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### **Review Series**

Obesity originates from an imbalance between caloric intake and energy expenditure that promotes adipose tissue expansion, which is necessary to buffer nutrient excess. Patients with higher visceral fat mass are at a higher risk of developing severe complications such as type 2 diabetes and cardiovascular and liver diseases. However, increased fat mass does not fully explain obesity's propensity to promote metabolic diseases. With chronic obesity, adipose tissue undergoes major remodeling, which can ultimately result in unresolved chronic inflammation leading to fibrosis accumulation. These features drive local tissue damage and initiate and/or maintain multiorgan dysfunction. Here, we review the current understanding of adipose tissue remodeling with a focus on obesity-induced adipose tissue fibrosis and its relevance to clinical manifestations.

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# Deciphering the cellular interplays underlying obesity-induced adipose tissue fibrosis

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**Obesity originates from an imbalance between caloric intake and energy expenditure that promotes adipose tissue expansion, which is necessary to buffer nutrient excess. Patients with higher visceral fat mass are at a higher risk of developing severe complications such as type 2 diabetes and cardiovascular and liver diseases. However, increased fat mass does not fully explain obesity's propensity to promote metabolic diseases. With chronic obesity, adipose tissue undergoes major remodeling, which can ultimately result in unresolved chronic inflammation leading to fibrosis accumulation. These features drive local tissue damage and initiate and/or maintain multiorgan dysfunction. Here, we review the current understanding of adipose tissue remodeling with a focus on obesity-induced adipose tissue fibrosis and its relevance to clinical manifestations.**

## Introduction

There are two morphologically distinct types of adipose tissue: white adipose tissue (WAT) and brown/beige adipose tissue (BAT). WAT is the predominant type and critically regulates whole-body energy homeostasis by acting as a key energy reservoir for the other organs. Efficient storage in times of food abundance is fundamental for survival during food shortage. Thus, the evolution of multicellular organisms has led to the development of specialized cells or organs that function to store nutrient excess as lipids, highly energy-dense nutrients (9 kcal/g versus 4 kcal/g for protein and carbohydrate). Excess caloric intake and low physical activity tips the energy balance into storage mode, and within the white adipocyte, free fatty acids (FFAs) are esterified into triglycerides that are packed into lipid droplets coated with regulatory proteins, ensuring lipid storage or mobilization (1).

In humans, WAT is organized as two major fat depots, subcutaneous and visceral, the latter of which surrounds the internal organs. In obesity, a high deposition of visceral adipose tissue is associated with increased risk of developing cardiometabolic diseases, such as type 2 diabetes, and their severe complications, whereas obese patients with predominantly subcutaneous fat storage may have a reduced risk of metabolic diseases (2–4) or at least exhibit delayed complications. However, the underlying mechanisms controlling the depot-specific growth of adipose tissue are not yet elucidated.

In adult mice, the paired gonadal fat depots around the ovaries (periovarian) or the testes (epididymal) found within the abdominal cavity are studied as a model of visceral adipose tissue in addition to the mesenteric, retroperitoneal, and perirenal fat (5). The inguinal depots in the anterior and upper

portion of the hind limbs are representative of subcutaneous adipose tissue in mice (5).

In addition to its energy-storing function, the adipose tissue displays critical endocrine functions. Leptin (6, 7), adiponectin (8–10), and a myriad of other peptidic mediators or lipid metabolites derived from adipocytes or from the stroma (called adipokines) exert critical endocrine functions that maintain energy balance by targeting the central nervous system and/or by modulating the metabolic activities of peripheral organs. The role of these molecules has been extensively reviewed (11, 12).

By contrast to WAT, BAT is found subcutaneously in specific locations mostly in newborns and in smaller amounts in adults and functions primarily as a thermogenic organ owing to the presence of multilocular adipocytes enriched with mitochondria and uncoupling protein 1 (UCP1) (13). BAT might also have a secretory role (14). Similarly, the development of beige adipose tissue in the subcutaneous or visceral WAT in response to cold or  $\beta_3$ -adrenergic stimulation is referred to as “browning” (15, 16). Several studies associated brown/beige adipose tissue activity with protection against obesity and metabolic disease development (17).

In response to excess energy, while the amount of activity of brown/beige fat is reduced (18, 19), WAT depots undergo a massive expansion to buffer the nutrient overload. With chronic obesity, which is eventually accompanied by periods of weight variation, WAT depots display continual remodeling. It is now recognized that inflammatory cell accumulation and activation within the WAT mediate at least some aspects of obesity-related morbidity, such as insulin resistance (20). Besides immune cell accumulation, prolonged positive energy balance induces adipocyte hypertrophy and neovascularization. In addition, extracellular matrix accumulation resulting in adipose tissue fibrosis participates in adipose tissue dysfunction. Inflamed and fibrotic WAT depots become deleterious for proper energy storage and endocrine functions, resulting in altered local and systemic metabolic control. We here review the current knowledge on obesity-induced WAT fibrosis and its local and systemic consequences.

