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Extracellular Matrix (ECM) and Fibrosis in Adipose Tissue: Overview and Perspectives

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Abstract

Fibrosis in adipose tissue is a major driver of obesity-related metabolic dysregulation. It is characterized by an overaccumulation of extracellular matrix (ECM) during unhealthy expansion of adipose tissue in response to over nutrition. In obese adipose-depots, hypoxia stimulates multiple pro-fibrotic signaling pathways in different cell populations, thereby inducing the overproduction of the ECM components, including collagens, noncollagenous proteins, and additional enzymatic components of ECM synthesis. As a consequence, local fibrosis develops. The result of fibrosis-induced mechanical stress not only triggers cell necrosis and inflammation locally in adipose tissue but also leads to system-wide lipotoxicity and insulin resistance. A better understanding of the mechanisms underlying the obesity-induced fibrosis will help design therapeutic approaches to reduce or reverse the pathological changes associated with obese adipose tissue. Here, we aim to summarize the major advances in the field, which include newly identified fibrotic factors, cell populations that contribute to the fibrosis in adipose tissue, as well as novel mechanisms underlying the development of fibrosis. We further discuss the potential therapeutic strategies to target fibrosis in adipose tissue for the treatment of obesity-linked metabolic diseases and cancer.

Introduction

Obesity is a severe epidemic in industrialized and developing countries (242, 263). It has been recognized as a significant risk factor for many chronic diseases, including type 2

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Author Contributions

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Conflicts of Interest

The authors declare that no competing interests exist.

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diabetes, cardiovascular disease, hypertension, dyslipidemia, and certain types of cancer (68, 242, 263). Obesity is caused by interactions of multiple complex factors, such as overnutrition, reduced physical activity, and environmental and genetic factors. Adipose tissue is the primary organ that is, conveying the negative impact of its unhealthy expansion on the system at large (242). Adipose tissue plasticity means its ability to acquire new structural identities or adopt alternative cellular sizes and compositions in response to different nutritional conditions. In response to excessive caloric intake, adipose tissue experiences a dynamic remodeling process which puts high demands on the plasticity at adipocytes and adipose tissue. The extracellular matrix (ECM) of adipose tissue faces many challenges to accommodate the necessary dynamic changes required for expansion (49, 163, 164, 245). In parallel, the growth of blood vessels via angiogenesis cannot keep pace with the expansion. As a result, local hypoxia develops in obese adipose tissue (79, 163, 241).

Hypoxia initiates multiple pathological changes in the obese adipose tissue (242). Fibrosis is one of the major consequences caused by hypoxia (241, 242), with fibrosis being increasingly appreciated as a predominant player in adipose tissue dysfunction (49, 85, 116, 143, 197, 236, 245). Abnormal ECM accumulation during fibrosis is tightly associated with chronic low-grade inflammation in obese adipose tissue (37, 48, 71, 118, 143). Moreover, the pro-inflammatory factors and free fatty acids (FAs) released from the dysfunctional adipose tissue further circulate to other metabolically active tissues/organs, such as the liver, kidney, and muscles, thereby triggering an elevated degree of lipotoxicity in other organs (131, 258). As a result, the whole system develops insulin resistance and other metabolic disorders.

Below, we offer a brief synopsis of recent findings about the pathological process of fibrosis, underlying mechanisms that govern the whole process, as well as the resulting disorders in adipose tissue. Further, we highlight several recently identified fibrotic factors that play key roles in metabolic dysregulation during obesity. Finally, we discuss the therapeutic perspectives of targeting fibrosis in adipose tissue to treat obesity-related diseases.

ECM Components in Adipose Tissue

The ECM is a three-dimensional network that facilitates the proper structure and function of mature adipocytes, preadipocytes, and other cell populations in the stromal fraction of the adipose tissue (245). It not only provides the mechanical support but also contributes to the cell signaling pathways that are essential for adipogenesis and other proper functions of adipose tissue. The ECM is composed of a variety of highly organized protein factors, including collagens and noncollagenous proteins, multiple regulators that closely interact with ECM, and several other components, such as polysaccharides, glycoproteins, and proteoglycans as well (46). The ECM in adipose tissue is the most flexible structure that experiences dynamic remodeling during the tissue expansion in response to overnutrition (116). While it shares a lot of common components with ECM in other tissues, it also displays several unique structural features, such as the enrichment of collagen VI (Col6) (116). While some of these components only occupy a very small portion of the ECM, they play key roles in maintaining the integrity and normal function of whole adipose tissue.

Collagens

Collagens are the main component of ECM in adipose tissue (116). They occupy significant portion of the noncell mass of adipose tissue (116). Several types of collagens, including Col I, IV, V, VI, VII, VIII, and IX are an integral part of the structure of ECM of adipose tissue. They are secreted by many types of cells in the adipose tissue, including adipocytes, progenitor cells, and other components of the stromal vascular fraction (SVF) (49, 116, 162, 236, 262). Intriguingly, the collagen proteins show diverse distribution patterns in different white adipose tissue (WAT) depots (49). Among them, ColVI is the most abundant subcategory in obese adipose tissue (225). ColVI is a large glycoprotein that is, composed of three subunits—α1, α2, and α3. The three chains are assembled into hetero-tetramers and further form oligomers (116). The complex of ColVI with a high level of tertiary structure is secreted into ECM space where they further associate with other factors to form mature microfibrils that are integrated into the mature ECM (197). The levels of ColVI are tightly regulated during the diet-induced obesity development (116, 150). Clinical studies revealed that the expression levels of ColVIα3 are correlated with fat mass and total body mass during obesity (200). Our recent studies demonstrated that ColVIα3 can be digested by the metalloproteinase MMP14 (150). ColVI and its cleaved product(s) play a key role in adipocyte hypertrophy, local fibrosis and inflammation, and whole-body insulin resistance during obesity (116, 243). In particular, the carboxyterminal cleavage product of Col6 referred to as endotrophin has been found to exert a multitude of functions in adipose tissue as well as other metabolically active tissues/organs and in malignant tumors (197, 198, 244).

Noncollagen proteins

Secreted protein, acidic and rich in cysteine (SPARC)—Secreted protein, acidic and rich in cysteine (SPARC), also known as osteonectin or BM-40, is ubiquitously expressed in adipocytes and stromal cells in adipose tissue. The expression of SPARC is upregulated during obesity (28). Its protein levels are further regulated by insulin, leptin, and circulating glucose under multiple physio/pathological conditions (124). Animal studies reveal that SPARC is involved in growth and differentiation of adipocyte precursors (28). Functional studies indicate that upon being secreted into the ECM lumen, SPARC actively interacts with other factors and hence contributes to the dynamic remodeling of the network (16). Specifically, it modulates the density and the diameters of the type I collagen fibrils (19, 20). Lack of SPARC leads to increased adiposity as well as shortened collagen fibrils and impaired tensile strength of the ECM in adipose tissue (20). This pathological change has been demonstrated to directly affect the expansion capacity of the adipose tissue (20). Clinical observations reveal that the circulating levels of SPARC are elevated in obese patients and SPARC in the plasma may be involved in the progression to cardiovascular disease (12, 247, 256). Furthermore, adipose tissue-specific SPARC expression is tightly linked to obesity-related insulin resistance as well as other diabetic complications (123).

Fibronectin—Fibronectin is one of the essential ECM components in most tissues/organs. Fibronectin is expressed at a high level in mature adipose tissue and preadipocytes as well (177, 287). Intriguingly, clinical studies indicate that fibronectin levels in different adipose depots are dramatically reduced in the obese patients (141). Moreover, its levels are negatively correlated with leptin but positively associated with adiponectin (141). Numerous

studies have suggested that fibronectin in adipose tissue contributes to the metabolic dysregulation during obesity. Mechanistically, its regulatory function is through its higher molecular weight oligomers that are assembled in the abundant ECM components in obese adipose tissue. Indeed, oligomerization of fibronectin is required for its cross-linking with other pericellular ECM components, such as thrombospondin (TSP) and type I collagens to stabilize the whole ECM (119, 178, 234). Intriguingly, fibronectin also serves as a key signaling molecule by functioning as a high-affinity ligand for α5β1 integrin (239). The binding of fibronectin may trigger α5β1 integrin-mediated downstream signaling response that is, involved in adipogenesis and maturation of adipocytes. Furthermore, the fibronectin-integrin pathway is also regulated by protein-protein interactions between fibronectin and the soluble protein DLK1 (also known as Pref-1) which activates integrin downstream pathway and inhibits adipocyte differentiation (267).

