New perspectives on obesity-induced adipose tissue fibrosis and related clinical manifestations

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Abstract. Adipose tissue is a complex heterogeneous tissue composed of adipocytes along with several non-adipocyte populations, including blood, stromal, endothelial, and progenitor cells, as well as extracellular matrix (ECM) components. As obesity progresses, the adipose tissue expands dynamically through adipocyte hypertrophy and/or hyperplasia. This expansion requires continuous ECM remodeling to properly accommodate the size increase as well as functional changes. Upon reaching a hypertrophic threshold beyond the adipocyte buffering capacity, excess ECM components are deposited, causing fibrosis and ultimately resulting in unhealthy metabolic maladaptation. These complex ECM remodeling processes in adipose tissues are regulated by the local environment, several key mediators, and genetic factors that are closely linked to insulin sensitivity. It is crucial to understand how adipocytes interact with nonadipocyte populations and various mediators (i.e., immune cells, ECM components, and adipokines) during these processes. This mini-review provides an overview of the latest research into the biology of obesity-induced adipose tissue fibrosis and its related clinical manifestations, providing insight for further studies aimed at controlling metabolic syndrome and its comorbidities.

Key words: Obesity, Adipose tissue fibrosis, Brown/beige adipocytes, Extracellular matrix components, Insulin resistance

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Introduction

Obesity and its related health complications are major public health challenges worldwide. The progression of obesity is closely associated with the enlargement of adipose tissue, which responds dynamically and rapidly to a variety of internal and external stimuli [1]. As obesity progresses, the adipose tissue dynamically expands by increasing its lipid storage capacity (hypertrophy) and/or increasing the number of adipocytes (hyperplasia), thereby necessitating ongoing extracellular matrix (ECM) remodeling to accommodate this expansion [2-5]. Maintenance of marked flexibility in the ECM environment is a prerequisite for healthy adipose tissue. This flexibility is thought to characterize the tissue expansion of “healthy” adipose tissue, representing so-called “metabolic adaptation”. However, after the hypertrophic threshold exceeds the adipocyte buffering capacity, ectopic lipid deposition in adipose tissue induces persistent hypoxia, fibrosis, and necrotic adipocyte death, ultimately leading to “unhealthy” adipose tissue expansion, known as “metabolic maladaptation” [5, 6] (Fig. 1). Excess ECM deposition in the form of fibrosis in adipose tissue is characteristic of subjects with obesity and is thought to contribute to systemic metabolic disturbances that are features of obesity and type 2 diabetes. However, adipocyte size and fibrosis are inversely correlated in humans [7, 8]. Thus, the consequences of the fibrosis in adipose tissue remain a controversial issue [9].

Thermogenic adipocytes, such as brown and beige adipocytes, play pivotal roles in the adaptation of adipose tissues to worsening obesity. Recent studies revealed that adipogenesis of beige adipocytes in white adipose tissue (WAT), the so-called browning phenomenon, effectively alleviates adipose tissue fibrosis [10, 11]. Promoting thermogenic brown/beige adipocytes counteracts obesity and its associated adipose tissue fibrosis [12-14]. CD81, recently identified as a beige fat progenitor marker, forms a complex with αV/β1 and αV/β5 integrins [15]. CD81 was shown to control the proliferation of beige adipocyte progenitors and mediate adipose tissue remodeling by activating integrin-focal adhesion kinase (FAK) signaling [15]. Furthermore, certain drugs (CL316,243, rosiglitazone, berberine, etc.) and food types can induce the browning, leading to beneficial effects in terms of preventing obesity [16, 17]. However, effective and safe clinical methods to promote brown/beige adipocytes have yet to be established in humans.

The features of obesity-related WAT dysfunction
include unresolved inflammation [18], local hypoxia in adipose tissue [19], inappropriate ECM remodeling, alterations in the adipokine secretome [20], and insufficient angiogenic potential [5, 21]. Among these features, we focus on the mechanism of ECM remodeling associated with adipose tissue fibrosis in this review (Fig. 1).