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## Adipocytes and progenitors in adipose tissue growth

In obesity, the growth of the adipose mass is mediated by adipocyte hypertrophy (enlarged adipocytes) or hyperplasia (increased cell number). Both types of expansion are regulated by the local environment and genetic factors, although the molecular factors favoring one or the other pathway are largely unknown. A growing body of evidence indicates that these processes are closely associated with the maintenance of adipose tissue homeostasis. Adipocyte hyperplasia, in general, is more metabolically favorable than increased adipocyte size (21), as enlarged adipocytes exhibit numerous necrotic-like abnormalities such as ruptured plasma membranes, dilated endoplasmic reticulum, cell debris in the extracellular space, and the appearance of small lipid droplets in the cytoplasm (22, 23). In addition to these morphological abnormalities, hypertrophic adipocytes are dysfunctional, with increased expression and secretion of proinflammatory cytokines, including TNF- $\alpha$ , IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), and acute-phase serum amyloid A proteins, among others (24). Basal lipolysis is also elevated in these cells (25, 26), increasing the leakage of FFAs to ectopic locations. As a consequence, hypertrophic adipocytes and associated features contribute to the loss of tissue homeostasis and can promote or at least maintain insulin resistance when initiated (24, 26). On the other hand, hyperplastic expansion of the adipose tissue requires the proliferation and differentiation of precursor cells (also called progenitors or adipose tissue progenitor cells [APCs]) that reside within the adipose tissue stroma, since mature adipocytes are postmitotic cells (27–29). In rodents, lineage tracing studies have revealed that the mode of adipose depot expansion in obese mice occurs in a depot- and sex-dependent manner, suggesting the importance of sex hormones in driving the energy storage mode (30–32).

To identify WAT progenitors, studies tracing PPAR $\gamma$ -expressing cells revealed an adipocyte lineage tightly associated with the adipose vasculature (33). Concomitantly, Friedman's group established a strategy to purify an enriched cell population prone to adipogenesis from the stromal vascular fraction of adipose tissue (27). Combining the use of various antibodies previously reported as mesenchymal stem cell antigens to target cell surface epitopes, they delineated a cell population with a strong adipogenic potential that exhibited Sca1, CD34, CD29, and PDGFR $\alpha$  expression (27, 34). The progenitors also coexpressed PDGFR $\beta$  (35, 36). Interestingly, this population is not homogeneous, and subpopulations with specific features could be discriminated (Figure 1). For instance, CD24 $^{+}$  precursors exhibit stem cell-like properties that play a role in the maintenance or the growth of local adipocyte precursors in line with the local microenvironment (27, 37). Specifically, the C2H2 zinc finger protein 423-expressing (Zfp423 $^{+}$ ) precursors constitute a subpopulation of progenitors with high adipogenic potential (38, 39).

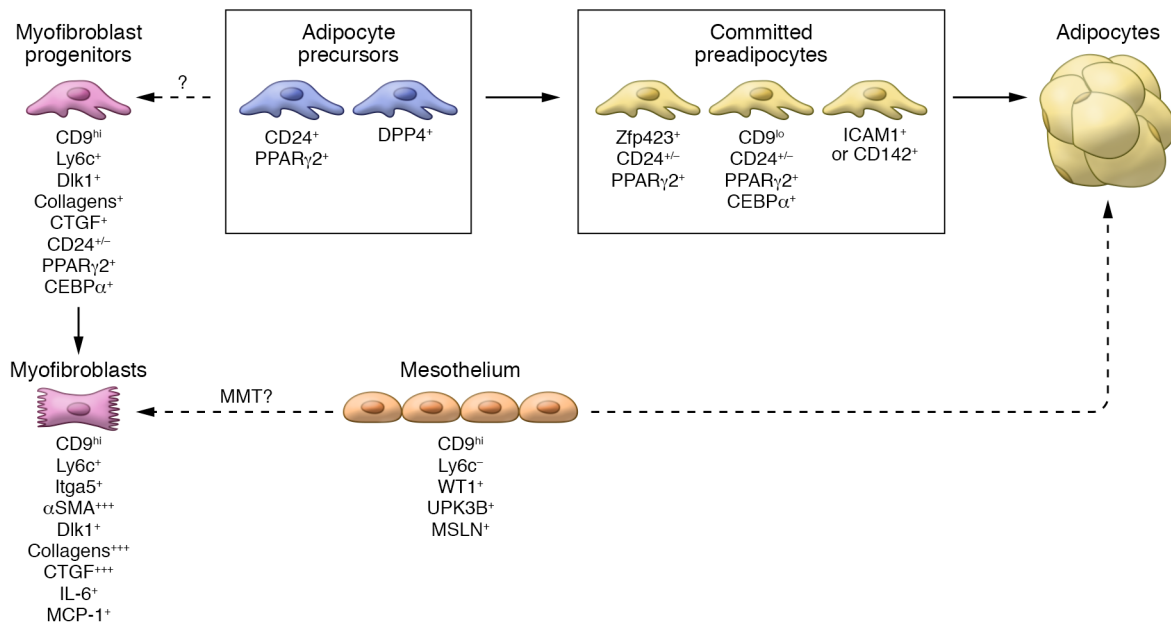
Since the identification of specific markers allowing the tracking of adipose tissue progenitors within the adipose tissue, APCs have received considerable attention and have been classified as precursors undergoing adipocyte differentiation linked not only to developmental (40), homeostatic, and obesogenic (32, 37, 38) conditions, or beige adipogenesis in response to cold or  $\beta_3$ -adrenergic stimulation (41, 42), but also to fibrosis accumulation (43).

