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Adipose Tissue Fibrosis in Obesity: Etiology and Challenges

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obesity, adipose tissue, fibrosis, progenitors, adipogenesis, macrophages

Abstract

Obesity is a chronic and progressive process affecting whole-body energy balance and is associated with comorbidity development. In addition to increased fat mass, obesity induces white adipose tissue (WAT) inflammation and fibrosis, leading to local and systemic metabolic dysfunctions, such as insulin resistance (IR). Accordingly, limiting inflammation or fibrosis deposition may improve IR and glucose homeostasis. Although no targeted therapy yet exists to slow or reverse adipose tissue fibrosis, a number of findings have clarified the underlying cellular and molecular mechanisms. In this review, we highlight adipose tissue remodeling events shown to be associated with fibrosis deposition, with a focus on adipose progenitors involved in obesity-induced healthy as well as unhealthy WAT expansion.

INTRODUCTION

Obesity and its multiple complications (diabetes and cardiovascular, pulmonary, and liver diseases and cancers) have increased dramatically over the past decades, and recent data show that obesity cases steadily progress into extreme forms (1). High morbidity and mortality rates are principally linked to diabetes and other obesity-associated morbidities, and they represent a major individual and societal burden. Indeed, the global costs of obesity range from 4% to 10% of total health-care budgets, whereas effective and safe treatments are still scarce. In this context, it is crucial to further improve our understanding of the cellular and molecular mechanisms underlying obesity pathogenesis. This will eventually pave the way to innovative therapeutic strategies.

White adipose tissue (WAT) is a complex tissue with major regulatory functions. In addition to playing a well-known role in storing and mobilizing lipids, WAT secretes a myriad of signaling molecules with central and peripheral activity that control whole-body energy homeostasis (2). During obesity, WAT undergoes massive expansion through progressive adipocyte hyperplasia and hypertrophy that are accompanied by continual remodeling and functional alterations as the disease progresses. Those defects are numerous and include, among others, impaired vascularization, local hypoxia facilitating adipocyte necrosis, infiltration of proinflammatory leukocytes, and fibrosis. Evidence from human and mouse studies suggests that the WAT alterations limit lipid storage capacity, which may result in ectopic fat accumulation in liver, pancreas, or muscles, driving insulin resistance. Furthermore, the altered WAT secretome, characterized by increased production of inflammatory molecules and decreased secretion of insulin sensitizers, affects the central regulation of energy homeostasis and the functions of key metabolic organs (3). Here, we review the current knowledge on the cellular events governing obesity-induced unhealthy WAT expansion. We focus on adipose tissue (AT) remodeling events shown to be associated with fibrosis deposition.

THE ADIPOSE TISSUE: A MULTIFACETED ORGAN

In mammals, morphologically and functionally different types of AT can be distinguished. Beige and brown adipocytes display capacity to dissipate energy through heat production. The brown adipose tissue (BAT) is found subcutaneously in specific locations, mostly in newborns and in smaller amounts in adults. BAT primarily functions as a thermogenic organ owing to the presence of multilocular adipocytes enriched with mitochondria and uncoupling protein 1 (UCP1) (4, 5). The overall morphology of beige adipocytes is similar to that of the brown adipocytes, but beige cells infiltrate more diffuse areas within WAT depots. Beige adipogenesis, considered to be a healthy remodeling process in the WAT, significantly increases in response to thermogenic stimuli, such as decreased temperature (6, 7) or β3-adrenergic receptor activation (8–10), or in response to some metabolites (11, 12). With obesity development, both brown and beige fat depots are reduced (13–15). Conversely, WAT depots expand with obesity in order to store excess energy. WAT displays functional differences according to its subcutaneous (thigh, hip) or visceral (surrounding the internal organs) location (**Table 1**). The visceral WAT is mostly represented by the omental WAT (surrounding the liver, gut, and stomach) and the mesenteric WAT, which is closely attached to the intestine. In lean individuals, the subcutaneous WAT represents the main white fat depot (80% versus 20% of visceral WAT) with sex differences regarding WAT depot location. In addition to this differential location and to differences in their embryonic origins (16, 17), the subcutaneous and the visceral WAT show different structural features. The subcutaneous WAT of the abdomen comprises a superficial adipose layer and a deep adipose layer, separated by a continuous fibrous membrane rich in elastic fibers (18). By contrast, the visceral WAT is differentially

Table 1 Differences between visceral and subcutaneous white adipose tissues

	Visceral WAT	Subcutaneous WAT
Histological features		
Adipocyte size	+	+++
Leukocyte content	+++	+
Macrophage infiltration	+++	+
Adaptive features		
Angiogenesis	+	+++
Adipogenesis	+	+++
Beiging	+	+++
Steady-state metabolism		
Lipogenesis	+	+++
FFA production	+++	+
Insulin sensitivity	+	+++
Adiponectin secretion	+	+++
Obesity metabolism		
Glucose uptake	+++	+
Induced lipolysis	+++	+
Proinflammatory cytokine production	+++	+

The table compares the two fat depots regarding histological characteristics, adipose tissue remodeling features, and adipose tissue metabolism at steady state or during obesity. + and +++ describe the relative comparison of the parameters between visceral and subcutaneous WAT as lower and higher, respectively.
Abbreviations: FFA, free fatty acid; WAT, white adipose tissue.