Thrombospondin (TSP)-1—TSP-1 is a multifunctional matrix protein in adipose tissue. TSP-1 levels are upregulated in obese adipose tissue. It binds to the other ECM molecules and stimulates the production of growth factors and cytokines, thereby triggering cellular signaling that is, involved in ECM remodeling, cell metabolism, and pro-inflammatory responses (122). Specifically, TSP-1 has been demonstrated to activate the latent transforming growth factor-β1 (TGF-β1) pathway which initiates a pro-fibrotic reaction in adipocytes (171). Moreover, its physical interaction with CD36 is involved in enhanced free FA uptake by adipocytes (77, 78). TSP-1 levels are positively correlated with adipose tissue inflammation. Increased TSP-1 further triggers an increase in local proinflammatory responses in obese adipose tissue (151, 171). Intriguingly, the effects on lipid uptake and inflammation for TSP-1 can be reversed by pioglitazone treatment, but the underlying mechanisms remain unclear (259). Loss-of-function of TSP-1 protected the mice from diet-induced inflammation and insulin resistance by reducing macrophage accumulation in adipose tissue (151). Given its positive correlation with obesity and its multifaceted function on adipose tissue remodeling and systemic metabolism, TSP-1 has been considered as a sensitive prognostic and diagnostic indicator for obesity and related type 2 diabetic sequelae (74).

Hyaluronic acid (HA)—Hyaluronic acid (HA) (also known as hyaluronan) is a heterogenous disaccharide polymer that is, an important component of the ECM in most tissues. Historically, its role in the ECM remodeling and metabolic regulation in adipose tissue has been underestimated (294). Most recently, its profound contribution to the metabolic regulation of obese adipose tissue has been better understood with the improvement of more sensitive methods for its isolation, characterization, and visualization, as well as several newly developed animal models (110, 295, 296). As an important structural component, HA actively interacts with other protein factors in the ECM. It may further bind to several receptors on the surface of adipocytes. Through these HA-induced protein-protein interactions, HA triggers multiple downstream signaling pathways that potentially affect adipogenesis as well as lipid and glucose metabolism, cell migration, angiogenesis, fibrosis, apoptosis, and proinflammatory responses (294–296). Mechanistically, binding of HA to the cell surface protein CD44 promotes the proliferation of $CD44^{+}$/$PDGFR\alpha^{+}$ preadipocytes, while its binding to RHAMM/HMMR receptors blunts

the CD44-activated signaling and suppresses adipogenesis (5, 7, 142). Furthermore, given the critical roles of CD44 and RHAMM/HMMR receptors in the regulation of lipid and glucose metabolic pathways, it is suggested that HA is involved in the development of type-2 diabetes (121, 271).

Intriguingly, the level of inflammation is tightly correlated with the size of the HA polymers in different cells. Large HA polymers may suppress the local inflammation, while under pro-inflammatory conditions, the high-molecular-weight-HA may undergo a depolarization process and hence produce the fragments that exert pro-inflammatory functions (40, 175). In diet-induced obese adipose tissue and muscles, the content of HA is significantly increased and its levels are highly correlated with whole-body insulin resistance (110).

Elastin—Many other noncollagenous proteins, such as elastin, have also been found in the ECM of adipose tissue. However, there is limited information about their detailed function and regulation in the adipose tissue. Elastin fibers have been found to be unevenly distributed around adipocytes in different adipose depots, with a dramatic increase of the elastin network in epididymal WAT when compared with subcutaneous WAT. The differences might be caused by specific post-translational modifications of the elastin protein (3, 167). The density of the elastin network is significantly increased in the obese adipose tissue (236). This change is tightly regulated by the increased activity of the cross-linking enzyme Lox (79, 160). Interestingly, in the Col6 knockout adipose tissue, elastin levels were also decreased, suggesting a mutual regulatory effect between elastin and collagen (116). Notably, several peptide products derived from elastin have been demonstrated to induce insulin resistance in both adipose tissue and in muscles, pinpointing its critical role in systemic metabolic regulation (14). The detailed mechanisms leading to cleavage products and the respective enzymes mediating the cleavage remain to be elucidated.

Proteinases and their inhibiting factors

Matrix metalloproteinases (MMPs)—The protein components of the ECM are dynamically remodeled and the process is tightly regulated by enzymes mediating the digestion, including collagenases and other proteinases. Among all the enzymes, matrix metalloproteinases (MMPs) are a large family of proteolytic endopeptidases that are actively involved in the dynamics of ECM remodeling (29, 35, 36, 150). The MMP family is composed of more than 20 members and almost all of the MMPs are produced in an inactive form and need to be activated by other enzymes or by autodigestion (99). Of note, even though theoretically they have the ability to degrade most components in the ECM, they prefer to digest collagens (23, 99). In fact, MMPs exhibit substrate specificities when degrading the proteins during ECM remodeling (165).

Among the family of MMPs, MMP14 (also known as MT1-MMP) is the predominant membrane-bound-type MMP in adipose tissue (35, 36). MMP14 is key for the modulation of stiff pericellular collagens to allow cells to grow out of the stromal regions and is directly involved in overall ECM remodeling under both physiological and pathological conditions (35, 36, 97, 127, 150, 183, 252). It exerts its enzymatic function not only to digest collagen proteins but also to activate other MMPs, such as MMP2 and MMP9, upon tethering onto

the plasma membranes of adipocytes (214, 297). During obesity development, the level of MMP14 in adipose tissue is upregulated (29, 150). A genetic variant of the human *Mmp14* gene located in proximity to its catalytic domain has been found to be closely associated with obesity and diabetes traits (36). These observations suggest a direct correlation between MMP14 and obesity. Importantly, our recent findings further link MMP14 to the HIF1α-mediated pathological changes in obese adipose tissue (150). We discovered that HIF1α directly upregulates MMP14 expression by binding to its promoter region (150). Meanwhile, HIF1α induces a massive fibrotic program, prominently inducing, amongst many other collagens, ColVI in obese adipose tissue (79, 241). MMP14 cleaves the ColVIα3 chain and releases its carboxy-terminal C5 fragment (197, 243). The C5 fragment, that we refer to as endotrophin, stimulates in turn further wide-spread pro-fibrotic and pro-inflammatory responses in the tissue (see below), ultimately leading to systemic insulin resistance and impaired lipid homeostasis (150). Notably, in addition to MMP14 and other members of the MMP family, a sub-family of MMPs called a disintegrin and metalloproteinase with TSP motif (ADAMTSs) also plays crucial roles in adipose tissue development and various metabolic disease through their ECM remodeling activities (9, 10, 31, 293).

Tissue inhibitors of MMPs (TIMPs)—The counter players for MMPs, the so-called tissue inhibitors of MMPs (TIMPs), have also been demonstrated to be key for the ECM remodeling in obese adipose tissue (23, 67, 161, 183, 224). There are a total of four TIMPs in adipose tissue. Their levels are varied during adipogenesis and adipose tissue remodeling (126, 161). Particularly, TIMP1 is the most widely studied TIMP in adipose tissue. In addition to directly affecting ECM turnover via inhibiting the activity of MMPs, TIMP1 has been reported to have additional profound effects on adipose tissue (67). For example, it negatively regulates adipogenesis in obese mice and in humans (170). TIMP4 is another inhibitor for MMPs that is, enriched in adipose tissue. Based on UniGene analysis, TIMP4 is exclusively expressed in the adipose tissue in humans (165). Its levels are further elevated in response to nutritional stress (273). Lack of TIMP4 leads to reduced hypertrophy and ameliorated fibrosis in obese adipose tissue, demonstrating the effects it exerts on adipose tissue expansion (224).

Other ECM enzymes—In addition to MMPs, there are other important enzymes that function on the formation and remodeling of the ECM in adipose tissue. Among them, lysyl oxidase (LOX) is a copper-containing amine oxidase that has been identified to be expressed in adipose tissue and malignant tumors. It exists in the cytosol or is secreted into the ECM upon synthesis in adipocytes. Depending on its subcellular localization, LOX may play multiple functions in the physiology/pathology of tissues (39). Particularly in the ECM, LOX post-translationally modifies collagens and noncollagen proteins, such as elastin, thereby catalyzing the covalent cross-linking of the fibers formed by the proteins (39, 108). This cross-linking process is essential for the stabilization, elasticity, and flexibility of fibrils and fibers when being integrated into the ECM (39). The levels and function of LOX are highly regulated in obese adipose tissue. We first found that in diet-induced obese adipose tissue, HIF1α upregulates the expression of LOX and the higher LOX levels facilitate the overaccumulation of ECM in the obese adipose tissue (79). In line with this finding, inhibition of LOX significantly reduced the level of local fibrosis (79, 202). The

function of another cross-linking enzyme referred to as factor XIII-A (FXIII-A) on adipose tissue remodeling has also drawn attention recently (182). Recent observations demonstrated that FXIII-A in WAT has a causative relationship with obesity in humans (106, 107). In preadipocytes, FXIII-A translocates to the surface of cells where it promotes the assembly of fibronectin to form the ECM surrounding the preadipocytes. As a result, FXIII-A negatively regulates adipogenesis by reducing the proliferation and differentiation of the preadipocytes through remodeling of ECM at the cell surface (182).