In humans, adipocyte turnover was quantified by analysis of the integration of atmospheric  $^{14}\text{C}$  into genomic DNA. This work proposed that adipocyte hyperplasia occurs from birth to early adulthood (20 years of age). By contrast, adipocyte renewal represents only 10% of adipocytes each year in adults (44), indicating that adipocyte hyperplasia is limited in adults. However, precursors undergoing adipogenesis *in vitro* have been identified (45), and findings support that different subpopulations of precursors do exist in humans as in mouse models. Adipocyte precursors are enriched in CD34 $^{+}$ , PDGFR $\alpha^{+}$ , CD45 $^{-}$  (a leukocyte marker), and CD31 $^{-}$  (an endothelial cell-specific marker) cell populations derived from the stromal vascular fraction of WAT. Various degrees of adipogenesis can also be observed in populations expressing CD36 (encoding the primary cellular fatty acid translocase) (46) and Msca1 (mesenchymal stromal cell antigen-1), which are induced during adipogenesis (47, 48). Importantly, small adipocyte size is associated with insulin sensitivity (49), and a better understanding of pathways controlling the production of new adipocytes (to limit adipocyte hypertrophy) could be of interest to limit the deleterious effects of obesity.

## Suboptimal angiogenesis and low-grade inflammation in obese WAT

Fat mass expansion requires the formation of new blood vessels (angiogenesis), which develop from those preexisting within the adipose tissue. To stimulate angiogenesis, growing adipocytes produce many angiogenic factors, such as leptin, VEGF, FGF-2, hepatocyte growth factor (HGF), insulin-like growth factor (IGF), placental growth factor (PLGF), VEGF-C, heparin-binding epidermal growth factor (HB-EGF), and angiopoietins. APCs also secrete high levels of angiogenic factors, including VEGF, HGF, and FGF-2 (50). Consequently, antiangiogenic agents were first believed to represent encouraging therapeutic options to limit fat mass expansion during obesity. However, analysis of the mechanisms underlying the pathological events associated with obesity suggests that over the course of obesity, capillary density and function fail to meet the demands for adipose growth. Most interestingly, promoting angiogenesis favors healthy adipose tissue expansion with enhanced adipogenesis and reduced adipose tissue inflammation and fibrosis (51–55). In humans, endothelial cells isolated from obese adipose tissue exhibit phenotypic alterations with increased expression of inflammatory and senescence-related genes (56). Moreover, a GWAS analysis revealed a link between angiogenesis gene loci and insulin resistance markers, supporting the notion that suboptimal vascularization could be of importance in maintaining insulin resistance in obesity (57).

Local inflammation is another critical alteration observed in obese adipose tissue depots. A potential mechanism to explain this finding is that impaired vascularization precipitates local hypoxia, leading to adipocyte necrosis that favors the infiltration of proinflammatory leukocytes (58). A seminal study highlighted a causative link between adipose tissue inflammation and insulin resistance, albeit in rodents (59). This finding was later substantiated in humans with the discovery that macrophages accumulate in obese subjects' adipose tissue (60). Since then, macrophages have been shown to critically control adipose tissue inflammation and favor the onset of insulin resistance, one of the major obesity comorbidities. Concomitantly, other innate and adaptive immune



**Figure 1. Heterogeneity among progenitors in the adipose tissue.** Adipose tissue progenitors (or precursors), often located in the vicinity of the vascular network, constitute a heterogeneous population. They can be discriminated through their capacity to differentiate into mature adipocytes and also by their level of commitment into the adipocyte differentiation program. The application of flow cytometry using various markers as well as single-cell RNA sequencing has enabled the identification of multiple cell populations. The CD9<sup>hi</sup> progenitors exhibited very limited adipogenic capacity with a high propensity for the production of extracellular matrix components. CD9<sup>hi</sup> progenitors include mesothelial cells, whose contribution in adipose tissue remodeling is currently unresolved. Further investigations are still needed to establish the relationship between these various populations of progenitors. In addition, a better understanding of the critical functional determinants and whether acquired phenotypes are reversible is needed.

cells (e.g., T cells, B cells, NK and NKT cells, eosinophils) are modulated in obesity (61) and insulin-resistant states (62).