organized, covered by a layer of mesothelial cells known as the mesothelium. Mesothelial cells are polygonal cells that form a cobblestone monolayer over the visceral and parietal surfaces of the peritoneal, pleural, and pericardial cavities (19). These cells share many features with epithelial cells, including polarity and intercellular junctions. The main roles attributed to the mesothelium have been those of a protective barrier against physical damage and invading organisms and of a frictionless interface for the free movement of apposing organs and tissues. In visceral WAT, cell lineage analysis with the tamoxifen inducible Wt1-Cre^{ERT2}; mTmG mice suggested that Wt1-expressing mesothelial cells could produce adipocytes (16). However, this adipogenic capacity was not replicated in vitro (20) or in a recent study using the Krt19-Cre^{ERT2}; mTmG mouse line, as Krt19 was classically defined as a mesothelial cell marker (21). Discrepancy between Wt1-Cre^{ERT2} and Krt19-Cre^{ERT2} mouse lines may be explained by the lower specificity of Wt1 as a mesothelial marker. Indeed, Wt1 is expressed by AT progenitors, which may have led to these confounding observations. Overall, further investigation of the peculiar functions of the mesothelium compartment in visceral WAT depots would be of interest.

With obesity, both subcutaneous and visceral WAT depots can expand, and a massive deposition of visceral fat is generally associated with increased risk of developing cardiometabolic diseases. By contrast, predominant subcutaneous WAT storage may reduce the risk of developing comorbidities in some individuals (22–24). In addition to the functional differences between subcutaneous and visceral WAT (listed in **Table 1**), a more damaging consequence of visceral WAT accrual was hypothesized to be due to its close proximity to the portal system. Thus, the liver can be directly exposed to free fatty acids and cytokines released from the visceral WAT into the portal vein, thereby favoring obesity-associated hepatic dysfunction (23, 25, 26).

The fundamental mechanisms underlying the regional distribution of the WAT still remain to be elucidated. Both genetic determinants (27, 28) and sex hormones can influence AT distribution. Indeed, visceral WAT accretion is preferentially observed in men (android distribution), whereas women mostly show AT accumulation in subcutaneous areas (gynoid distribution) (24, 29). Whether visceral and subcutaneous WAT growths are coregulated remains unsolved, but the evidence could support such a hypothesis. In individuals with severe obesity, subcutaneous WAT senescence was recently found to be significantly linked to visceral fat mass and heightened markers of insulin resistance (30). Similarly, subcutaneous WAT fibrosis accumulation was positively associated to visceral adiposity (31). However, whether expansion and/or preservation of subcutaneous WAT function would help in reducing the deleterious consequences of visceral WAT expansion still remains to be elucidated.

PROGRESS IN UNDERSTANDING ADIPOGENESIS DURING WHITE ADIPOSE TISSUE EXPANSION

With obesity, the WAT is tipped into storage mode, and fat pad growth is ensured by both adipocyte hypertrophy (enlarged adipocytes) and adipocyte hyperplasia (increased cell number). Evidence supports the hypothesis that the maintenance of metabolic health involves an increased number of adipocytes rather than an enlargement of adipocytes, given that bigger cells are more dysfunctional. Indeed, electronic microscopy analysis of enlarged adipocytes revealed ultrastructural changes such as reduced cytoplasmic membrane thickness or reduced mitochondria size (32). Those morphological modifications associate with defective production of molecules including increased free fatty acids, tumor necrosis factor α (TNFα), interleukin-6 (IL-6), IL-8, monocyte chemoattractant protein-1, and acute-phase serum amyloid A proteins, among others (33–35). These factors may compromise local and systemic metabolism. As a consequence, maintaining adipogenic capacity to restrain fat growth associated with adipocyte hypertrophy could be targeted to promote healthy AT remodeling. As such, understanding the processes governing in vivo adipogenesis may be useful to dampen the coupling between obesity and metabolic diseases.

The formation of new adipocytes requires the proliferation and differentiation of precursor cells (also called progenitors), since mature adipocytes are postmitotic cells (36). The use of in vivo lineage tracing studies in rodents revealed that WAT expansion in obese mice occurs in a depot- and sex-dependent manner (29, 37), suggesting the importance of the sex hormone context to regulate the preferred process for energy storage between adipocyte hyperplasia and hypertrophia. Within the WAT, adipocyte precursors reside closely associated with the vasculature (38). In addition to a strong adipogenic potential, those cells can also differentiate into other cell lineages, including chondrocytes or osteoblasts (39, 40). Initially identified as PPARγ (peroxisome proliferator-activated receptor gamma)-expressing cells, progenitors were later delineated as a cell population expressing mesenchymal cell surface markers such as CD44, CD34, CD29, PDGFRα (platelet-derived growth factor receptor alpha), and PDGFRβ (36, 41). A hierarchical organization was first described with the identification of a CD24-expressing ($CD24^+$) progenitor subset (29, 36). In WAT, $CD24^+$ progenitors encompass a small fraction of the whole progenitor population (<1%) that can regenerate a functional white fat pad in lipodystrophic mice thanks to their stem cell–like properties (36).

In more committed adipocyte progenitors, Pref-1 (preadipocyte factor 1) expression defines cells with proliferative capacity. The deletion of Pref1-expressing progenitors prevents WAT development and expansion (42). In undifferentiated cells, the active expression of Pref-1 prevents adipocyte differentiation by maintaining progenitor stemness, whereas its expression is lost in later stage of adipogenesis (43). Highly committed preadipocytes are defined with the coexpression of

proadipogenic transcription factors such as PPARγ and ZFP423 (44). In the visceral WAT, these committed preadipocytes can also be identified as cells with low expression of the surface marker CD9 (45).