Progenitors of Adipocytes and the Origin of ECM

It was initially established that the CD34+/CD31− cell population from the human WAT stromal vascular fraction (SVF) has adipogenic capacity [22]. Recent flow cytometric approaches and single-cell RNA sequencing analyses have revealed progenitors expressing several surface markers exhibit adipogenic commitment [23-27]. Notably, the expression level of CD9 defines two distinct progenitor populations. Adipocytes expressing platelet-derived growth factor receptor-α-positive (PDGFRα+) CD9high progenitors were reportedly prone to producing ECM and showed a fibrogenic phenotype in the visceral adipose tissue of obese individuals, whereas PDGFRα−CD9low progenitors were committed to the adipogenic phenotype [28]. Myofibroblasts, which originate from adipocytes expressing adiponectin, contribute to ECM production in the dermal WAT [29]. In addition, macrophages and mature adipocytes produce pro-fibrotic collagens, fibronectin, and tenascin-C, which in turn accommodate increases in the size of adipose tissue and induce the production of ECM [10, 30]. Importantly, myocardin-related transcription factor A (MRTFA) is a critical regulator of the myofibroblast differentiation that induces α-SMA and collagens [31]. MRTFA deficiency in mice shifts the Sca1−, Sma+, and ITGA5+ perivascular progenitors to become fibrogenic adipocyte precursor cells, thereby protecting against chronic obesity-induced fibrosis and its accompanying metabolic dysfunction, without altering energy expenditure [32]. Furthermore, lineage tracing studies in rodents revealed that WAT expansion in obese subjects occurs in an adipogenic-depot and in a gender-dependent manner, suggesting the importance of sex hormones in maintaining healthy adipose tissue [33, 34]. Overall, these data suggest that multiple cell types produce depot-specific ECM and contribute to adipose tissue fibrosis.

Fig. 1  Metabolic adaptation and maladaptation during obesity progression

Unhealthy WAT expansion leads to metabolic maladaptation, which ultimately leads to adipose tissue fibrosis and metabolic dysfunction.
Function of ECM in Adipose Tissue Fibrosis

Adipocytes are mechanically and structurally supported by the ECM (several collagen, laminin, fibronectin, and proteoglycan molecules), and interactions among these components maintain the ECM physiology through extensive signaling events [35, 36]. It is well-established that the protein content of the ECM in adipose tissue is similar to that of other tissues, although the relative and molecular quantities and assembly of ECM proteins in the adipose tissue differ from those in other organs and tissues [37]. Collagens, laminins, and fibronectin are highly expressed components of subcutaneous adipose tissue [35]. Notably, expression profile analysis revealed that collagens I, III, V, and VI are increased in subjects with obesity [8, 38, 39]. Among the collagens, type VI is the dominant form necessary for sustaining the structure and function of adipose tissue [37, 39-41]. Particularly, mature collagen VI is highly expressed in visceral adipose tissue, and its expression increases with obesity [42]. In addition, Col6-deficient mice reportedly exhibit lower tissue fibrosis and inflammation in WAT, while showing improved glucose tolerance, insulin sensitivity, and greater fatty acid consumption [40]. These results were confirmed in a study of C-terminal cleavage products focusing on the C5 domain of collagen VI α3 (endotrophin). Blocking endotrophin signaling with a neutralizing antibody ameliorated metabolic dysfunction and its adverse effects [43]. Thus, blocking fiber production in adipose tissue may improve obesity-related metabolic disorders.

Adipose tissue fibrosis is dynamically regulated and maintained by matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases [44-47]. Among the 28 members of the MMP superfamily, MMP-3, -9, -11, -12, -13, -14, -16, and -24 are highly expressed and modulated under different physiological conditions in adipose tissue [48-50]. A series of studies targeting MMP genes were performed to examine the functions of each MMP in obesity and insulin resistance but the results have not been entirely consistent [51-53].