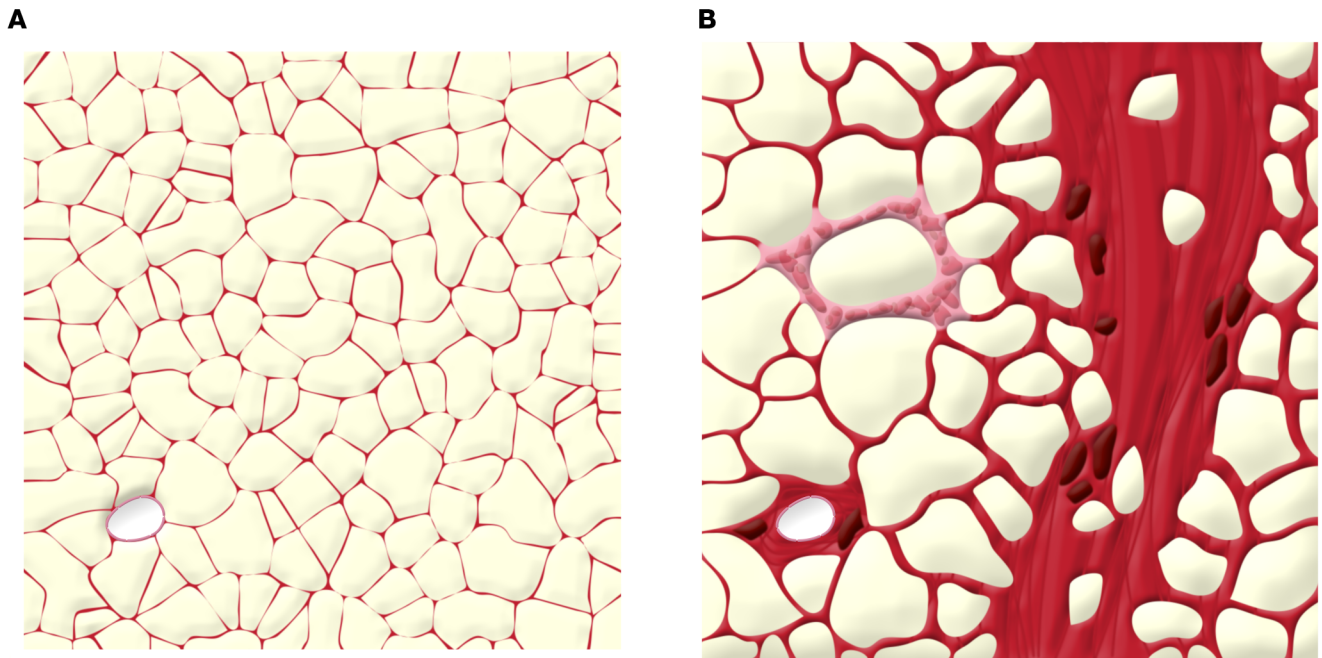
Overall, the relationship between adipose tissue inflammation and metabolic alterations is better established in mouse models than in human conditions. As such, overfeeding experiments in humans have shown that insulin resistance can be rapidly induced without substantial modification of systemic or tissue inflammation (63). These observations have raised questions regarding the kinetics of inflammatory events in humans and whether they are involved in the development or maintenance of metabolic diseases. Nevertheless, the identification of key inflammatory mediators is of interest to understand and eventually control adipose tissue remodeling over the course of obesity. We have, for example, characterized the phenotype of PAFR<sup>-/-</sup> mice, which are deficient in platelet-activating factor receptor (PAFR). The platelet-activating factor (PAF) is a glycerophospholipid able to initiate acute inflammation through activation of its G protein-coupled receptor (64). Activation of PAFR in adipose tissue promotes leukocyte recruitment and stimulates local production of proinflammatory cytokines such as TNF- $\alpha$ , IL1- $\beta$ , and IL-6. PAFR<sup>-/-</sup> mice are protected against WAT inflammation and exhibit improved insulin sensitivity, albeit with increased adiposity and without any change in calorie intake (65). Thus, the phenotype of PAFR<sup>-/-</sup> mice, similarly to mice lacking leptin while overexpressing adiponectin (66) or other mouse models (67–69), illustrates the beneficial impact of limiting local inflammation while maintaining storage capacity in the adipose tissue. This increase or maintenance of storage capacity limits ectopic fat deposition and insulin resistance, as well as related complications.