Currently, single-cell RNA sequencing (scRNAseq) applied to the WAT has highlighted multiple clusters of progenitors based on differentially expressed networks of genes and has revealed a large heterogeneity and complexity among the cell populations. In subcutaneous WAT, a hierarchical organization was suggested, with the analysis depicting the cellular trajectory in the adipogenic fate with dipeptidyl peptidase–4 ($DPP4^+$) cells as multipotent progenitors giving rise to both $CD54^+$ and $CD142^+$ cells, which further differentiate into mature adipocytes (46). Importantly, different studies suggest that proper adipogenic capacity is progressively lost with obesity. The molecular pathways associated with this dysfunctionality still remain to be elucidated, but studies suggest that the pool of preadipocytes is reduced, as shown by the loss of the $CD9^{low}$ or $DPP4^+$ progenitors in independent studies (20, 45, 46).

In humans, the analysis of adipocyte turnover revealed that the newly formed adipocytes can be observed mostly from birth to early adulthood (47). However, despite limited adipogenesis in adults, adipocyte precursors can still be observed in the AT (41) and are enriched in $CD34^+$, $PDGFR\alpha^+$, $CD45^-$ (leukocyte), and $CD31^-$ (endothelium) cell populations. The use of CD36 (encoding the primary cellular fatty acid translocase) (48) and Msca1 (mesenchymal stromal cell antigen-1), whose expressions are induced during adipogenesis (49), suggests that various degrees of adipogenic commitment can also be observed. Another level of organization is also suggested as $CD34^{high}$, $CD34^{low}$, and $CD34^-$ progenitors differentiate into adipocytes characterized by divergent metabolic properties (50). Their relative abundance varies in the WAT from type 2 diabetes patients. In that case, identifying the critical triggers and how they affect WAT remodeling could be of interest.

As in mice, scRNAseq in human WAT revealed a large heterogeneity modulated by the metabolic status of the individual (51). Progenitor subsets are also rearranged with WAT remodeling, and differences between the subcutaneous and the visceral WAT can be observed (51, 52). In human as well as in mice, the AT provides a heterogeneous spatial microenvironment that could shape the phenotype of the adipose progenitors in a region-specific fashion. For instance, the lobular organization of the human AT was proposed to be associated with the progenitor phenotype and functionalities (53). Indeed, nonadipocytes derived from the WAT septa versus the WAT stroma exhibit marked differences in extracellular matrix-related gene expression (53). In mice, a lineage-tracing study revealed the anterior-posterior regionality of the male perigonadal AT. Along this depot axis, a gradient of adipocytes derived from the somatic mesoderm could be observed. This developmental patterning was associated with a difference in the proliferation rate of the progenitors (17).

Overall, the importance of considering the progenitor diversity when studying obesity is just starting to be appreciated, and it may help to identify pathways controlling the production of new adipocytes to favor the healthy expansion of AT mass. However, links between the subsets highlighted by the different published single-cell analyses are lacking, preventing a full understanding of the biology of the AT progenitors.

COORDINATED VASCULATURE AND WHITE ADIPOSE TISSUE GROWTHS ENABLE HEALTHY EXPANSION

The WAT exhibits a unique ability to rapidly expand or shrink in response to the whole-body energy balance. This remarkable plasticity relies on a dynamic and versatile metabolism. Thus, in the presence of the caloric overload associated with obesogenic conditions, the most physiological

response is the esterification of fatty acids, which are subsequently stored as triglycerides in white adipocytes. To accomplish a healthy expansion with a preserved WAT function, a coordinated growth of the vasculature network appears to be necessary to ensure a proper perfusion of the tissue with the nutrients, oxygen, and hormones that are essential to maintain adipocyte survival and functions. The new blood vessels develop from those preexisting within the WAT under the control of angiogenic factors that can be produced locally by the adipocytes and the preadipocytes (54, 55) [i.e., leptin, vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (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]. Consequently, mirroring the cancer therapy using antiangiogenic agent to limit tumor growth, researchers have proposed adopting this strategy to block fat mass expansion. However, subsequent studies revealed that appropriate capillary density and functions are required to maintain a healthy and functional WAT. The findings regarding oxygen tension measurements in human AT from lean and obese patients are discordant (56, 57). Nevertheless, dysfunctional endothelial cells were also described in the WAT of obese individuals (58, 59) that may contribute to unhealthy WAT expansion. In mouse models, the use of the hydroxyprobe marker system or direct measurements of oxygen tension enabled the identification of hypoxic areas in the visceral AT of genetically or dietary-induced obese mice (60–62).

The decreased oxygen availability can activate HIFs (hypoxia-inducible factors) and other transcription factors that regulate the molecular response to hypoxia (63). HIF target genes are involved in a wide range of cellular functions, including glucose utilization, angiogenesis, apoptosis, extracellular matrix (ECM) remodeling, and inflammation (64–66). Within the WAT, the hypoxic areas colocalize with macrophages. Local hypoxia could result in dead and necrotic adipocytes. Therefore, the recruitment of macrophages may also reflect the need of removing remnant adipocytes (67). As a consequence of the inappropriate vascularization, wound healing processes seem to be engaged. In acute tissue injury, the inflammatory cells clear the wound and release factors that stimulate the migration of fibroblasts acting as producers of ECM components to fill the wound. The fibroblast-rich tissue is then replaced by a scar, which is mostly acellular. In the resolution phase of classical acute tissue injury, the ECM-producing cells are cleared from the site, and the activation of collagen degradation through proteolytic enzymes called matrix metalloproteinases (MMPs) allows tissue repair and renewal. MMPs are secreted by a number of cells, including macrophages, endothelial cells, and fibroblasts (68). In contrast to the processes associated with acute tissue injury, the processes activated during tissue repair do not cease in the obese WAT. This gradually leads to a progressive fibrotic transformation of the WAT that is highly detrimental for its functions (3). In transgenic mouse models in which angiogenesis is boosted thanks to VEGF-A overexpression, the high-fat-diet-induced pathological remodeling of the AT (hypoxia, fibrosis, and proinflammatory responses) is not only attenuated but also accompanied by beiging of the WAT (69–71). The mechanisms driving white adipocytes' beiging is not clearly identified but is closely related to the proangiogenic signaling, as the phenotypic switch from white to beige adipocytes was quickly reversed when the induced expression of VEGF-A was stopped (69). Taken as a whole, adequate vascularization appears to be pivotal to controlling unhealthy versus healthy AT expansion.