Abnormal ECM Remodeling and Fibrosis

The flexibility of the ECM in adipose tissue is illustrated by its ability to accommodate the rapid expansion or shrinking of the tissue in response to a differential nutritional status (219). However, we appreciate that the WAT cannot expand without limits, both in animal models and in humans (27, 70, 260). There exists a threshold for the expansion that keeps the whole tissue in a normal functional range. Beyond this threshold, the extremely stiff ECM gives rise to profound pathological alterations, including the development of local fibrosis (245). Meanwhile, the ECM-laden adipocytes lose their plasticity and undergo pathological changes, including cellular inflammation, ER stress, and apoptosis (218, 242). There are multiple steps that eventually lead to the abnormal ECM remodeling (Figure 1). Hypoxia has been recognized as a key initiating step; fibrosis and its associated inflammation are both pathological *consequences* not the initiating factors for the further development and progression of a myriad of the obesity-induced metabolic diseases (62, 64, 79, 92, 125, 136, 139).

Hypoxia: the initiating step

Hypoxia is a challenge that any tissue may face when the local oxygen pressure (pO_2) is decreased. Well-known hypoxic conditions persist in the central region of solid tumors. Indeed, hypoxia has been recognized as the major driver for malignant tumor progression in most types of cancer (52, 227). Adipose tissue is the only nontransformed tissue in the body that has the ability to expand over the course of developing obesity to an almost unlimited extent, just like a tumor mass. However, the formation of blood vessels via angiogenesis and vasculogenesis cannot keep pace (79, 246). Indeed, the blood flow rates in an obese fat pad are 30% to 40% lower compared to lean adipose tissue (15). As a result, local hypoxia develops (1, 241).

Detection of hypoxia in obese adipose tissue—The adipocytes are rather large cells and their size can easily excess 200μm in diameter in obese individuals (79, 233). However, the effective diffusion rates of O_2 are much less than 200μm in tissue (21). This unique feature of adipocytes further worsens the local hypoxic environment. To detect hypoxia quantitatively in adipose tissue, several approaches have been developed by our group and others, including pimonidazole staining, pO_2 tracking *in situ*, and hypoxia-induced factor (HIF) activity measurements. Experimental results with these techniques have clearly demonstrated that a higher level of hypoxia persists in obese adipose tissue of genetic and diet-induced obese animal models and obese humans (92, 201, 212, 279, 280). Specifically, by tracking the local pO_2 with an oxygen sensor using an electron paramagnetic resonance

(EPR) system, we revealed that the pO_2 in the epididymal WAT is dynamically decreased during diet-induced obesity (241). Intriguingly, compared to the levels measured in mouse models, the hypoxia level is relative minor in obese human fat tissue (201, 253). However, a recent clinical study argues that highly significant hypoxic conditions exist in severely obese patients (253). More clinical studies with larger populations of obese individuals may be necessary to better define the hypoxic state in obese adipose tissue.

Hypoxia-induced factors (HIFs) and their regulation—Hypoxia exerts profound effects on adipose tissue, ultimately leading to insulin resistance (242). The cells in adipose tissue respond to low oxygen conditions by activating multiple transcriptional factors, such as HIFs, CREB family members, and NF-κB (255). Among these factors, HIF1 has been demonstrated to function as a "Master Regulator" (1, 79, 241). HIF1 is an essential transcription factor that plays a fundamental role in oxygen homeostasis in almost all tissues and in cancer (228). HIF1 contains two subunits, HIF1α and β and they form a basic helix-loop-helix structure when binding to the cis-acting HIF response element (HRE) to exert their function on transcriptional activation/suppression (228). Our groups have utilized adipose-specific gain- and loss-of-function mouse models to study the role of HIF1α in the obesity-associated pathogenesis (79, 241). We have reported that HIF1α plays a pivotal role in shaping the unhealthy microenvironment in obese adipose tissue. During obesity, HIF1 is massively upregulated at both the microRNA (mRNA) and protein level in adipocytes (79, 241). Intriguingly, HIF1 fails to upregulate a typical target gene, VEGF-A in adipocytes, resulting in the lack of angiogenesis in the largely expanded adipose tissue (79, 241). Instead, it triggers a massive "fibrosis program" by upregulating collagen proteins and ECM remodeling enzymes, such as MMP14 and LOX (79, 150, 202, 241). LOX can cross-link lysyl residues in collagens and in elastin. This cross-linking reaction may stabilize the collagens to form the building blocks for the ECM (88, 216). Overexpression of LOX enhances the fibrotic streaks by acting to cross-link the accumulated Col1 and 3 to form the fibrillar collagen fibers (282).

HIF1 is also induced in other cell populations, such as the M1-like polarized macrophages and preadipocytes in obese adipose tissue (208, 231, 232). The function of HIF1α in the macrophages is to drive low-grade inflammation by upregulating IL-1β (208, 232). Interestingly, a recent study demonstrated that inhibition of HIFα in $PDGFR\beta^+$ preadipocytes facilitates adipogenesis and healthy expansion of different adipose depots during obesity (231).

The levels and activity of HIF1 are dynamically regulated by multiple signals associated with obesity, such as local oxygen tension, ANT2, insulin, and adipogenesis (65, 84, 229). Intriguingly, MMP14 has been shown to affect HIF1α transcriptional activity by physically retaining its suppressor, *f*actor *i*nhibiting *H*IF-1α−1 (FIH-1) in the cytoplasm in a subset of cancer cells (159, 204, 205, 221, 223). FIH-1 is an asparaginyl hydroxylase that targets and hence hydroxylates the Asn-803 residue in HIF1α. The hydroxylation (Asn803-OH) significantly blocks the recruitment of P300/CBP to HIF1α, which in turn impairs its overall transcriptional activity (100, 134, 159, 217, 264). The cytosolic region of MMP14 (but not of any other MMPs) interacts with FIH-1, thereby preventing its translocation into the nucleus, and hence allowing HIF1α to evade the suppression by FIH-1 (222).

Nevertheless, the importance of FIH-1 in MMP14-mediated HIF1α activation has not yet been directly evaluated in obese adipose tissue. Given that the loss-of-function study of FIH-1 has revealed a profound impact on adipose tissue metabolism (284), we reason that it is an integral component of HIF1α regulation in adipose tissue, mediated by MMP14.

This leads us to propose that HIF1 induction represents an early event during obesity development, while it is a critical step in the sequential processes of obesity-related pathological changes including fibrosis and inflammation.

HIF2α, a protein related to HIF1α, is also broadly expressed in adipocytes and macrophages in adipose tissue (34, 64, 69, 153). It also plays multifaceted roles in metabolism, physiology, and pathology of adipose tissue. Even though it shares similar target genes with HIF1α, it also has some unique functions which are, in some instances, opposite to those of HIF1α (113). Of note, studies have highlighted the important role of HIF2α in protecting adipocytes from dysfunction, predominantly through its proangiogenic actions by upregulating VEGF-A in obese adipose tissue (61, 64, 174, 253). Further insights need to be gained to better understand the mechanistic details of the interactions between HIF1α and HIF2α.

Abnormal ECM formation driven by hypoxia

Fibrosis in adipose tissue is caused by the disproportionate accumulation of ECM proteins. During the process of fibrosis, excessive amounts of ECM proteins are produced, while their degradation is reduced. The overarching pathophysiological role of the ECM is driven by the obesity-induced hypoxic conditions, but the detailed events and underlying mechanisms remain to be further clarified (242, 245). Of note, even though there is an established link between obesity and fibrosis in rodent models, clinical observations reveal that not all obese individuals develop local fibrosis in adipose tissue, suggesting fibrosis is a pathological process that is, controlled by other factors aside from obesity *per se*, including environmental and genetic factors [reviewed in Sun et al. (242)].

Regulation of collagens in obese adipose tissue—Collagen proteins are massively upregulated in hypoxic adipose tissue (4, 42, 79, 149, 156, 241). Gene profiling data from the WAT of HIF1α transgenic mice show a widespread induction of fibrotic genes. They include multiple types of collagens, such as Col1, 3, 5, 6, and 8 (95). Specifically, Col6 is one of the most abundant collagens and it plays an essential role in shaping dysfunctional ECM (116). Col6 levels are further increased in the obese adipose tissue (116, 225). Clinically, it has been found that the levels of Col6, especially its α3 subunit, strongly correlate with the degree of hypoxia in adipose tissue (136, 200, 201). The excessive accumulation of Col6 may disrupt the normal structure of the ECM and cause increased stiffness of the ECM scaffold. This creates a mechanical stress in the rapidly expanding adipose tissue (245). To support this notion, lack of Col6 results in reduced rigidity which facilitates the expansion of the adipose tissue in both diet-induced obese and *ob/ob* mice (116). As a result, the lack of Col6 leads to improved metabolic profiles (49, 116).