## Adipose tissue fibrosis identifies unhealthy remodeling in obesity

Unresolved inflammation is often associated with altered tissue remodeling in a number of pathological states and often progresses to fibrosis as a result of the persistence of inflammatory stress. Fibrosis is characterized by excessive extracellular matrix (ECM) component deposition, a dysfunctional process that ultimately causes severe disturbances in organ functions. Ten years ago, major changes in the expression of genes encoding ECM were described in the adipose tissue during obesity (70, 71). The ECM is a noncellular component of all tissues that is essential for tissue morphogenesis, differentiation, and homeostasis and includes structural (collagens) and adhesion proteins (fibronectin) as well as proteoglycans (biglycan, decorin), which preserve tissue architecture (72). The ECM is considered as a reservoir of secreted growth factors, cytokines, and proteases whose availability is highly regulated during ECM remodeling (73) while being particularly crucial for maintaining structural integrity of adipocytes and playing pivotal roles during adipogenesis (74–76). In obese human adipose tissue, collagens accumulate around the adipocytes to form pericellular fibrosis, or, alternatively, collagen fibers can be organized as fibrotic bundles of various thicknesses containing few adipocytes isolated from the rest of the parenchyma (Figure 2).

## Loss of adipose tissue plasticity in obesity

Studies in humans and rodents indicate that fibrosis alters adipose tissue plasticity. Several findings support the concept that the global upregulation of ECM constituents may represent a physical constraint to adipose tissue expansion (69, 77). In mice, the pre-



**Figure 2. Illustration of adipose tissue fibrosis in obese subjects.** Obesity increases collagen deposition and myofibrocyte distribution in adipose tissue. **(A)** A section of adipose tissue with no fibrosis. **(B)** In contrast, fibrotic adipose tissue contains fibrosis-forming collagen bundles that trap adipocytes. Fibrosis can also be observed around a blood vessel (lower left) and around a crown-like structure with macrophages and inflammatory cells.

dominantly expressed collagen mRNAs in adipose tissue encode type I, IV, and VI collagens, the latter being the most abundantly expressed. In collagen VI-null *ob/ob* mice, adipose tissue mass increases as a result of uninhibited volume expansion of individual adipocytes. As in mouse models discussed above, this increased adiposity is associated with lowered local inflammation together with a global improvement of metabolism in obese animals relative to collagen VI-expressing mice (69). Accumulation of ECM in adipose tissue might thus contribute to a failure to adequately limit the expansion in fat mass. This hypothesis is corroborated by other studies, such as those using mice lacking the pericellular collagenase MT1-matrix metalloproteinase (MT1-MMP). MT1-MMP inactivation results in the formation of a rigid network of collagen fibrils, which compromises adipocyte differentiation and lipid accumulation (77). Similarly, inhibition of lysyl oxidase (LOX), an enzyme involved in collagen cross-linking, dampens metabolic dysfunctions and WAT inflammation in obese mice (78). In human adipose tissue, decreased adipocyte size is detected in regions with fibrosis as compared with fibrosis-free cells (71). The development of a prototypic tool (AdipoScan) based on elastography shows that adipose tissue fibrosis is associated with significant change in tissue stiffness (79).

To further investigate the functional impact of increased interstitial fibrosis, the consequences of collagen deposition for adipocyte biology have been examined. Mature adipocytes, cultured in a peptide hydrogel containing decellularized material isolated from adipose tissue of obese subjects, showed that fibrosis itself induces adipocyte functional alterations similar to those observed in obese adipose tissue, such as decreased lipolysis and adipokine secretion and increased proinflammatory cytokines production. Those effects appear to be dependent on mechanosensitive sig-

naling involving integrin and Yes-associated protein (YAP)/transcriptional enhancer-associated domain (TEAD) pathways (80).

Consistently, numerous studies have linked ECM deposition to modified adipose tissue metabolic and endocrine functions (81–84). Pasarica et al. reported that type VI collagen gene expression is elevated in obese subjects, and obese subjects with high collagen VI display increased adipose tissue inflammation (82). Spencer et al. also described an association between collagen VI, fibrosis, and alternative activation of macrophages in the adipose tissue of insulin-resistant subjects (83).

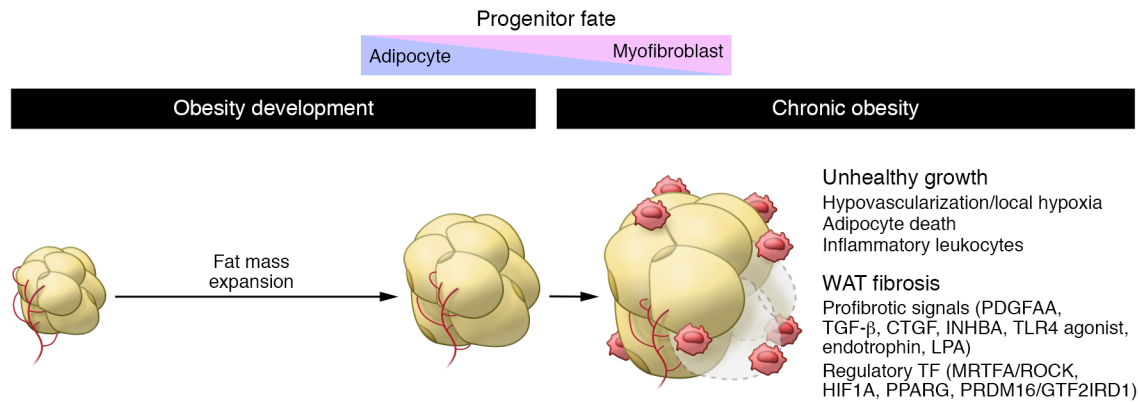
In addition to the deleterious impact of fibrosis on adipose tissue functions, subcutaneous adipose tissue fibrosis measured in severe obesity is associated with resistance to weight loss induced by bariatric surgery (71, 79).