NEWLY RECRUITED MACROPHAGES ORCHESTRATE ADIPOSE TISSUE INFLAMMATION DURING OBESITY

Macrophages (Macs) are specialized in the degradation of endogenous and exogenous materials, including lipids, thanks to their potent lysosomal activity (72). AT-resident Macs (atrMacs) are

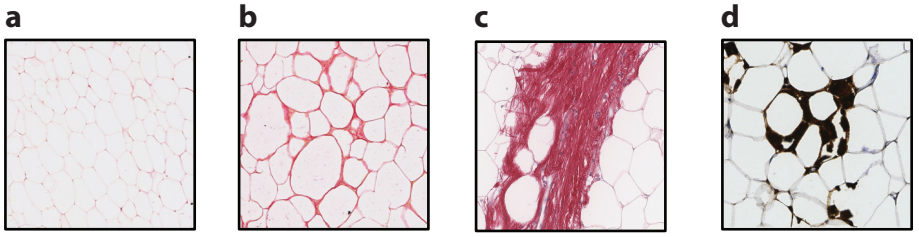

Figure 1

Obesity and inflammation in adipose tissue associate with fibrosis deposition. Collagen deposition stained with red picrosirius staining in adipose tissue section obtained from (*a*) lean (without fibrosis) and (*b*,*c*) obese (with fibrosis) individuals. Fibrosis is organized around adipocytes or creates large collagen bundles containing isolated adipocytes from the rest of parenchyma. (*d*) Infiltrated macrophages (CD68 positive; *brown*) are arranged as crown-like structure around adipocytes.

distributed throughout the lean WAT and, for the vast majority, may develop early in life and then maintain in the adult stage by proliferating locally, independently from the circulating monocyte pool (73, 74). It is worth noting that, compared to other tissue-resident Mac populations, the ontogeny of atrMacs and their maintenance have not been studied in full detail so far.

Obesity-induced WAT inflammation is characterized by Mac accumulation, including of monocyte-derived Macs (moMacs). Indeed, monocytes recruited to the obese WAT can locally differentiate into moMacs and contribute to the adipose Mac pool (75), whereas the exact contributions of atrMacs relative to MoMacs remain underappreciated. The CCL2–CCR2 axis is a key driver of monocyte recruitment to tissues (76), and enhanced CCL2 expression is observed in the obese WAT (77). Consequently, Mac infiltration and accumulation are reduced in *Ccl2*-deficient mice (77) as well as in mice that lack *Ccr2* (75). Importantly, both *Ccl2*- and *Ccr2*-deficient obese animals are more insulin sensitive and have limited liver steatosis (75, 77), suggesting a detrimental impact of moMacs on glucose metabolism. A proportion of moMacs induces CD11c expression in obese mice (78), and the ablation of $CD11c^+$ myeloid cells, including moMacs, protects mice from obesity-induced comorbidities (79, 80), again underlining the harmful impact of moMacs on the pathophysiology of the disease. Beyond monocyte recruitment, proliferation may also contribute to increased Mac density in the obese WAT (81), and IL-6 has been shown to favor such proliferative activity (82). On histological sections of obese WAT, Macs are found to accumulate in defined areas, termed crown-like structures (CLS), that surround adipocytes (32, 67, 83, 84) (**Figure 1*d***). In those areas, macrophages were shown to engulf lipid droplets from dying adipocytes. Indeed, adipocytes from CLS exhibit abnormal disrupted basal membrane and loss of lipid droplet integrity (67). This associates with the marked downregulation of the lipid droplet–associated protein perilipin, an event that is classically used to identify dysfunctional or dying adipocytes (85). The fact that WAT CCL2 induction coincides with an increased frequency of dead adipocytes suggests that dying adipocytes could be a key driver of monocyte recruitment (86). Along these lines, FAT-ATTAC mice, in which adipocyte apoptosis is triggered through the inducible overexpression of Caspase 8, display macrophages infiltration in fat depots (87). However, this model induces severe lipoatrophy, which represents a different condition. Thus, the specific contribution of adipocyte death as a driving event in WAT macrophages recruitment remains to be fully documented in the obesity context.

Macs display critical secretory functions that can fuel the chronic low-grade inflammation typically associated with obesity, notably by releasing inflammatory cytokines. Such an inflammatory milieu is known to drive obesity-associated comorbidities, including insulin resistance (88). Along

these lines, TNFα, the prototypical cytokine expressed by Macs, critically controls WAT inflammation and favors the onset of insulin resistance in mice (89). In humans, several studies equally support the role of Macs in the metabolic deterioration associated with obesity, although a direct causal link is less well established. However, Macs infiltration in the omental WAT of obese patients correlates with insulin resistance and associates with hepatic fibroinflammatory lesions (84, 90–92). As in mice, WAT in humans with obesity exhibits increased expression of genes encoding proinflammatory cytokines and contains increased Mac numbers compared to lean controls (84). On the whole, Mac accumulation, partly driven by moMac infiltration, promotes local AT injury and alters metabolic functions in obesity.

