity [Internet]. *Nat Metab* [pub-
718 lished online ahead of print: November 2, 2020] [https://doi.org/](https://doi.org/10.1038/s42255-020-00301-7)
719 [10.1038/s42255-020-00301-7](https://doi.org/10.1038/s42255-020-00301-7)
- 720 81. Olson LE, Soriano P. Increased PDGFR α activation disrupts
721 connective tissue development and drives systemic fibrosis. *Dev*
722 *Cell.* 2009;16(2):303–13.
- 723 82. Iwayama T, et al. PDGFR α signaling drives adipose tissue
724 fibrosis by targeting progenitor cell plasticity. *Genes Dev.*
725 2015;29(11):1106–19.
- 726 83. Shao M, et al. De novo adipocyte differentiation from Pdgfr β +
727 preadipocytes protects against pathologic visceral adipose expan-
728 sion in obesity. *Nat Commun.* 2018;9(1):890.
- 729 84. Spallanzani RG et al. Distinct immunocyte-promoting and adipocyte-
730 generating stromal components coordinate adipose tissue immune
731 and metabolic tenors. *Sci Immunol.* 2019;4(35):eaaw3658.
- 732 85. Brestoff JR, et al. Group 2 innate lymphoid cells promote beiging
733 of adipose and limit obesity. *Nature.* 2015;519(7542):242–6.
- 734 86. Ding X, et al. IL-33-driven ILC2/eosinophil Axis in Fat Is
735 Induced by Sympathetic Tone and Suppressed by Obesity. *J*
736 *Endocrinol.* 2016;231(1):35–48.
- 737 87. Kim SM, et al. Loss of White Adipose Hyperplastic Potential Is
738 Associated with Enhanced Susceptibility to Insulin Resistance.
739 *Cell Metab.* 2014;20(6):1049–58.
- 740 88. Jernäs M, et al. Separation of human adipocytes by size: hyper-
741 trophic fat cells display distinct gene expression. *FASEB J.*
742 2006;20(9):1540–2.
- 743 89. Berger JJ, Barnard RJ. Effect of diet on fat cell size and hormone-
744 sensitive lipase activity. *J Appl Physiol.* 1999;87(1):227–32.
- 745 90. Wueest S, Rapold RA, Rytka JM, Schoenle EJ, Konrad D. Basal
746 lipolysis, not the degree of insulin resistance, differentiates large
747 from small isolated adipocytes in high-fat fed mice. *Diabetologia.*
748 2009;52(3):541–6.
- 749 91. Lancaster GI, et al. Evidence that TLR4 Is Not a Receptor for
750 Saturated Fatty Acids but Mediates Lipid-Induced Inflammation
751 by Reprogramming Macrophage Metabolism. *Cell Metab.*
752 2018;27(5):1096-1110.e5.
- 753 92. Tang W, et al. White fat progenitor cells reside in the adipose
754 vasculature. *Science.* 2008;322(5901):583–6.
- 755 93. Rodeheffer MS, Birsoy K, Friedman JM. Identification of white
756 adipocyte progenitor cells in vivo. *Cell.* 2008;135(2):240–9.
- 757 94. Berry R, Jeffery E, Rodeheffer MS. Weighing in on adipocyte
758 precursors. *Cell Metab.* 2014;19(1):8–20.
- 759 95. Gupta RK, et al. Zfp423 expression identifies committed preadi-
760 pocytes and localizes to adipose endothelial and perivascular
761 cells. *Cell Metab.* 2012;15(2):230–9.
- 762 96. Gupta RK, et al. Transcriptional control of preadipocyte deter-
763 mination by Zfp423. *Nature.* 2010;464(7288):619–23.
- 764 97. Hudak CS, Sul HS. Pref-1, a Gatekeeper of Adipogenesis [Inter-
765 net]. *Front Endocrinol.* 2013;4. [https://doi.org/10.3389/fendo.](https://doi.org/10.3389/fendo.2013.00079)
766 [2013.00079](https://doi.org/10.3389/fendo.2013.00079)
- 767 98. Merrick D et al. Identification of a mesenchymal progenitor cell
768 hierarchy in adipose tissue. *Developmental biology* 2019;13.