Regulation of ECM enzymes during obesity—The formation and turnover of the ECM are dynamically regulated by different enzymes that act on ECM factors. One of the

key enzymes is LOX. As mentioned above, LOX cross-links collagens and elastin and hence facilitates the formation of the ECM (4, 39, 160, 202). The function of LOX is tightly regulated by hypoxia in obese adipose tissue. Indeed, LOX is a direct transcriptional target for HIF1 induction (79). Furthermore, LOX expression has also been shown to be closely correlated with elevated Col1 expression during the development of adipose tissue (277). Importantly, inhibition of LOX activity not only ameliorates fibrosis but also improves local inflammation and several metabolic parameters (79). Clinical results have confirmed that LOX levels were significantly increased in obese adipose tissue and weight-loss surgery attenuated its expression levels (94, 202).

On the other hand, the ECM digesting enzymes in adipose tissue are also dynamically regulated during obesity. Particularly, MMP14 expression and protein levels are significantly increased in obese adipose tissue (36, 127, 150). We recently demonstrated that HIF1α binds to the promoter regions of MMP14 and hence upregulates its expression (150). Intriguingly, the activated MMP14 exerts dichotomous effects on ECM remodeling depending on the metabolic status: At the early stages during obesity, MMP14 upregulated by HIF1α induction turns over collagen proteins and hence release the mechanical stress on the enlarged adipocytes. In that context, MMP14 brings about metabolically beneficial effects for the adipose tissue expansion; On the other hand, at the later stages of obesity, MMP14 digests Col6 and produces endotrophin, which stimulates local pro-fibrotic and pro-inflammatory reactions in obese adipose tissue, thereby worsening the metabolically unhealthy microenvironment in the tissue. As a direct result, the mice exhibit metabolic dysregulation and insulin resistance (150, 290). Other MMPs and their endogenous inhibitors, the TIMPs, are also dramatically changed during obesity. Specifically, the expression levels of MMP2, 3, 12, 14, and 19 as well as TIMP1 are dramatically upregulated, while MMP7 and TIMP3 were downregulated during obesity in the mice (2, 29, 126, 161, 170, 224). The studies further indicated that the activities of MMP3 and MMP12 are enhanced in the obese adipose tissue (29, 273). TIMP4 levels and activity are also increased in the high fat-diet (HFD)-fed mice while suppression of TIMP4 has been shown to protect the mice from obesity-induced fibrosis in adipose tissue (224, 273). All these observations suggest that there is a finely tuned balance between collagen digesting enzymes and their inhibitors in obese adipose tissue (29). Of note, the dynamic changes of MMPs also exert a profound impact on adipogenesis, angiogenesis, as well as inflammation in adipose tissue [reviewed by Ruiz-Ojeda et al. (218)]. Clinical observations reveal that the levels of MMP7, MMP9, and TIMP1 correlate well with fat mass during obesity. Particularly, MMP9 levels are increased in the insulin-resistant individuals and in the patients with higher body mass index (BMI) as well (2, 136).

Fibrosis and angiogenesis

Healthy expansion of adipose tissue requires proper formation and proliferation of new blood vessels via angiogenesis and vasculogenesis. The functional blood vessels provide nutrients, hormones, growth factors, and stem cells for maintaining the homeostasis of the adipose tissue (24, 25, 195, 242). Pro-angiogenic factors, such as VEGF-A and VEGF receptors 1 and 2, Angiopoietin receptors, and NOX2 are upregulated by HIFs in most tissues, including in the liver, kidney, and tumor tissue (26, 47, 269, 276). In these tissues,

the stimulated angiogenesis has been demonstrated to be closely associated with ECM remodeling and the level of fibrosis (51). In that context, targeting angiogenesis has been considered to be an efficient way to reduce local fibrosis (45, 51). However, in obese adipose tissue, HIF1α fails to upregulate VEGF-A for formation of adequate new blood vessels to keep the pace with the expansion of adipose tissue (79). This deficiency further exacerbates the local hypoxic state in the obese adipose tissue (79). Lack of adequate angiogenesis is a unique feature of the obese adipose tissue and the vasculatures may not contribute to the development of fibrosis in the tissue. The underlying mechanisms governing this phenomenon are not yet completely understood.

Fibrosis and inflammation

Fibrosis induces inflammation—The enhanced stiffness during the development of fibrosis causes mechanical stress to the ECM-laden adipocytes, which eventually leads to a pro-inflammatory response in the tissue (242). The detailed molecular events governing the mechanical stress on adipocytes are not completely understood. Several cellular pathways, such as RhoA and NF-κB signals, have been reported to be involved in the whole process. Briefly, RhoA is activated by mechanical shear stress and the increased size of adipocytes (81). Activation of RhoA signaling pathways reduces PPARγ transcriptional activity on adipogenesis, which affects the recruitment of newer adipocytes for healthy expansion (101, 168). Moreover, RhoA and its downstream RhoA kinase activation stimulate multiple pro-inflammatory cytokines, including plasminogen activator inhibitor-1 (PAI-1) and mast cell protease-1 (MCP-1), which trigger local inflammation (148, 184). Enhanced ECM density in adipose tissue also activates the NF-κB pathway, which plays a central role in shaping the inflammatory environment by initiating a pro-inflammatory cascade (8). Specifically, the activated NF-κB induces activation of monocytes and blunts metabolic signaling in obese adipocytes (148).

We and others have observed the fibrosis-induced inflammation in adipose tissue in both diet-induced and genetically obese mouse models. In fibrotic obese adipose tissue, adipocytes experience a significant enlargement through hypertrophy (163, 179, 243). We demonstrated that large lipid droplets rapidly lose their surface covering proteins, such as perilipin-1, upon cell death in adipocytes surrounded by the abnormally high levels of ECM (246) (Figure 1). The dead adipocytes carrying large lipid droplets attract massive infiltration of macrophages, and the accumulated macrophages surrounding the lipid droplets form a typical “crown-like” structure, a characteristic feature of inflammation in the tissue (180). The infiltrated macrophages, upon disposing lipids from the lipid droplets, may polarize into M1-like pro-inflammatory subtypes. They further induce chronic mild inflammation which has been recognized as the root cause of obesity-related insulin resistance and other metabolic disorders (135, 189). Particularly, this phenomenon has been well characterized in our “FAT-ATTAC” (*FAT* *A*poptosis *T*hrough *T*argeted *A*ctivation of *C*aspase 8) mouse model, in which the adipocytes are induced to undergo synchronized apoptosis via Caspase 8 activation (157, 193, 257). In this model, the adipocytes quickly undergo cell death within 2 days upon induction of Caspase 8, while the lipid droplets remain in the original regions for many weeks to form “ghost fat cells.” Meanwhile, the number of “crown-like” structures is significantly increased, reflecting the increased local

inflammation (59, 157, 193). Of note, even though the “FAT-ATTAC” mouse model mimics adipocyte death which attracts macrophage accumulation in the obese adipose tissue, it may not fully recapitulate all of the pathological changes associated with obesity. Based on related observations by us and others, we have built a working model in which inflammation happens in the later stages following local hypoxia and fibrosis in adipose tissue (Figure 1).

Inflammation exacerbates fibrosis—Another set of observations support a different working model in which hypoxia may trigger local inflammation before the development of fibrosis. In this model, fibrosis is induced by inflammation [reviewed in Debari and Abbott (46)]. Hypoxia induces infiltration of macrophages and other immune cells in obese adipose tissue (93, 270). Abnormal metabolic signaling, in part due to an increase in free FAs and prolonged exacerbated circulating glucose levels, promotes activation of immune cells. The activated immune cells produce pro-inflammatory cytokines and initiate different levels of inflammation. Particularly, the M1-like macrophages secrete IL-6, TNFα, and several other cytokines that lead to a chronic low-grade inflammatory response (93, 111, 268, 270). Moreover, the innate T cells also exhibit functional abnormalities that further contribute to the overall inflamed state (50, 209). The chronic inflammation offers additional mechanisms for the development of local fibrosis in the obese adipose tissue (245). The pro-fibrotic program is coordinated by a variety of activated or polarized innate and adaptive immune cells (158).

Notably, even though we have two models describing the relationship between fibrosis and inflammation in the obese adipose tissue, they are not contradictory to each other. Instead, the two major pathological changes may promote each other and hence coordinate to shape the unhealthy microenvironment in obese adipose tissue. In the future, with the development of novel tools applied *in vitro* and *in vivo*, it will hopefully be possible to better define which is the initial mechanism in response to the stimulation of hypoxia.

Key cellular components involved in fibrosis-induced inflammation—The proinflammatory microenvironment in the fibrotic adipose tissue is shaped by a broad spectrum of inflammatory factors, adipokines, lipid species, and exosomal mRNAs that are produced by different cells (60, 80, 192, 194). Among them, macrophages have been recognized as a major contributor for the factors [reviewed in Sun et al. (242)]. Macrophages infiltrate into obese adipose tissue, polarize into M1-like subtypes and hence secrete pro-inflammatory cytokines, such as TNFα, IL-1β, and IL-6. The cytokines not only exert local effects in the adipose tissue but also circulate into other metabolically active organs, thereby affecting the local inflammatory and metabolic state, ultimately leading to the development of metabolic complications in the whole system (75, 213, 270, 275).