MMP14, also known as membrane-bound type 1-MMP (MT1-MMP), is the predominant pericellular collagenase involved in collagen I degradation in adipose tissue [54]. Furthermore, MMP14, which is induced by hypoxia-inducible factor 1α (HIF1α), mechanistically digests collagen 6α3 [55]. Genetic ablation of MMP14 leads to dysregulated collagen deposition and subsequent development of severe metabolic disorders [54]. In contrast, overexpression of MMP14 in adipose tissue with established obesity stimulates local fibrosis and inflammation [55].

Multiple factors contribute to adipose tissue fibrosis associated with obesity progression, as summarized in Fig. 2. ECM synthesis by myofibroblasts is a crucial step in adipose tissue expansion. The mechanical interaction between adipocytes and the ECM may serve as a target for treating adipocyte dysfunction and metabolic diseases [50].

Transcriptional Regulation of Adipose Tissue Fibrosis

Brown and beige adipocytes are regulated by epigenetics and several transcriptional regulators [56]. Brown adipocytes arise from Myf5+ dermatomal precursors through the transcriptional action of PR domain containing protein16 (PRDM16), which plays crucial roles in brown/beige adipogenesis and maintenance of cell fate [57, 58]. In fact, our research group recently identified a cold-inducible transcriptional factor, named “general transcription factor II-I repeat domain-containing protein 1 (GTF2IRD1)”, as a member of the transcription factor II-I family of DNA-binding proteins. GTF2IRD1 forms a transcriptional complex with PRDM16 and euchromatic histone lysine methyltransferase 1 (EHMT1). GTF2IRD1 inhibits several fibrosis-related gene expressions through the PRDM16-EHMT1-GTF2IRD1 transcriptional complex, thereby improving systemic glucose homeostasis [10]. Interestingly, this transcription factor initially suppresses several genes encoding pro-fibrosis proteins such as collagens, MMPs, and galectins, suggesting its involvement in fibrosis development. In addition, hydroxybutyrate derived from PRDM16-expressing adipocytes may reduce fibrogenic activities and enhance beige adipogenesis [11]. Although it is not considered as a target for slowing or reversing adipose tissue fibrosis, this transcription factor may serve as a target for inhibiting fibrosis deposition.

Adipokines and Fibrosis

Adipose tissue is recognized as an endocrine organ capable of secreting a vast array of cytokines, known as adipokines, that control whole-body energy homeostasis [59]. The adipokine profile changes dynamically in response to nutritional stimuli [59]. To date, several adipose tissue-derived secretory products have been identified and their functions have been studied [60]. Among these numerous adipokines, adiponectin and leptin are the most intensively studied, given their effects on the expansion of healthy adipose tissue [61-63]. Adiponectin, a key adipokine involved in energy homeostasis, exhibits anti-inflammatory properties. Adiponectin acts on macrophages, inhibiting the development of foam cells,
and decreases endothelial cell activation and monocyte adhesion, resulting in the marked polarization of M2-like macrophages [64]. Leptin is another important adipokine involved in fibrosis in multiple peripheral organs [65, 66]. To date, studies have shown that leptin activates the expression of PRDM16 through its downstream Janus kinase 2-signal transducer and activator of transcription signaling pathway, thereby promoting browning of white adipose tissue [67].

During obesity progression, pro-inflammatory adipokines, such as tumor necrosis factor-α, interleukin-6, monocyte chemotactic protein-1, and resistin, are highly expressed and secreted, contributing to the activation of a chronic inflammatory state and the recruitment of pro-inflammatory immune cells [68, 69].

Other adipokines that regulate ECM remodeling in adipose tissue have been identified [70-74]. Specifically, C-X-C motif chemokine ligand 14 (CXCL14) is secreted from brown adipose tissue in response to thermogenic activation [75]. CXCL14 promotes the browning of WAT through the activation of type 2 immune cells. These findings suggest that CXCL14 plays a pivotal role in adiposity and related metabolic disorders. Interestingly, serum CXCL14 levels were reported to be associated with the fatty liver index and serum C-peptide levels in patients with type 2 diabetes [76].