- 769 99. Vijay J, et al. Single-cell analysis of human adipose tissue
770 identifies depot- and disease-specific cell types. *Nat Metab.*
771 2020;2(1):97–109.
- 772 100. Cho DS, Lee B, Doles JD. Refining the adipose progenitor
773 cell landscape in healthy and obese visceral adipose tissue
774 using single-cell gene expression profiling. *Life Sci. Alliance*
775 2019;2(6):e201900561.

- 776 101. Berry DC, Jiang Y, Graff JM. Mouse strains to study cold-inducible
777 beige progenitors and beige adipocyte formation and function [Inter-
778 net]. *Nat Commun.* 2016;7. <https://doi.org/10.1038/ncomms10184>
779 102. Shao M, et al. Cellular Origins of Beige Fat Cells Revisited.
780 *Diabetes.* 2019;68(10):1874–85.
781 103. Hasegawa Y, et al. Repression of Adipose Tissue Fibrosis
782 through a PRDM16-GTF2IRD1 Complex Improves Systemic
783 Glucose Homeostasis. *Cell Metab.* 2018;27(1):180-194.e6.
784 104. Shapira SN, Seale P. Transcriptional Control of Brown and Beige
785 Fat Development and Function. *Obesity.* 2019;27(1):13–21.
786 105. McDonald ME, et al. Myocardin-Related Transcription Factor A
787 Regulates Conversion of Progenitors to Beige Adipocytes. *Cell.*
788 2015;160(1):105–18.
789 106. Lin JZ, Rabhi N, Farmer SR. Myocardin-Related Transcription
790 Factor A Promotes Recruitment of ITGA5+ Profibrotic Progeni-
791 tors during Obesity-Induced Adipose Tissue Fibrosis. *Cell Rep.*
792 2018;23(7):1977–87.
793 107. Qian S-W, et al. BMP4-mediated brown fat-like changes in white
794 adipose tissue alter glucose and energy homeostasis. *Proc Natl*
795 *Acad Sci.* 2013;110(9):E798–807.
796 108. Hoffmann JM, et al. BMP4 gene therapy enhances insulin sensi-
797 tivity but not adipose tissue browning in obese mice. *Molecular*
798 *Metabolism.* 2020;32:15–26.
799 109. Plikus MV, et al. Regeneration of fat cells from myofibroblasts
800 during wound healing. *Science.* 2017;355(6326):748–52.
110. Marcelin G et al. Autophagy inhibition blunts PDGFR α + adipose
801 progenitors' cell-autonomous fibrogenic response to high fat diet.
802 *Autophagy* (in press). 2020 803
111. Frontini A et al. White-to-brown transdifferentiation of omen-
804 tal adipocytes in patients affected by pheochromocytoma. *Bio-*
805 *chimica et Biophysica Acta (BBA) - Mol and Cell Biol Lipids*
806 2013;1831(5):950–959. 807
112. Sidossis LS, et al. Browning of Subcutaneous White Adipose
808 Tissue in Humans after Severe Adrenergic Stress. *Cell Metab.*
809 2015;22(2):219–27. 810
113. Estève D, et al. Human white and brite adipogenesis is sup-
811 ported by MSCA1 and is impaired by immune cells. *Stem Cells.*
812 2015;33(4):1277–91. 813
114. Raajendiran A, et al. Identification of Metabolically Distinct Adi-
814 pocyte Progenitor Cells in Human Adipose Tissues. *Cell Rep.*
815 2019;27(5):1528-1540.e7. 816
115. Estève D, et al. Lobular architecture of human adipose tissue
817 defines the niche and fate of progenitor cells. *Nat Commun.*
818 2019;10(1):2549. 819
116. Sebo ZL, Jeffery E, Holtrup B, Rodeheffer MS. A mesodermal
820 fate map for adipose tissue. *Development* 2018;145(17). <https://doi.org/10.1242/dev.166801> 821
822
- Publisher's Note** Springer Nature remains neutral with regard to
823 jurisdictional claims in published maps and institutional affiliations. 824

825