ADIPOSE TISSUE MACROPHAGE PHENOTYPES DURING OBESITY

Beside an increase in the Mac pool, it is also important to consider obesity-induced changes in Mac phenotypes. It was initially proposed that Macs can switch from classical (M1) to nonclassical (M2) activation and vice versa (78). The M1/M2 paradigm originally classified macrophages in regard to their state of activation after interferon gamma (IFNγ; alone or in combination with lipopolysaccharides) or IL-4 stimulation in vitro, respectively (93). However, such a classification needs to be revisited in the context of obesity, where the metabolic microenvironment drives Mac activation toward a state distinct from the one described by the M1/M2 paradigm (94). Whether these in vitro–generated signatures resemble the in vivo activation status is not clear. Indeed, Macs are responsive to a vast number of single or combined stimuli (95), which leads them to a vast range of activation states when sampled in a complex environment, such as the obese WAT. In addition, as mentioned above, adipose Macs with different developmental pathways and precursors cohabitate, and they may respond differentially to the obese WAT milieu.

The use of scRNAseq has recently extended our ability to better investigate AT Mac diversity. Along these lines, analysis performed on total WAT leukocytes or myeloid cells, including Macs, after various times of high-fat diet feeding (83, 96) have started to highlight such diversity. For example, a $CD9^+$ $CD63^+$ Mac subset infiltrates the obese WAT and is thought to derive from monocytes. $CD9^+$ $CD63^+$ Macs accumulate in CLS and have strong lipid metabolism and phagocytosis transcriptomic signatures, leading to their designation as lipid-associated macrophages (LAMs) (83, 96). A similar population of highly phagocytic Macs increases after weight loss–induced lipid release (97), providing evidence for the importance of these cells in lipid buffering. LAMs are further characterized by the expression of *Trem2*, and a whole-body knockout of this transporter prevents the appearance of LAMs and leads to massive adipocyte hypertrophy as well as worsened metabolic dysfunctions (96). Of note, the presence of $TREM2^+$ Macs was observed in human visceral WAT, and their number positively correlated with body mass index (96). However, the phenotype of *Trem2*-deficient mice was recently attributed to nonhematopoietic cells (98).

In the obese WAT, metabolic stressors, such as saturated fatty acids (SFAs), can reprogram adipose Macs (94). Specifically, SFAs activate Jun N-terminal kinase (JNK) and induce inflammation, but this is only effective in Toll-like receptor 4 (TLR4)-primed macrophages (99). Significantly, the production of various endogenous TLR4 activators, including lipopolysaccharides, tenascin-C (TNC), HMGB1, and fetuin-A, is augmented in obesity (85, 100–104). On a mechanistic basis, TLR4 priming alters cellular metabolism and membrane lipid composition, allowing cells to respond to SFAs by activating the JNK pathway in vitro (99). In vivo, mice with impaired JNK signaling in macrophages were markedly protected against diet-induced insulin resistance (105). Thus, an SFA–JNK axis is essential to activate macrophages and drive metabolic inflammation as well as obesity-induced metabolic dysfunctions.

A recent study suggests that the phenotype of WAT Macs can be modulated in vivo through the phagocytosis of mitochondria released from other cell types, including adipocytes, at the steady state (106). Importantly, such mitochondrial uptake defines transcriptionally distinct Macs. During obesity, these intercellular mitochondria transfers, which depend on Mac-derived heparan sulfate, are impaired. This was proposed to modulate energy balance, as mice with myeloid cells deficient for mitochondrial uptake exhibit decreased energy expenditure and increased susceptibility to obesity (106). Thus, adipose Macs, which can differ by origins and activation states, have a profound impact on metabolic homeostasis.

MACROPHAGE, AN ACTOR IN OBESITY-INDUCED ADIPOSE TISSUE FIBROSIS

Unresolved inflammation is often associated with fibrosis progression in many pathological states (68). Although more specific studies are still needed, some evidence suggests a role for Macs in obesity-induced WAT fibrosis. TLR4 activation in Macs can mediate the development of obesity-associated WAT fibrosis (85). Mechanistically, macrophage TLR4 activation recruits the macrophage-inducible C-type lectin (Mincle) to stimulate pathways involved in ECM production and degradation as well as in fibroblast proliferation and differentiation (107). Additionally, as mentioned above, TLR4-mediated potentiation of SFA-mediated inflammation could also contribute to WAT fibrosis by fueling local inflammation (99).

Besides their role in fibrogenesis, Macs participate in ECM clearance through collagen uptake and degradation. Collagen phagocytosis by Macs depends on the mannose receptor (Mrc1), the urokinase plasminogen activator receptor–associated protein (Endo180 and Mrc2) (108), or the milk fat globule epidermal growth factor 8 (Mfge8), a secreted glycoprotein that binds collagen and is then recognized by Macs (109). Whether collagen clearance operated by AT macrophages is impaired during obesity still remains to be explored.

Overall, AT Mac accumulation and activation maintains a chronic, low-grade meta-inflammatory state in WAT that provides and maintains a profibrotic environment. Nevertheless, the involvement of other immune cell types in the fibrotic transformation of AT cannot be excluded and deserves further investigation.