Recently, other immune cells have been appreciated to play critical roles in local inflammation as well as insulin resistance in the obese adipose tissue (169, 181). In the past years, many types of immune cells have been reported to infiltrate unhealthy obese adipose tissue [reviewed in Lackey and Olefsky (133)]. They include both innate and adaptive immune cells, such as T cells, B cells, NK and NKT cells, dendritic cells, mast cells, and neutrophils cells [reviewed in Osborn and Olefsky (191); Ferrante (57)]. Among them, neutrophils belong to innate immune cells (109). Even though their overall numbers

are relatively small, they are among the first immune cells that are recruited by adipose tissue where they exert prolonged pro-inflammatory effects via secreting TNFα, MCP-1, and elastase up to 3 months in response to HFD (32, 41, 248, 266). Mast cells also belong to innate immune cells and adipose tissue is a major site of residence of mast cells. Diet-induced obesity dramatically increases the total number of mast cells in the tissue (155, 283). During obesity, mast cells experience a degranulation process which promotes the secretion of multiple pro-inflammatory factors, thereby facilitating a chronic low-grade pro-inflammation microenvironment in the obese adipose tissue (155, 169, 283). T cells and B cells are lymphocytes. Normally they contribute up to 10% of nonadipocytes in adipose tissue (169). Specifically, B cells are actively recruited into obese adipose tissue where they promote the accumulation of other immune cells, including the M1-like macrophages and the T cells (144, 272). T cells represent the second largest population, aside from macrophages in the obese adipose tissue (144). T cells have two subtypes, named CD4-positive and CD8-positive T cells, respectively. CD8-positive T cells are associated with metabolically unhealthy outcomes in obese adipose tissue (120). CD4-positive cells are further subclassified into several groups: pro-inflammatory T helper (Th1) and Th17 cells, anti-inflammatory Th2 cells, and T regulatory (Treg) cells (188). Among them, the Treg cells play a key role in maintaining healthy anti-inflammatory state in lean adipose tissue. Previous studies have demonstrated that decreased numbers of Treg cells are associated with higher level of local inflammation in obese adipose tissue, which might further lead to whole-body insulin resistance (58, 292). More recent research further revealed that other memory T cells increase in the diet-induced obese adipose tissue, leading to severe pathological changes including enhanced lipase activity and calcification of the whole tissue (176).

Even though each immune cell exerts its own function in the inflammatory response, the interplay between them is essential for their contributions to the chronic local inflammation in obese adipose tissue (173). For example, both B cells and T cells, as well as the interplay between them, critically influence the M1-like macrophage infiltration in obese adipose tissue. Moreover, the CD8-positive T cells promote macrophage differentiation and enhance their chemotaxis, thereby leading to their accumulation in the obese adipose tissue (185). Based on previous findings, it is well accepted that infiltrating M1-like macrophages are the end effectors and orchestrate functional communication among all immune cells [reviewed in Lee et al. (144)].

Other pathological consequences of fibrosis

Fibrosis also leads to other effects on adipose tissue. The mechanical stress on the fibrotic adipocytes may enhance *de novo* lipogenesis and lipolysis in the cells, which further induces the formation of the abnormally large lipid droplets (46, 128, 129, 150, 243, 288). The enlarged lipid droplets caused by fibrosis in adipocytes may further induce the ectopic deposition of lipid in other metabolic tissues, an effect known as lipotoxicity (150, 243). Fibrosis links directly to adipogenesis in adipose tissue. Indeed, ECM factors have been appreciated to play an important role in adipogenesis (6, 38, 140, 289). Consistent with that, an abnormal function of MMP14 during fibrosis has been reported to affect adipogenesis (36, 150). Moreover, ECM proteins upregulated by TGF-β1 or PAI-1 cause the impaired

differentiation of adipocytes in *in vitro* studies (17, 152). Finally, more recent reports argue that the pathologically upregulated HIF1α also drives abnormal adipogenesis in the obese adipose tissue (231).

Nonclassical Fibrotic Factors: Endotrophin as an Example

A number of studies have identified numerous novel factors that potently stimulate fibrosis in adipose tissue (197). Members of these nonclassical “hormone-like” molecules include endostatin, endotrophin, asprosin, and platencin, all of which derive from cleavage events under multiple cellular stress situations (250). Among them, endotrophin has been highlighted to be a potent pro-fibrotic and pro-inflammatory small molecule that triggers profound pathological changes in different tissues and certain types of cancer (226). Endotrophin is the proteolytic product of Col6 α3 chain in the adipose tissue (56, 89, 138, 197–199, 211, 215, 243, 244). Its levels are significantly increased in obese and diabetic mice and in humans (243). Endotrophin can be released into circulation and accumulate in other metabolic tissues (Figure 2). Recently, extensive studies have demonstrated that endotrophin has potent bioactivity, stimulating massive fibrosis and inflammation locally in metabolically active tissues, including in adipose tissue, heart, liver, and kidney (54, 56, 112, 117, 138). It is also enriched in certain types of cancer lesions and serves as a driver of malignant tumor growth (22, 196, 197, 199). Particularly in obese adipose tissue, endotrophin is a powerful driving factor for local fibrosis, macrophage infiltration, and other metabolic unfavorable consequences, including lipotoxicity and insulin resistance (243, 290). In line with its function as a necessary and sufficient factor responsible for the diet-induced pathological changes, treatment with an anti-endotrophin neutralizing antibody significantly reverses the metabolically adverse effects induced by HFD in the obese mice (243). Endotrophin has divergent functions on different cell populations in obese adipose tissue (290). However, the details regarding the signaling pathway(s) that endotrophin triggers in cells remain to be further elucidated.

While numerous studies have demonstrated endotrophin to be a sensitive biomarker of local fibrosis and inflammation and have highlighted it as a key regulator in adipose tissue dysfunction, insulin resistance, and cancer development, the mechanistic details of the cleavage event, including the identity of the key processing enzyme, were unknown for a long period of time. In that context, we recently made a major breakthrough by finding that MMP14 cleaves Col6 α3 to release endotrophin (150). The cleavage region is located at a consensus-cleavage site for MMP14 (Figure 2). The resulting fragment has been confirmed using an endotrophin-specific antibody (150). We further found that the levels and activity of MMP14 are increased during obesity (150). Aside from MMP14, several other MMPs induced by hypoxia, including MMP2, MMP9, and MMP16 in adipose tissue have recently been reported to cleave Col VI and produce endotrophin (or endotrophin-like molecules) (104).

Importantly, endotrophin is also detected at high levels in many other tissues. Recent reports have demonstrated that endotrophin is a sensitive biomarker for local fibrosis and inflammation in many diseases (Table 1). For example, endotrophin levels in urine correlate with local fibrosis, tubular atrophy, and monocyte infiltration in *lupus nephritis* patients

(66). Studies also established a strong association between the pretransplant plasma levels of endotrophin and the risk of the delayed graft function after kidney transplantation, pinpointing it as a new marker for the prediction of the effects of the transplantation (250). Intriguingly, the levels of endotrophin are significantly higher in the females with polycystic ovary syndrome (PCOS), while other adipose-derived hormones, such as adiponectin and ghrelin, displayed no changes in the patients, suggesting it may also serve as a unique biomarker for the diagnosis of PCOS (72). The circulating levels of endotrophin are also tightly associated with many fibrotic diseases, such as fibrotic interstitial lung disease (ILD) (44). Moreover, the levels of endotrophin in metabolically active tissues, such as adipose tissue, the liver, and the tumor tissues, are also highly correlated with many metabolic diseases, such as obesity and related diabetes, cardiovascular disease, kidney disease, and cancer (summarized in Table 1).

In summary, endotrophin has drawn a significant attention recently due to its direct link to many vital diseases. It has been demonstrated to have potent bioactivity to trigger local pro-fibrotic and pro-inflammatory reactions and hence systemic metabolic disorders. Its local or circulating levels are highly correlated with the development of these diseases. Therefore, endotrophin bears a great potential to serve as a sensitive biomarker and be targeted to treat pathological aspects of these diseases.

Cellular Regulation of Fibrosis

While it is clear that the root cause of fibrosis in adipose tissue is obesity, the detailed mechanisms governing the development of fibrosis orchestrated by multiple cell populations remain to be further clarified. Furthermore, many other factors, including genetic variants and environmental factors, may profoundly affect the pathological changes during the development of fibrosis. In obese adipose tissue, the large lipid-laden mature adipocytes are surrounded by various cell types which are collectively named SVF (86, 203). The SVF is composed of endothelial cells, preadipocytes, adipose-derived stem cells (ASCs), pericytes, fibroblasts, macrophages, B cells, T cells, and other types of innate immune cells (86, 87). Different types of cells respond to the hypoxia condition during obesity and hence contribute to the fibrotic development respectively (Figure 3) (86, 87, 290). Recently, the development of single-cell or single-nucleus RNA sequencing (specifically for adipocytes) provides a powerful tool to characterize the divergent roles of the subpopulations of adipose tissue in ECM formation and fibrosis (33, 172, 261).