In the future, use of scoring of adipose tissue fibrosis could be of interest to adapt the medical standard of care of obese patients in order to optimize patient follow-up and outcomes in obesity treatment (85).

### Pathways perpetuating adipose tissue fibrosis

In various organs, the common underlying mechanism leading to fibrosis involves the generation and the proliferation of myofibroblasts producing excessive amounts of ECM components (86). In adipose tissue derived from obese humans, fibroblastic  $\alpha$ -smooth muscle actin-positive ( $\alpha$ SMA<sup>+</sup>) cells are enriched in fibrotic bundles (Figure 2 and ref. 71). TGF- $\beta$ 1 usually represents the prototypic inducer of profibrotic myofibroblast differentiation from all precursor cell types (87). However, a combination of fibrogenic signals, increased in the fibrotic adipose tissue (43), cooperates to sustain the adipose tissue fibrotic transformation. TGF- $\beta$ 1 (88) and activin A (89, 90) belong to the TGF- $\beta$  superfamily and pro-





**Figure 3. Adipose tissue fibrosis in obese subjects.** With chronic obesity, WAT depots undergo continual remodeling, becoming pathological. Combined with unadapted vascularization promoting hypoxia and unresolved inflammation, alteration of the equilibrium between the myofibroblast and the adipogenic fate of adipose progenitors is important in the unhealthy growth of adipose tissue. Various signals and transcription factors were found to be important in controlling the fate of progenitors.

mote activation of SMAD2/3 transcription factors (91). Activation of SMAD2/3 modulates the expression of several profibrotic genes (91), including collagens, ECM-remodeling enzymes such as matrix metalloproteinases (92), or the integrin transmembrane receptor, activation of which can perpetuate fibrotic signaling (93). In addition, multiple studies, using activation or inhibition approaches, show that platelet-derived growth factor- $\alpha$  (PDGFA) is another critical profibrotic signal that binds tyrosine kinase receptors such as PDGFR $\alpha$  and PDGFR $\beta$  for an important contribution to the proliferative phenotype of fibrosis-producing cells (94–97). PDGFR $\beta$  was also found expressed on adipose progenitors, but its exact role in adipose tissue needs to be clarified, though its profibrotic activity was described in the liver (98). Moreover, connective tissue growth factor (CTGF), a secreted matricellular protein, can affect multiple signaling pathways that contribute to the persistence of fibrosis. CTGF is indeed involved in ECM remodeling and deposition, myofibroblast activation, cell adhesion, and migration (80, 99).

Emerging knowledge has provided the necessary information to start deciphering the molecular networks involved in the fibrotic process (Figure 3). During obesity, the production of various endogenous activators of TLR4 is augmented (including LPS, tenascin C, HMGB1, and fetuin-A) (100–104). Such activation of TLR4 on bone marrow-derived cells mediates the development of obesity-associated adipose tissue fibrosis (88). This suggests that obesity-induced adipose tissue inflammation (105) involves TLR4 activation on leukocytes, which in turn may secrete factors critical for the promotion of fibrogenesis. For example, stimulation of TLR4 potentiates PDGFR $\alpha$  signaling (106) and TGF- $\beta$  production (88), and adipose tissue fibrosis is dampened upon treatment with a neutralizing anti-TGF- $\beta$  antibody (88). In addition, macrophage-inducible C-type lectin (also known as Mincle, Clec4e, or Clec5f9) is induced in macrophages by LPS via TLR4; during obesity, *Mincle* is localized to macrophages within crown-like structures (CLSs) in adipose tissue. CLSs represent a site of interaction between adipocytes and macrophages that facilitates scavenging of residual lipid droplets, and increased CLS formation is associated with insulin resistance in humans (22, 107). Interestingly, *Mincle*-KO mice are protected against obesity-induced CLS

formation and adipose tissue fibrosis (108). Transcriptomic profiling of macrophages showed that Mincle modulates macrophage functions important for the control of ECM production, fibroblast proliferation, and ECM degradation, further suggesting that macrophages may be of importance in myofibroblastic transformation with ECM deposition (108). Additionally, macrophages participate in fibrosis clearance through collagen uptake and lysosomal degradation involving the collagen receptors mannose receptor 1 (Mrc1) and urokinase plasminogen activator receptor-associated protein (Endo180, also known as Mrc2) (109), or milk fat globule epidermal growth factor 8 (Mfge8), a secreted glycoprotein that binds collagen to target it for removal from the ECM (110). Nonetheless, the involvement of other bone marrow-derived cell types in this process cannot be ruled out (111).