### Hypoxia

WAT is a highly dynamic and heterogeneous organ. The expansion of WAT requires coordinated adaptations to maintain its microenvironment healthy. Substantial evidence has indicated that the oxygen tension is low and the expression of the master regulator hypoxia inducible factor (HIF)-1α is increased in the WAT from obese subjects [19, 77]. HIF-1α, in turn, induces the expression of several fibrotic proteins including various collagens, elastin, lysyl oxidase, and connective tissue growth factor [78-80]. Vascular endothelial growth factor (VEGF)-A regulates blood vessel permeability and growth. Additionally, VEGF-A and VEGF-B balance the energy homeostasis in the WAT [81]. Using a doxycycline-regulated VEGF-A suppression mouse model, Lu et al. found that suppression of VEGF-A leads to increased thermogenic activity in the WAT and resistance to high-fat diet-induced obesity [82]. Interestingly, in two...
genetic models, VEGF-A overexpression produced a rapid beiging phenotype in the WAT and increased the number of M2 anti-inflammatory macrophages with improved insulin sensitivity [83].

**Inflammation**

Inflammation and fibrosis in adipose tissue have an extremely complex relationship [84, 85]. The mechanisms underlying fibrosis are fundamentally similar to the tissue damage characteristics of the normal wound healing response. These responses entail an activation of local immune cells, followed by the activation of local mesenchymal cells and fibroblasts, resulting in the deposition of excessive and/or inappropriate ECM components. These actions further increase the production of pro-inflammatory cytokines and chemokines, which are angiogenic factors [86, 87]. Visceral WAT in the setting of obesity is characterized by chronic, low-grade inflammation, which is regarded as both a cause and consequence of immune responses [84, 85, 88, 89]. The function of obese adipose tissue macrophages, which can be resident or recruited, can be used to predict metabolic dysfunction [90]. Macrophages are classified according to their cell surface markers and secretory profile as M1, referred to as “classically activated”, and M2, also known as “alternatively activated” [91]. They can also be classified into two highly different profiles, with opposite actions: “pro-inflammatory (M1)” and “anti-inflammatory (M2)”. M1 macrophages play key roles in initiating and sustaining inflammatory responses, secreting pro-inflammatory cytokines, and recruiting other immune cells. In contrast, M2 macrophages resolve inflammation, coordinate tissue injury, release anti-inflammatory mediators, and promote repair [92]. In addition, Foxp3+ CD4+ regulatory T cells are abundant in the visceral adipose tissue of lean subjects, whereas their number is greatly reduced in obese subjects [93]. Obesity also induces another important immune response involving other adaptive immune cells (B and T lymphocytes, e.g., CD8+ effector T cells) [94-96] as well as innate immune cells (neutrophils, dendritic cells, mast cells or eosinophils, and innate lymphoid cells type 2) [97-101]. A unique feature of obese adipose tissue is a crown-like structure (CLS), a histological hallmark of the inflammatory response. This CLS indicates a dying or dead adipocyte surrounded by macrophages [84, 85, 102]. Macrophage-inducible C-type lectin (MINCLE) is induced in macrophages constituting CLS through Toll-like receptor 4 signaling [103, 104]. MINCLE-deficient mice are protected against obesity-induced CLS formation and adipose tissue fibrosis [105]. Furthermore, the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome is a key sensor that functions in the innate immune system and is the predominant determinant of metabolic disorders [106, 107]. Blockade of NLRP3 inflammasome reduces adipose tissue inflammation and significantly attenuates fibrosis [108].

Crosstalk between adipocytes and endothelial cells potentially regulates systemic energy homeostasis in metabolic disorders [109]. Blockade of endothelial nuclear factor-kappa B signaling prevents obesity-induced inflammation, insulin resistance, and adipose tissue remodeling [110]. These complex interactions regulate systemic metabolism and insulin sensitivity [111].