FIBROSIS IS CHARACTERISTIC OF UNHEALTHY ADIPOSE TISSUE MILIEU

Obesity-induced WAT fibrosis is characterized by excessive ECM deposition, a dysfunctional process ultimately causing organ failure. ECM accumulation is accompanied by exacerbated expression of ECM-encoding genes in the obese WAT (110, 111). At steady state, the ECM is a non-cellular component that preserves tissue architecture and is essential for tissue morphogenesis, differentiation, and homeostasis. ECM includes structural collagens and adhesion proteins, such as fibronectin and proteoglycans (biglycan, decorin) (112). The ECM maintains the structural integrity of adipocytes and is pivotal during adipogenesis (113–115). In human obese WAT, fibrosis can be visualized on tissue sections with the picrosirius red staining. Collagens accumulate around adipocytes to form pericellular fibrosis. Collagen fibers can be organized as fibrotic bundles of various thickness traversing the parenchyma and containing few adipocytes isolated from the rest of the parenchyma (**Figure 1*a–c***). The human WAT is structured as small fat lobules surrounded by fibrous septa. With obesity, perilobular fibrosis can also be observed (116).

Different lines of investigation support that increased ECM deposition could represent a physical constraint to WAT expansion (117, 118). Within the ECM, collagen VI isoforms associate to

form a beaded microfibrillar network. *Col6a1* invalidation in mice results in a complete loss of collagen VI fibers within the ECM, and this disentangles adipocytes from fibrosis but not from the obesogenic environment. As a consequence, adipocytes display uninhibited enlargement, which is associated with global metabolic healthiness in obese *Col6a1*-deficient mice. Thus, limiting WAT fibrosis appears to be beneficial at both local and systemic levels. In obese subjects, collagen VI expression levels are also linked to WAT remodeling and insulin resistance (56, 117, 119). Conversely, limiting collagen degradation, as in mice lacking the collagenase MMP14 (metalloproteinase 14), enables fibrosis stiffening and markedly limits lipid accumulation in adipocytes (118). MMP14 overexpression in the early stage of obesity improves fibrosis and inflammation, suggesting that the release of mechanical constraint results in a healthy WAT expansion (120). Similarly, inhibition of lysyl oxidase (LOX), an enzyme involved in collagen cross-linking and ECM stiffening, limits WAT inflammation as well as metabolic dysfunctions in obese mice (63). Accordingly, in human WAT, smaller adipocytes were found in fibrotic areas compared to nonfibrotic areas (111). The development of a prototypic tool (AdipoScan) based on elastography suggested that WAT fibrosis is associated with a significant change in tissue stiffness (121). Along these lines, modeling the physical constraints applied to adipocytes showed that mechanical compression can modify the functions of adipocytes by inducing an inflammatory secretome; altering lipolysis, adipokines, and profibrotic molecule secretion; and decreasing insulin sensitivity (122). These effects were proposed to be regulated by mechanosensitive pathways involving integrin β1, focal adhesion kinase, and caveolin activation (123).

Furthermore, changes in ECM composition may engage pathways that can potentiate WAT alterations. For instance, endotrophin (a soluble cleavage product of collagen VI chain a3) potently drives systemic insulin resistance through WAT inflammation and fibrosis (124). Similarly, TNC and osteopontin (SPP1) are matricellular proteins found to be upregulated in fibrotic conditions that associate with a pathological WAT remodeling. WAT macrophages express high levels of SPP1 in the obese state (9), and its neutralization partially decreases obesity-associated WAT inflammation and reverses signal transduction related to insulin resistance (125). Likewise, TNC expression is increased in obese mice (101), and fibrosis is attenuated in mice devoid of TNC (126). Clinical studies have confirmed an association between TNC, SPP1, and altered WAT functions (101, 127).

Overall, understanding the molecular actors of fibrosis production/degradation balance will be useful in strategies aiming at improving AT remodeling and health.

A SHIFT IN WHITE ADIPOSE TISSUE PROGENITOR DIVERSITY DRIVES WHITE ADIPOSE TISSUE FIBROSIS

Fibrotic transformation is usually mediated by cell activation toward a so-called myofibroblast phenotype (68, 128). Obese C3H/HeOuj (C3H) mice that are prone to WAT fibrosis mimic the pathological remodeling observed in human AT (45, 85). Probing for mechanisms underlying fibrosis accumulation in obese WAT, PDGFRα$^+$ progenitors (CD34$^+$ Gp38$^+$ Sca1$^+$ CD45$^-$ CD31$^-$) were identified as the main source of ECM components and fibrosis (45). These PDGFRα$^+$ progenitors were initially characterized for their ability to differentiate into white adipocytes during WAT development or during WAT growth in response to obesogenic conditions (41). However, in fibrotic WAT, the PDGFRα$^+$ progenitors rather adopt a myofibroblastic phenotype (**Figure 2**). Furthermore, PDGFRα$^+$ cells proliferate, thus accumulating in the fibrotic AT (45). Due to this double capacity to differentiate into adipocytes or myofibroblasts, exploring heterogeneity among WAT progenitors was first considered a way to demonstrate that various progenitor subsets were engaged in the fibrotic transformation of WAT. In the injured heart,