Limited vascular outgrowth is also of importance in unhealthy adipose tissue remodeling, since it results in hypoxia. In adipose tissue, HIF1 $\alpha$  links the hypoxic milieu to fibrosis and inflammation (78, 112). Overexpression of HIF1 $\alpha$  promotes a transcriptional program associated with the induction of ECM proteins and inflammation. Conversely, the selective inhibition of HIF1 $\alpha$  using an inhibitor or induction of WAT-specific dominant-negative *Hif1a* in obese mice alleviates WAT fibrosis and inflammation (112).

### Progenitors in fibrosis: adipogenic versus myofibroblastic precursors

In fibrotic organs, the excessive deposition of ECM, a defining feature of fibrosis, starts with cells that are sensitive to profibrotic stimuli acquiring a myofibroblastic phenotype. Myofibroblasts are characterized by de novo expression of  $\alpha$ SMA, formation of cellular stress fibers, and abundant production of ECM proteins and autocrine growth factor that maintains cell proliferation and survival (113). Some studies suggest that in mouse models of renal, hepatic, or pulmonary fibrosis, myofibroblasts could arise from the differentiation of local epithelial cells via epithelial-mesenchymal transition (114). However, this view is now challenged by strong evidence from lineage tracing studies in various organs highlighting that myofibroblasts originate from local mesenchymal cells (115, 116). As such, ADAM12 $^{+}$  and Gli1 $^{+}$  cells were identified as a minimal subset originating myofibroblasts (115, 116).

In injured muscle or in muscular dystrophy, bipotent fibro/adipogenic progenitors have been shown to give rise to adipocytes and collagen-producing cells that compromise muscle function. These progenitors were identified with markers very similar to those found on adipogenic progenitors isolated from WAT (117–119).

In adipose tissue fibrosis accumulation, PDGFR $\alpha$ <sup>+</sup> progenitors are identified as the main contributors to ECM production. PDGFR $\alpha$ <sup>+</sup> progenitors were initially identified for their ability to differentiate into white adipocytes (34). However, in fibrotic adipose tissue, we and others observed that PDGFR $\alpha$ <sup>+</sup> cells produce the highest levels of fibrosis markers such as collagens as compared with adipocytes, endothelial cells, or macrophages, and they accumulate in fibrotic adipose tissue (43, 88).

This bipotent capacity to differentiate into adipocyte or myofibroblast suggests that heterogeneity among adipose tissue progenitors could be pathologically relevant. Accordingly, the expression level of CD9, a surface marker protein whose expression was coregulated with fibrosis markers (70), defines two progenitor populations. In lean mouse adipose tissue, PDGFR $\alpha$ <sup>+</sup>CD9<sup>hi</sup> progenitors are driven toward ECM production, whereas PDGFR $\alpha$ <sup>+</sup>CD9<sup>lo</sup> cells are committed to adipogenesis. In the fibrotic WAT, the PDGFR $\alpha$ <sup>+</sup>CD9<sup>hi</sup> subset accumulates, while the PDGFR $\alpha$ <sup>+</sup>CD9<sup>lo</sup> population is lost. These observations in mice were further translated by observations in visceral fat (i.e., omental adipose tissue) from severely obese subjects. CD9 expression also defines two populations among the CD34<sup>+</sup>CD45<sup>+</sup>CD31<sup>+</sup> cells. An increased frequency of CD9<sup>hi</sup> over CD9<sup>lo</sup> progenitors is also observed together with omental adipose tissue fibrosis in these subjects with severe obesity with or without diabetes. Interestingly, the number of CD9<sup>hi</sup> progenitors was also associated with glucose control in this population.

Furthermore, boosting PDGFR $\alpha$ -mediated profibrotic signaling in PDGFR $\alpha$ <sup>+</sup> progenitors (94, 120, 121) favored the accumulation of CD9<sup>hi</sup> over CD9<sup>lo</sup> cells. This phenotypic switch was concomitant with collagen deposition, reduced fat accretion, and local insulin resistance, supporting a direct local role for PDGFR $\alpha$ <sup>+</sup> progenitors in WAT metabolic alterations (43).

The use of single-cell RNA sequencing to examine the transcriptional profile of individual cells enables exploration of the cellular diversity in different adipose tissue microenvironments. An elegant study confirmed the fibrotic fate of CD9<sup>hi</sup> progenitors and added a layer of complexity, showing that CD9<sup>hi</sup> progenitors also include mesothelial cells (122). Mesothelial cells form a monolayer, known as the mesothelium, that covers internal organs. In some circumstances, they are shown to be able to undergo mesothelial-mesenchymal transition to acquire a myofibroblastic phenotype with secretion of inflammatory mediators and ECM components (123, 124). However, to date, the exact role of mesothelial cells in visceral adipose tissue homeostasis remains unelucidated, especially in the context of energy imbalances.