**Clinical Manifestations Related to Adipose Tissue Fibrosis**

It is now established that obesity induces WAT inflammation and fibrosis, leading to local and systemic insulin resistance, which results in metabolic dysfunction in rodents. However, studies in humans showed conflicting correlations between adipose tissue fibrosis and metabolic disorders [8, 112-114]. Adipose tissue fibrosis in the context of human obesity differs between people with and without diabetes [115]. In addition, the ECM itself regulates adipocyte metabolism and function, both of which are affected by diabetes mellitus [116]. However, contradictory evidence has been reported, that is, decreased adipose tissue fibrosis was observed in obese people with diabetes [112]. Adipose tissue fibrosis has both adaptive and maladaptive functions. Thus, the functional consequences of adipose tissue fibrosis remain a matter of debate, and patient demographics and blood glucose history should be considered when evaluating these consequences.

**Correlations with NAFLD and Metabolic Surgery**

Hypertrophic WAT is associated with limited lipid storage capacity, resulting in ectopic fat accumulation in the liver, pancreas, heart, and kidneys, as well as the skeletal and cardiac muscles, thereby exacerbating insulin resistance [117]. Ectopic lipid deposition in the liver is highly associated with nonalcoholic fatty liver disease (NAFLD) and liver fibrosis, which are associated with macrophage infiltration in the visceral adipose tissue and the degree of fibrosis in subcutaneous adipose tissue [118, 119].

Weight reduction after metabolic surgery leads to dramatic improvements in metabolic, hepatic, and cardiovascular complications, as well as alterations in the WAT, such as inflammation, changes in insulin sensitivity, and
abnormalities in numerous metabolic pathways [120]. Human omental WAT fibrosis is closely related to the degree of insulin resistance in severe obesity [121]. Among the approaches used to evaluate adipose tissue fibrosis, subcutaneous WAT stiffness, measured through noninvasive vibration-controlled transient elastography, called fibrosis score of adipose tissue (FAT score), has been proposed. This obtained value reflects fibrosis and correlates negatively with the body mass index and metabolic parameters (glucose, insulin, and lipid values) [114]. In addition, the FAT score, which reflects adipose tissue fibrosis, may facilitate the prediction of weight loss outcomes in patients undergoing metabolic surgery [122].

However, the impact of metabolic surgery on MMPs remains controversial. In patients with morbid obesity, serum MMP-2 and MMP-9 levels decrease significantly after surgery [123]. MMP-2 and MMP-9 activities were increased in obese patients without diabetes. In contrast, in obese patients with diabetes, there were no differences in MMP-2 and MMP-9 activities, and serum levels of MMP-7 were unchanged postoperatively [124, 125].

These observations support the “adipose tissue expandability hypothesis” [126], which states that increased WAT stiffness represents a mechanical limit of WAT expansion. When the storage capacity of subcutaneous WAT reaches its limit, excess lipids shift to ectopic sites, such as the liver, heart, muscle, and pancreas, thereby causing and exacerbating metabolic complications [127, 128].

Summary and Future Perspectives

This review highlighted the biology of adipose tissue fibrosis, focusing on the complex interplay among adipocytes, non-adipocytes, ECM components, and associated mediators in obesity. This interplay, involving adipocytes, progenitors, inflammatory blood cells, and vascular endothelial cells, determines the remodeling conditions in the ECM and impacts the overall metabolic health of individuals. Inducers of browning/beigeing adipocytes and adipokines, as well as modulations of matrix remodeling enzymes, inhibitors, and associated gene regulators, are potential pharmacological targets for treating metabolic disorders such as obesity. The influence of adipose tissue fibrosis and its components on metabolic dysfunction is not completely understood. Further studies are thus needed to explore the pathogenesis and mechanisms of adipose tissue fibrosis, which is essential for alleviating metabolic disorders.

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Conflict of Interest Disclosure

The author has no competing interests to disclose.

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