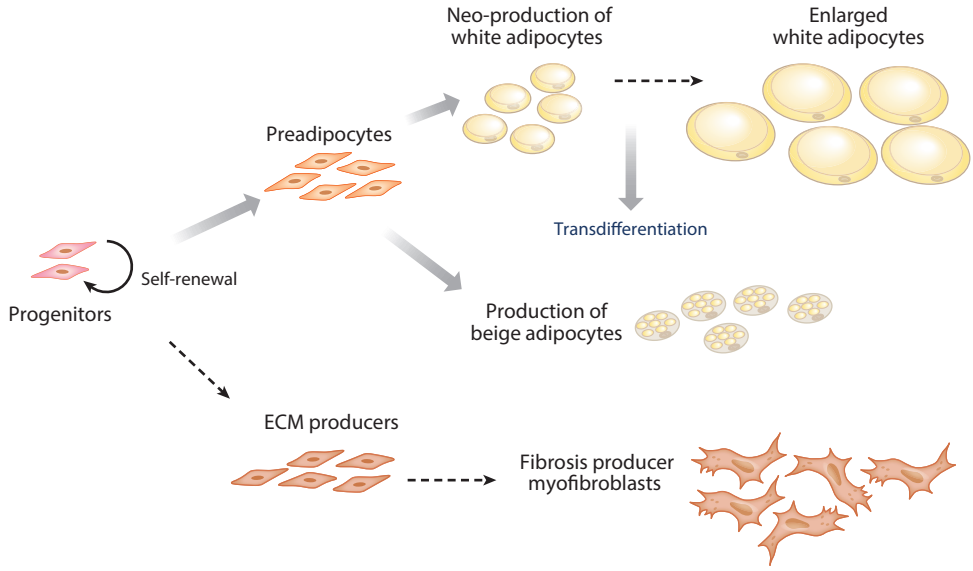

Figure 2

Understanding adipose progenitor fates in adipose tissue remodeling. In different studies, undifferentiated progenitors were identified as cell subsets expressing markers such as CD24, Pref1, or DPP4. To date, it is not known whether such progenitors are a homogeneous population that could originate both preadipocytes (identified with various markers: $CD142^+$, $CD54^+$, $CD36^+$, and $MSCA1^+$ or $CD9^{low}$) and extracellular matrix/fibrosis producer cells ($CD9^{high}$ $LY6C^+$). Promoting white and beige adipocyte fates over fibrosis producer progenitors favors healthy adipose tissue remodeling that can efficiently minimize the systemic metabolic alteration driven by obesity. White adipogenesis may limit white adipocyte enlargement that is eventually detrimental for the white adipocyte metabolic and secretory functions. Additionally, the production of energy-dissipating beige adipocytes (through beige adipogenesis or white-to-beige adipocyte transdifferentiation) could be a means to reduce lipid storage in white adipocytes. Furthermore, molecular pathways underlying both white and beige adipogenesis reduce the activation of fibrogenic pathways, leading to the accumulation of myofibroblasts (characterized by de novo expression of α smooth muscle actin). Bold gray arrows indicate prominent mechanisms; dashed black arrows refer to minimized pathways that can be observed in healthy adipose tissue remodeling.

kidneys, lungs, and liver, lineage tracing experiments suggested that ADAM12- or GLI1-expressing $PDGFR\alpha^+$ progenitors give rise to profibrotic cells (129, 130). In the WAT, ADAM12 was found to be important to support progenitor proliferation and adipogenesis during obesity (131, 132), while the involvement of Gli1 remains unexplored. Studying WAT fibrosis in the C3H mouse strain revealed that the expression levels of the tetraspanin CD9 defined two $PDGFR\alpha^+$ progenitor populations. In mice, $PDGFR\alpha^+$ $CD9^{high}$ progenitors driven toward a myofibroblastic phenotype accumulate in the fibrotic WAT. By contrast, their $PDGFR\alpha^+$ $CD9^{low}$ counterparts, committed to adipogenesis, gradually decrease during the course of obesity (45). In human WAT, $PDGFR\alpha^+$ $CD9^{high}$ cell frequency in the visceral WAT positively correlates with the degree of fibrosis and the deterioration of glycemic control in obese patients. Indeed, significant positive associations are observed between the number of $PDGFR\alpha^+$ $CD9^{high}$ cells in the visceral WAT and glucose control parameters such as glycated hemoglobin and the HOMA-IR (homeostatic model assessment for insulin resistance) index. Analysis of the subcutaneous WAT revealed that such functional subsets cannot be discriminated based on CD9 expression (20, 45). Thus, pathways favoring the accumulation of WAT $CD9^{high}$ progenitors over the $CD9^{low}$ subset may compromise WAT metabolic health and alter glucose homeostasis (45).

ScRNAseq performed on visceral WAT progenitors recently refined the definition of the profibrotic and proinflammatory progenitors [or fibro-inflammatory progenitors (FIPs), as $CD9^{high}$ $LY6C^{+}$ cells in mice] (20). In addition to their ability to produce ECM, FIPs also exert antiadipogenic effects. FIPs display important proinflammatory activities, as illustrated by their contribution to chemokine and cytokine production in obese WAT (20, 133, 134). The immunoregulatory potential of FIPs involves TLR4 signaling, and this was shown to control WAT Macs accumulation in response to a high-fat diet feeding (134). Thus, WAT progenitors harbor functions that can be highly detrimental for WAT homeostasis, especially in regard to inflammation and fibrosis.

The fates and functions of progenitors appear to be critically regulated through an interplay between adipogenic and fibrogenic pathways. Evidence suggests that beige or white adipogenic molecular triggers are antifibrotic and vice versa (**Figure 2**). Limiting the adipogenic fate through deletion of the master regulator of adipogenesis, PPARγ, precipitates the onset of WAT fibrosis (135), suggesting an interaction between adipogenic and myofibroblastic fates. Conversely, forced activation of the profibrotic receptor PDGFRα hampers both white and beige adipogenesis (136–138).

The PRDM16 transcriptional complex, known for its role in brown/beige fat development, can also potently repress WAT fibrosis through direct and indirect pathways. In brown adipocytes, the profibrotic signals of TGF-β (transforming growth factor beta) are abrogated by PRDM16 overexpression. Those effects, independent of UCP1 uncoupling activity, involve the direct interaction of GTF2IRD1 (general transcription factor II-I repeat domain-containing protein 1) with genetic loci regulating profibrotic gene expression. Furthermore, PRDM16 drives β-hydroxybutyrate metabolic signals arising from the adipocytes that can lower the progenitor fibrogenic activity and enhance beige adipogenesis (12).