Adipocytes

As the major type of cells in the adipose tissue, adipocytes are embedded in the dense ECM of the adipose depots. Diet-induced obesity induces the upregulation of pro-fibrotic genes in adipocytes (105). A recent transcriptome analysis of adipocytes isolated from diet-induced obese visceral WAT revealed that the adipocytes are switched to a “fibroblast-like” phenotype in lieu of the obese adipose tissue (105). Among all the ECM proteins, Col6 is highly enriched in the adipocytes (116). Metabolically challenged adipocytes express even higher levels of Col6, which has been considered to be a hallmark of adipose tissue fibrosis (116). Even though adipocytes have low metabolic rates and a relatively low demand for the

oxygen, they are quite sensitive to hypoxic conditions (241). HIFs are induced in adipocytes in response to diet-induced obesity (1). By using both gain-of-function and loss-of-function genetic tools, we have revealed that HIF1 exerts unique functions on local fibrosis in the obese adipose tissue (79, 241). Particularly, LOX is directly upregulated by HIF1 in the obese adipocytes (4, 79, 208). LOX promotes over-accumulation of ECM by cross-linking collagens and elastin to form the oligomer structures for the collagen and noncollagen fibers (79). Furthermore, HIF1 directly binds to the MMP14 promoter region, thereby activating their transcription (150). The upregulated MMP14 catalyzes the digestion of Col6 and hence produce endotrophin, which triggers massive fibrosis in the unhealthy microenvironments in the obese adipose tissue (150). Recently, we found that inhibition of lipid catabolic enzymes, such as carboxylesterase 1d (CES1) in adipocytes, may induce the upregulation of pro-fibrotic genes including Col3α1, Col6α, and LOX, suggesting the potential role of lipid signaling in fibrosis/inflammation in obese adipocytes (147). On the other hand, the level of fibrosis in the obese adipocytes is downregulated by the PRDM16-containing transcriptional complex, which is mediated by a TFII-I family protein called GTF2IRD1 in a cell-autonomous manner (82). Mechanistically, GTF2IRD1 suppresses the expression level of TGF-β-dependent genes through the recruitment of the PRDM-16 complex (82). Intriguingly, some transmembrane glycoproteins, such as CD248 and decorin, exert their deleterious effects through triggering the local fibrosis in obese adipocytes (43, 206).

Endothelial cells

Endothelial cells represent the most dynamic composition in the SVF and they line up both large and macro vasculature in the adipose tissue. Endothelial cells play a key role in the vascular remodeling of adipose tissue during obesity. Even though at the early stage of obesity, VEGF-A-mediated endothelial cell activation brings about metabolically beneficial effects by counteracting the local hypoxia development via angiogenesis, it eventually leads to exacerbated fibrosis, inflammation, and insulin resistance in the established obese adipose tissue (246). In unhealthy adipose tissue at the later stages of obesity, endothelial cells may form a vascular niche with other cell populations, such as the pericytes, macrophages, and hematopoietic stem cells. In this niche, endothelial cells crosstalk with other cell types, including adipocytes, immune cells, and fibroblasts, thereby contributing to the local fibrosis and inflammation through the so-called “angiocrine pathway” (291). Interestingly, in a bleomycin-induced lung fibrosis model and a cardiac fibrosis model, the endothelial cells transformed to fibroblasts through endothelial-mesenchymal transition (EMT), suggesting that endothelial cells might serve as sources of fibrotic cells under pathological conditions (83, 286). Endothelial cells also recruit macrophages during lung injury (137). Even though the endothelial cells and the vascular niche that they form have been studied in other fibrotic models, it needs to be further examined as to whether they exert similar function on fibrosis in adipose tissue.

Macrophages

The function of macrophages on fibrosis has been well established in many tissues/organs (186, 187, 249, 274). In particular, inflammatory monocytes reside in obese adipose tissue and hence accumulate as mature macrophages *in situ*. They are the major immune cells that initiate local fibrosis and inflammation, which ultimately leads to systemic insulin

resistance (210, 237). Macrophage crosstalk with adipocytes via secreting TNF-α and FFAs which aggravate local inflammation in obese adipose tissue (53, 132, 240). The alternatively activated macrophages have been reported to contribute to tissue fibrosis by stimulating the activation of fibroblasts and the formation of the ECM (63). The function is through multiple pathways and includes: (i) They secrete several pro-fibrotic cytokines including IGF1, CCL17, CCL22, and CTGF; (ii) They overexpress TGF-β which further triggers the downstream pro-fibrotic signaling pathways (166); (iii) They stimulate STAT6 signaling pathways (102, 103); (iv) Finally, the modulation of arginase activity in the M2 macrophages promotes fibrogenesis by regulating the production of collagens (251). Of note, recent work revealed that senescent macrophages accumulating in diet-induced obese adipose tissue promote fibrosis in lieu of the unhealthy microenvironment (210). On the other hand, distinct types of macrophages digest the ECM and hence prevent the development of fibrosis. For example, the classical activating macrophages secret TSLP, MMP2, MMP9, and MMP12, and the enzymes exert their fibrolytic function to release the stiffness of the ECM (146, 167, 220). Therefore, the macrophages play dichotomous roles in fibrosis and their functions are their polarization dependent.

Adipose tissue-derived stem cells (ASCs)

ASCs are dynamically regulated by different metabolic states (86, 87, 231). Particularly, the ASCs in the obese adipose tissue exhibit higher PDGFRα-positive population (98, 162). The progenitors are prone to differentiate to the ECM-synthesizing pro-fibrotic cells in the obese adipose tissue (98). Specifically, a subset of the PDGFα-positive progenitors with high expression of CD9 differentiate into pro-fibrotic cells which directly drive the pathological changes of fibrosis (162). A recent study further revealed that both PDGFα-and β-positive progenitors contribute essentially to the local ECM development in the diet-induced obese adipose tissue (210). Interplays between ASCs and other cell populations also contribute to the ECM remodeling.

Fibroblasts

Fibroblasts are a common cell type in the SVF of the adipose tissue. They provide an important niche for the adipogenesis and the whole tissue homeostasis (87, 231, 285). Fibroblasts are the major source of the ECM and serve as a central regulator for the dynamics of ECM remodeling and pathological fibrosis (114). Particularly, the αSMA-positive myofibroblasts have been recognized to produce the stiff ECM fibers, thereby initiating the kidney, liver, and lung fibrosis (254). In particular, fibroblast-specific protein-1 (FSP-1)-positive fibroblasts play a key role in the ECM remodeling and the whole tissue cellular regulation (285). However, the precise functions of fibroblasts in adipose tissue remain to be further clarified. Moreover, the origins of the myofibroblasts remain to be further defined (164).

Mast cells

Mast cells are a type of immune cell that exist with a large number in connective tissues including adipose tissue (207). In response to different cell stimuli, mast cells secrete histamine, hormones, and cytokines that promote allergic reactions and inflammation (130). Mature mast cells are present in obese adipose tissue in *db/db* mice where they exert

pro-fibrotic function through secretion of MCP-6 (90). Clinically, mast cells are abundant in the subcutaneous WAT in the patients with metabolic syndrome (73). In these patients, the number of mast cells is correlated with increased fibrosis and the local proinflammatory state (73). Moreover, the numbers are also correlated with diabetic parameters, such as insulin resistance (48). While it has been appreciated that mast cell accumulation in the obese adipose tissue accelerates the process of fibrosis and systemic metabolic dysregulation, the details of the whole process remain to be further characterized. Of note, while we identify the roles of each cell type in fibrosis (Figure 3), their functions are tightly regulated by cell-cell communication. The level of fibrosis is fine-tuned by the interplay between them (164). For example, the accrual of macrophages is highly controlled by the perivascular mesenchymal cells (230).

Therapeutic Perspectives on Targeting Fibrosis in Adipose Tissue

Given the severe local and systemic pathological consequences caused by adipose tissue fibrosis, such as loss of the adipose plasticity, increased local inflammation, impaired insulin sensitivity, and the poor prognosis of bariatric surgery (46), targeting fibrosis has become an ideal strategy to combat obesity and related metabolic diseases and cancer (46). Furthermore, the level of fibrosis has been quantitatively scored clinically and the scores have been demonstrated to be reversely correlated with the body-weight loss after the gastric bypass surgery, highlighting its significance in the diagnosis and prognosis of obesity-related dysregulations (11). Unfortunately, no direct therapies to block or reverse adipose tissue fibrosis have been developed to date (163).