Several recent studies now depict great heterogeneity among adipose progenitors, along with functional differences. In adipose tissue, these progenitors also produce chemokines and cytokines, suggesting that they may be involved in obesity-induced WAT fibrosis and the orchestration of adipose tissue inflammation (122, 125). Accordingly, among progenitor cells, those that exert a regulatory function on immunocyte expansion can be distinguished from adipocyte precursors. Through the production of IL-33, IL-33<sup>+</sup> progenitor

subsets function to control the accumulation of regulatory T cells in the adipose tissue, suggesting progenitors as an important orchestrator of the tissular immunological response (126). In addition, IL-33 was shown to be a positive inducer of fibrosis in lung and liver (127).

In addition to heterogeneity in function, progenitor subsets are defined along a developmental hierarchy with specific location. DPP4<sup>+</sup> progenitors located in the reticular interstitium surrounding the adipose depot give rise to precursors committed to adipocyte fate as ICAM1<sup>+</sup> and CD142<sup>+</sup> preadipocytes distributed between the mature adipocytes in the fat depot cells (128). Notably, in a separate work, a subpopulation identified as CD142<sup>+</sup> displays adipogenesis-regulating properties, as these cells can suppress adipocyte formation in a paracrine manner without adipogenic potential (35). Interestingly, TGF- $\beta$  signaling functions to maintain DPP4<sup>+</sup> progenitor identity and to inhibit the adipogenic transformation of DPP4<sup>+</sup> and CD142<sup>+</sup> cells (128).

Our current understanding is that adipose tissue progenitors can undergo differentiation toward either adipogenic or fibrogenic cell programs. Thus, a switch in progenitor orientation toward either the adipocyte or fibrotic lineage might be instrumental in the adipose tissue response to obesogenic conditions. This orientation is probably critical in cell fate determination, and fibrosis orientation may alter the healthy expansion of adipose tissue with a reduced ability to form new fat cells. In agreement with this view in which adipogenesis and fibrogenesis are interconnected, limiting of the precursor adipogenic phenotype through PPAR $\gamma$  deletion or PDGFR $\alpha$  activation favors the fibrotic transformation of WAT (21, 94), and results in a maladaptive response of the adipose tissue to obesogenic stress. These observations also argue for an interplay between the adipogenic and the myofibroblastic fate.

Generation of white adipocytes is not solely connected to the fibrotic pathway. Adipose progenitors can also form beige adipocytes (16, 41), a process named adipose beiging (wherein WAT develops characteristics of metabolically active BAT), and compelling evidence supports that adipose beiging and fibrosis are opposing pathways. As such, the PRDM16 transcriptional complex not only activates brown/beige fat development (17), but also potentially represses adipose tissue fibrosis through its direct interaction with GTF2IRD1. Interestingly, this phenomenon is independent of UCP1's uncoupling function (129).

In addition, PRDM16-dependent metabolic signals arising from adipocytes regulate progenitor fate, blocking fibrosis while enhancing beige adipogenesis (130). The transcription factor MRTFA has also consistently been highlighted as another critical inducer of progenitor fibrotic fate (131) with critical roles in beige adipogenic orientation (132) and improvement of the metabolic health of adipose tissue.

## An understanding of adipose tissue fibrosis resolution is still needed

Antiobesity treatments mostly rely on approaches limiting caloric intake in order to promote weight loss. In severe obesity, bariatric surgery is a therapeutic procedure that efficiently leads to drastic weight loss, amelioration of low-grade inflammation, and even diabetes resolution in some (but not all) patients along with reduction of cardiovascular risks. Surprisingly, analysis of human WAT revealed that weight loss induced by surgery is accompanied by increased

deposition of ECM (133), suggesting that weight loss has a profound impact on tissue remodeling. Other studies have confirmed these findings and suggest that adipose tissue inflammation could be of importance in this process, as leukocyte and macrophage infiltration remained after loss of fat mass (134, 135) and could then sustain the lack of fibrosis resolution. The functional consequences of this WAT remodeling deserve further attention, as this process could favor/potentiate tissue metabolic deteriorations in patients who frequently experience weight loss and rebound.

## Conclusions and perspectives

With excess energy pressure, expandability and remodeling appear to be critical adipose tissue functions for clinical outcomes (136). WAT fibrosis accumulation, characterized by pathological remodeling and reductions in adipose expandability, is considered to be an aggravating factor in obesity and associated metabolic diseases. As a solution to control the balance between adipose tissue expandability and fibrosis, adipose progenitors have become a target of interest. This is highlighted by the fact that intradermal adipose-derived myofibroblasts remain multipotent and can be reprogrammed during wound healing to generate fat cells (137, 138). More studies are necessary to delineate the critical pathways controlling adipocyte and myofibroblast balance in subcutaneous and visceral fat. Deeper understanding of these

pathways would lay the groundwork to develop new therapeutic strategies to maintain (or rescue) adipose tissue plasticity in order to break the deleterious link between obesity and associated metabolic dysfunctions.

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