Members of the conserved TGF-β/BMP (bone morphogenetic protein) family are involved both in fibrosis and in beige adipogenesis. The BMP7–ROCK (Rho associated kinase)–MRTFA (myocardin-related transcription factor A) axis was identified as a key driver of beige adipogenesis (139). In Mrtfa-deficient mice, the WAT contains more UCP1 expressing-multilocular adipocytes and lower ECM deposition, the latter being associated with a decrease in fibrogenic progenitor content (139). Along this line, a better understanding of the critical regulator of the transcriptional landscape of TGF-β/BMP family members would be of interest. In WAT, such understanding is still scarce and may involve various cell types, including the adipose progenitors (140).

METABOLIC ALTERATIONS AS A CONSEQUENCE OF ADIPOSE TISSUE FIBROSIS IN OBESITY

Preclinical and in vitro studies revealed that WAT fibrosis profoundly affects key WAT functions. Through diverse mechanisms, including physical constraint and limited adipogenesis, fibrosis may limit WAT expandability, which is detrimental. Indeed, mice in which massive healthy WAT expansion was permitted exhibited improved metabolism despite being massively obese (117, 141–143). Ectopic lipid deposition may lead to pathological outcomes such as defective insulin signaling, resulting in insulin resistance. In line with this assumption, increased subcutaneous WAT fibrosis was shown to be associated with visceral fat accretion in a cohort of Chinese American men and women (31). Ectopic lipid deposition in liver is also suggested with nonalcoholic fatty liver disease and liver fibrosis, which were found to be associated with macrophage infiltration in the visceral AT and with the degree of fibrosis in the subcutaneous AT (143–145).

Additionally, the altered secretome of the fibrotic WAT was proposed to perpetuate chronic low-grade inflammation, a pivotal mechanism believed to link obesity to its numerous systemic complications (3, 146, 147).

ECM accumulation located in fibrotic bundles as well as pericellular and perilobular fibrosis can be rapidly graded thanks to semiquantitative measures of fibrosis that provide a score called the FAT score (116). We have shown that WAT fibrosis, especially in the visceral WAT, was associated with type 2 diabetes and glucose control (45, 148). Moreover, total and pericellular fibrosis accumulation in subcutaneous WAT is linked to resistance to weight loss 1 year after bariatric surgery (116, 121), and such association remained after correcting for other clinical variables (age, diabetes, IL-6) that are also shown to be associated with limited weight loss after bariatric surgery.

Preclinical studies targeting WAT ECM remodeling improve glucose tolerance and insulin sensitivity in obese mice (147). It is probably important to consider future innovative therapeutic strategies targeting WAT, which should be designed to uncouple obesity from its associated comorbidities and optimize weight loss following therapeutic intervention (147). A recent study identified the mineralocorticoid receptor antagonist eplerenone as a potential antifibrotic in the subcutaneous AT (149), and the use of such a molecule in the context of bariatric surgery could be of interest.

RESOLUTION OF ADIPOSE TISSUE FIBROSIS

Obesity-induced WAT fibrosis is a process difficult to reverse in both humans (150) and mice (78, 151). By contrast, various other models of fibrosis in the liver (carbon tetrachloride), lungs (bleomycin), or skin (radiation) can undergo resolution when the profibrotic stimuli are ceased (152). In severe obesity, although bariatric surgery is the most prominent therapeutic procedure that efficiently leads to drastic and rapid fat mass loss in severe obesity, our analysis of human WAT surprisingly revealed that bariatric surgery did not affect fibrosis resolution. Indeed, ECM deposition steadily increased after weight loss induced by bariatric surgery during the first year. This indicates that weight loss does not rescue WAT structural alterations and may rather worsen WAT remodeling. The nature of the components and the mechanisms leading to this phenomenon need to be further defined (150). Mouse studies confirmed these findings and suggested that WAT inflammation could be of importance in this process, as leukocytes and some macrophages may remain after fat mass loss (151, 153), and these cells could sustain the lack of fibrosis resolution.

Thus, the functional consequences of WAT remodeling deserve careful investigation, as this could favor/potentiate tissue metabolic deteriorations in patients with obesity who frequently experience weight loss and rebound. Moreover, whether interventional strategies promoting WAT beiging are of interest to improve WAT healthiness remains to be investigated, especially because favoring WAT beiging might hamper fibrosis accumulation. For example, an intermittent fasting cycle in mice not only improves body fat but also promotes WAT beiging, a phenomenon that might also depend on gut microbiota–derived metabolites (i.e., short-chain fatty acids and others) (154). Along the same lines, it was also suggested that metabolic improvements induced by intermittent fasting could be recapitulated by overexpression of VEGF in AT, also contributing to WAT beiging (155). Fibrosis accumulation needs to be further explored in this context.

CONCLUSIONS

Pathological remodeling of AT in obesity is critical in altering adipose expandability. It also exerts deleterious effects in the obese state and links AT dysfunction to obesity-associated comorbidities. Considerable progress has been made in understanding the mechanisms involved in this WAT remodeling, and among these, fibrosis is an important element. The role of WAT progenitors has been highlighted recently, but other cell types could be involved. Moreover, further studies are also necessary to delineate the critical pathways controlling the balance between adipocytes,

macrophages, and progenitors and their interplay in visceral and subcutaneous WAT. In addition to understanding the local cellular interactions involved in the development of WAT fibrosis, we have to consider the prospect of therapeutic strategies aimed at controlling or even reducing WAT fibrosis in order to restore the plasticity of WAT. WAT whose structure and function are restored is indeed favorable for an individual's metabolic health. The field is ready for therapeutic innovations.

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