HIF1α initiates the whole pathological process of fibrosis and inflammation in the established obese adipose tissue. Therefore, targeting HIF1α might be an efficient way to suppress hypoxia-induced pathological changes. In that context, we tested the effect of a HIF1-specific inhibitor, PX-478 on reversing fibrosis in the diet-induced obese mice. Indeed, we found that PX-478 efficiently suppressed the local pro-fibrotic and pro-inflammatory reactions in the adipose tissue, thereby improving the whole-body metabolism (241). Further probing the efficacy of the PX-478 and other HIF1 inhibitors in obesity and related diseases warrants further studies. Hydroxylase domain (PHD) targets and destabilizes HIF1 (13). Inhibitors for PHDs, which can increase HIF1 expression, such as GSK1278863 and FG-4592, have been in clinical trials to treat kidney anemia. Aside from the observed effect on the kidney disease, the inhibitors also showed ability to lower circulating cholesterol levels, providing new insights into clinical implications for lipid dysregulations induced by obesity (30, 190). However, implication of these agents to directly target adipose tissue fibrosis has yet been examined.

The TGF-β pathway plays a central role in pro-fibrotic reaction during obesity. It is reasonable to design therapeutic strategies to target TGF-β and its downstream signals to block the development of fibrosis, though this is highly challenging. In agreement with the notion, berberine, a natural plant product originally known to exert its antidiabetic effect via stimulating the activation of AMPK (96), has been shown to decrease TGF-β mediated Smad3 phosphorylation, thereby attenuating collagen accumulation and reversing the upregulated fibrotic genes in the diet-induced adipose tissue (265).

Endotrophin is one of the promising targets for consideration. As a molecule that is, produced during the pathological expansion of adipose depots, endotrophin shapes an unhealthy microenvironment in adipose tissue and other metabolically active organs and tumors through triggering local fibrosis and macrophage accumulation in the tissues. It not only serves as a sensitive biomarker for the disease but also provides an ideal target for treatment. Indeed, blockage of bioactivity of endotrophin significantly reduced/reversed local fibrosis in the obese adipose tissue and in the tumors in mice (196, 197, 243). Importantly, we recently developed endotrophin-specific neutralizing antibodies which inhibit tumor growth by blocking the bioactivity of endotrophin (22).

MMP14 has been highlighted to be key for the ECM remodeling during obesity. Findings from us and others suggest the possible reversibility of adipose tissue fibrosis by inhibiting MMP14 (36, 43, 127, 150). Therefore, MMP14 bears a great promise from a therapeutic perspective for obesity and type 2 diabetes. Another key ECM remodeling enzyme, LOX in adipose tissue has been extensively studied in different diseases and it has been considered to be an attractive target for the therapeutic intervention to treat fibrotic diseases [reviewed in Yang et al. (278)].

Conclusion

In the past, obesity-induced fibrosis in adipose tissue has been extensively investigated *in vitro* by 3-D culture, *ex vivo* by high-resolution magnetic resonance imaging (MRI), as well as *in vivo* in different animal models and humans (4, 11, 18, 46, 49, 79, 85, 86, 116, 118, 124, 150, 163, 241, 243, 245, 290). It has been well established that fibrosis developed in obese adipose tissue causes severe pathological changes, including adipocyte necrosis, impaired adipogenesis, metabolic disorders, and inflammation locally in the adipose tissue, ultimately leading to systemic lipotoxicity and insulin resistance (245). Previous findings have demonstrated that different cell populations in obese adipose tissue contribute individually to the development of fibrosis. The interplay between these cells finetunes the whole pathological process. Many additional findings further highlight the central role of hypoxia in the pro-fibrotic and pro-inflammatory reaction in obese adipose tissue (79, 241). While HIF1 stimulates both fibrosis and inflammation, the causal-effect relationship between the two pathological changes remains to be further defined with proper models. Moreover, the detailed mechanisms underlying the overdevelopment of ECM resulting in fibrosis need to be further characterized in depth.

It has been proposed that fibrosis can be reduced or reversed to treat obesity and related metabolic diseases and cancer. Several key fibrotic pathways, such as TGFβ and its downstream signaling, the HIF1-MMP14-endotrophin axis, and HIF1-PHD signaling have been considered to be potential targets to ameliorate fibrosis and related pathological changes. Excitingly, at least *in vitro* or in preclinical models, they have been demonstrated to be effective to improve metabolic disorders, including dyslipidemia, insulin resistance, and tumor growth (22, 150, 241, 243). In the future, well-designed clinical studies will hopefully validate this therapeutic relevance of these pathways in patients. Of note, even though fibrosis has been demonstrated to be the core constituent of unhealthy microenvironment that further induces local inflammation and other pathological changes in the obese adipose

tissue, metabolic dysfunction can be caused by many other profound factors, including nutritional and genetic factors. Therefore, anti-fibrotic therapeutics themselves may be insufficient to reverse the metabolic disorders. In that context, combination of the anti-fibrotic therapeutics with other interventions, such as reduced energy intake, regular physical activity, anti-inflammatory interventions, and/or metabolic (bariatric) surgery bear great promise to synergistically treat obesity and type-2 diabetes.

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Didactic Synopsis

Major teaching points

- Obesity is caused by interactions of multiple complex factors, such as overnutrition, reduced physical activity, the environmental, and genetic factors.
- Hypoxia initiates multiple pathological changes in the obese adipose tissue.
  - Fibrosis is one of the major consequences caused byhypoxia.
  - Abnormal ECM accumulation during fibrosis is tightly associated with chronic low-grade inflammation in the obese adipose tissue.
  - The pro-inflammatory factors and free fatty acids released from the dysfunctional adipose tissue further circulate to other metabolically active tissues/organs, thereby triggering an elevated degree of lipotoxicity in the other organs.
- Fibrosis in adipose tissue is a major driver of obesity-related metabolic dysregulation.
- The enhanced stiffness during the development of fibrosis causes the mechanical stress to the ECM-laden adipocytes, which eventually leads to necrosis of adipocytes and a pro-inflammatory reaction response in the tissue.
- The chronic inflammation is an important trigger for the development of the local fibrosis in the obese adipose tissue.
- The level of fibrosis is fine-tuned by the interplays between multiple cell types in obese adipose tissue.
- Targeting fibrosis has become a viable strategy to combat obesity and related metabolic diseases and cancer.

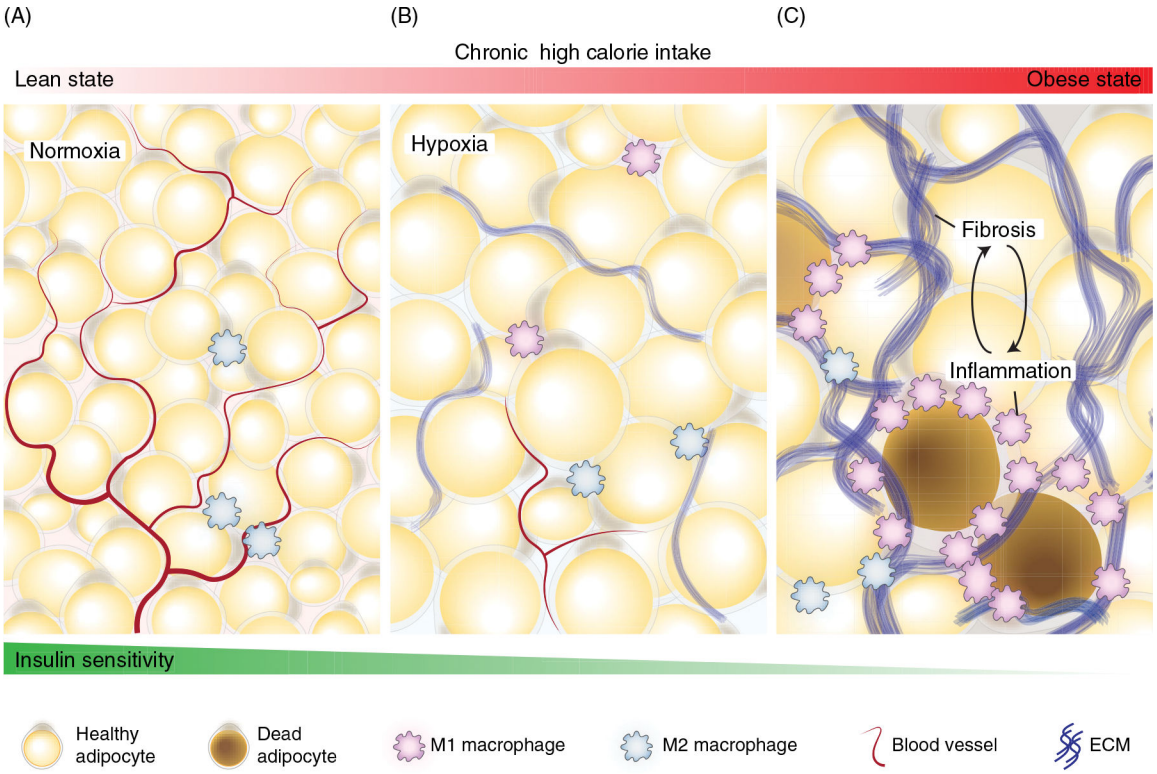

Figure 1.

Working model for the development of fibrosis and inflammation in obese adipose tissue. In lean adipose tissue, the adipocytes are small and healthy. Adequate blood vessels formed by proper angiogenesis provide oxygen, hormones, nutrients, and adipocyte precursors to support the healthy expansion of the tissue (A); during diet-induced obesity, adipose tissue expands rapidly through hyperplasia and hypertrophy. Meanwhile, new blood vessel formation cannot keep up with the expansion, the adipocytes become larger, and local hypoxia thus develops (B); At the late phase of obesity, hypoxia stimulates massive fibrosis. The mechanical stress induced by the overdeveloped ECM leads to necrosis of the adipocytes. As a result, macrophages are accumulated and polarized to the M1 subtype in the tissue. They form “crown-like” structures in obese adipose depots. The local fibrosis and inflammation further lead to the whole-body insulin resistance (C). Of note, not all the adipose tissue expansion has “unhealthy” consequences. In addition to the calorie excess, genetic variants and environmental factors also have profound effects on the expansion.

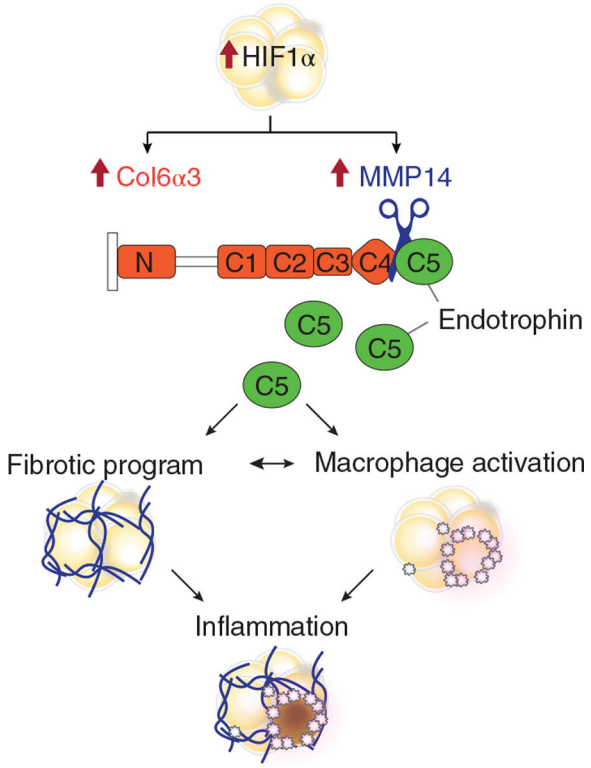

Figure 2.

MMP14 digests Col6 and produce endotrophin. During diet-induced obesity, local hypoxia induces HIF1α in adipose tissue. As a direct target of HIF1α, MMP14 is upregulated. Meanwhile, HIF1α also upregulates Col6 expression. MMP14 digests Col6α3 chain and produces endotrophin. Accumulation of endotrophin further shapes unhealthy microenvironment locally in the adipose tissue via triggering massive fibrosis and inflammation. The local pathological changes ultimately lead to systemic insulin resistance and other metabolic disorders.

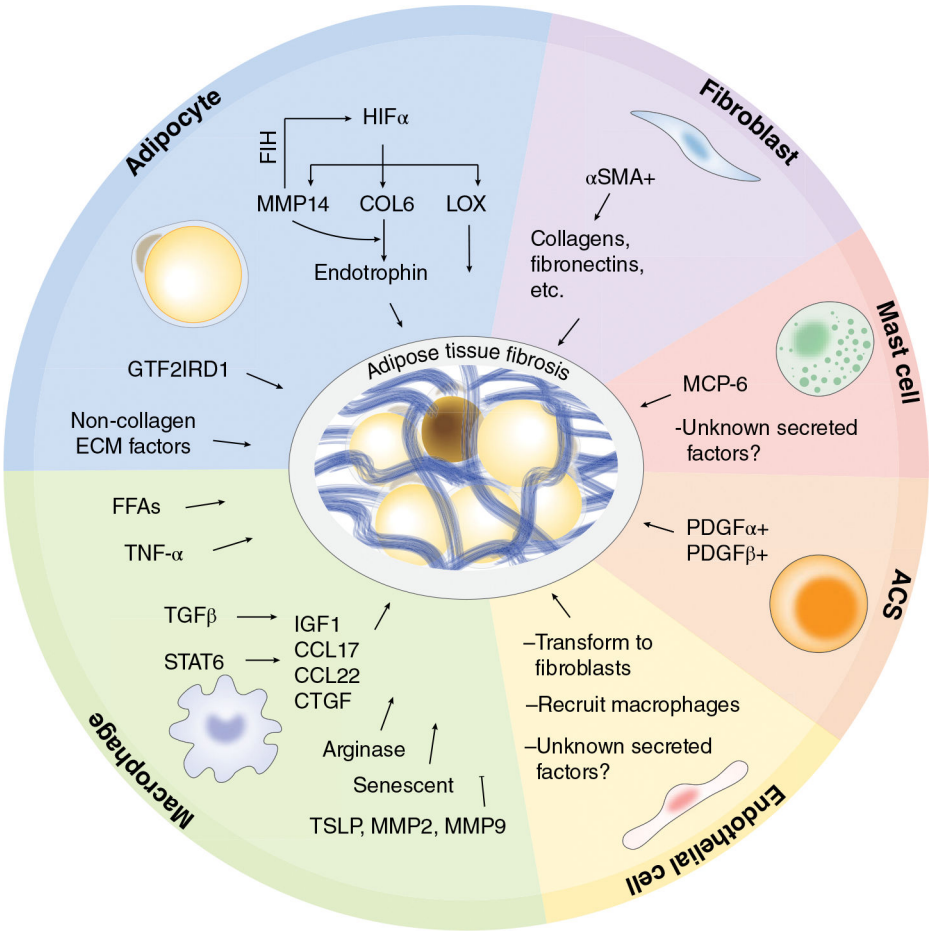

Figure 3.

The divergent function of different cell populations on fibrosis in obese adipose tissue. The fibrotic program is coordinated by multiple cell types in adipose tissue, including adipocytes, macrophages, endothelial cells, ACS, Mast cells and fibroblasts, etc. The cells secrete collagens and non-collagenous proteins, pro-inflammatory factors, ECM enzymes, and multiple unidentified factors which work together to fine-tune the level of fibrosis in response to different cell stimuli. Moreover, the cells interplay with each other and regulate their pro-fibrotic function through the cell-cell communication.

Table 1

The Correlation Between Levels of Endotrophin and Diseases

Disease	Correlation	Tissue/Serum/Plasma	References
Obesity and diabetes	Positive	Adipose tissue	Sun et al. (243)
Renal fibrosis	Positive	Kidney	Rasmussen et al. (211)
Type 2 diabetes	Positive	Serum	Karsdal et al. (112)
Chronic kidney disease	Positive	Serum	Fenton et al. (56)
Breast cancer	Positive	Plasma	Bu et al. (22)
Heart failure	Positive	Serum	Eruzun et al. (54)
Hepatocellular carcinoma	Positive	Tumor-neighboring regions	Lee et al. (138)
Cirrhotic patients with hepatocellular carcinoma	Positive	Plasma	Leeming et al. (145)
Obese children	Positive	Plasma	Ezzati-Mobaser et al. (55)
Chronic obstructive pulmonary disease (COPD)	Positive	Serum	Rønnow et al. (215)
Non-alcoholic fatty liver disease	Positive	Serum	Kim et al. (117)
Atherosclerotic	Positive	Atherosclerotic plaque	Holm Nielsen et al. (91)
Acute-on-chronic liver failure	Positive	Plasma	Kerbert et al. (115)
Nonalcoholic steatohepatitis	Positive	Serum	Hagström et al. (76)
Chronic multimorbidity	Positive	Serum	Staunstrup et al. (238)
Polycystic ovary syndrome (PCOS)	Positive	Serum	Guney et al. (72)
Crohn’s disease	Positive	Serum	Lindholm et al. (154)
Diabetic nephropathy	Positive	Serum	Yoldemir et al. (281)
Chronic kidney disease	Positive	Serum	Sparding et al. (235)
Kidney fibrosis	Positive	Serum	Genovese et al. (66)
Fibrotic interstitial lung diseases	Positive	Serum	Dasdemir Ilkhan et al. (44)
Kidney transplantation	Negative	Pretransplant plasma endotrophin	Tepel et al. (250)