Adipose extracellular matrix remodelling in obesity and insulin resistance

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Abstract
The extracellular matrix (ECM) of adipose tissues undergoes constant remodelling to allow adipocytes and their precursor cells to change cell shape and function in adaptation to nutritional cues. Abnormal accumulation of ECM components and their modifiers in adipose tissues has been recently demonstrated to cause obesity-associated insulin resistance, a hallmark of type 2 diabetes. Integrins and other ECM receptors (e.g. CD44) that are expressed in adipose tissues have been shown to regulate insulin sensitivity. It is well understood that a hypoxic response is observed in adipose tissue expansion during obesity progression and that hypoxic response accelerates fibrosis and inflammation in white adipose tissues. The expansion of adipose tissues should require angiogenesis; however, the excess deposition of ECM limits the angiogenic response of white adipose tissues in obesity. While recent studies have focused on the metabolic consequences and the mechanisms of adipose tissue expansion and remodelling, little attention has been paid to the role played by the interaction between peri-adipocyte ECM and their cognate cell surface receptors. This review will address what is currently known about the roles played by adipose ECM, their modifiers, and ECM receptors in obesity and insulin resistance. Understanding how excess ECM deposition in the adipose tissue deteriorates insulin sensitivity would provide us hints to develop a new therapeutic strategy for the treatment of insulin resistance and type 2 diabetes.

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integrins and CD44. In this review, we summarize the recent findings on adipose tissue ECM remodelling and the roles played by ECM receptors, e.g. integrins, CD44, and CD36. We propose a new concept that the interaction of adipose ECM molecules with their cognate receptors expressed not only by adipocytes but also by a diverse array of cells, i.e. pre-adipocytes, macrophages, and vascular endothelial cells, should contribute to adipose tissue inflammation, apoptosis, angiogenesis, and subsequent metabolic deteriorations in obesity. A similar concept has been proposed in the biology of pulmonary fibrosis, the biology of the skeletal muscle and liver, which was recently reviewed elsewhere [6]. Despite a novel perception in the context of obesity and insulin resistance, ECM–ECM receptor pathways have been long implicated in the biology of pulmonary fibrosis, wound healing, and tumour growth [7–9].

2. ECM components in the adipose tissue

2.1. Collagens

Collagens, as the most abundant structural components of the ECM, not only support tissue architecture but also cell functions, including cell adhesion, migration, differentiation, morphogenesis, and wound healing [10]. In adipose tissues, it is known that the ECM undergoes constant remodelling to allow adipocytes to rapidly expand and shrink in parallel with weight gain and loss [11]. Abnormal expression of ECM components, modifiers, and receptors in adipose tissues is a hallmark of obesogenic adipose tissue remodelling (Table 1). Excessive collagen deposition in adipose tissues has been seen in various animal models of metabolic diseases. In genetically obese and diabetic db/db mice, the mRNA levels of a group of collagens (mainly types I, III, V, and VI) are increased in white adipose tissues, and high-fat diet (HFD) further increases those collagen expressions [12]. Type VI collagen is highly enriched in adipose tissues, and its gene-targeted deletion (Col6a1) results in less restricted expansion of adipose tissues coupled with a substantial improvement in whole-body energy homeostasis [3]. The overexpression of a cleaved fragment of the α3 chain of collagen VI (Col6a3), named endotrophin, in mice stimulates fibrotic collagen deposition in adipose tissues and triggers adipose inflammation and insulin resistance [13]. In obese humans, the expression of collagen V is increased in adipose tissues that demonstrate a decreased number of capillaries [14]. Increased collagen V is colocalized with blood vessels, and the addition of collagen V to an angiogenesis assay inhibits endothelial budding, suggesting an inhibitory role of collagen V in angiogenesis [14]. These data suggest that excessive collagen deposition in the adipose tissue poses physical barriers against adipocyte hypertrophy during obesity progression and may also inhibit angiogenesis within adipose tissues.

2.2. Osteopontin

Osteopontin (OPN), also known as secreted phosphoprotein 1, is an ECM glycoprotein expressed in various cell types and tissues including the adipose tissue [15]. OPN expression is drastically increased in adipose tissues of HFD-induced and genetically obese mice as well as obese humans [16]. OPN is highly expressed in adipose tissue macrophages [17]. The genetic deletion of OPN in mice prevents HFD-induced obesity [18,19] and attenuates macrophage infiltration in adipose tissues, improving insulin sensitivity [17]. Similarly, neutralization of OPN using a monoclonal OPN antibody [20] or OPN gene silencing selective to adipose tissue macrophages [21] in mice suppresses adipose tissue inflammation and insulin resistance. It is hypothesized that action of OPN is mediated through engagement of a number of receptors, but particularly through CD44 and integrin αvβ3 [15].

2.3. Hyaluronan

Hyaluronan (HA) is a linear glycosaminoglycan consisting of chemically unmodified repeating disaccharide units of D-glucuronic acid and N-acetyl-D-glucosamine [22]. HA binds to cell-surface receptors (CD44 and HA-mediated motility receptor)

Table 1

| The ECM, ECM modifiers and ECM receptor remodelling in the adipose tissue of obesity and insulin resistance. |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| **ECM** | **Mice** | **Human** | **References** |
| Collagen I, III, V, and VI | (db/db; ob/ob; HFD) | (HFD) | [3,12,14] |
| Osteopontin | (db/db; HFD) | (HFD) | [16,17] |
| Hyaluronan | (ob/ob; HFD) | (HFD) | [24] |
| Thrombospondin 1 | (HFD) | (HFD) | [27,29] |
| MMP2, 3, 11, 12, 13, 14, 19 | (HFD, ob/ob, db/db) | (HFD, ob/ob, db/db) | [41,42] |
| MMP7, 16, 24 | (HFD, ob/ob, db/db) | (HFD, ob/ob, db/db) | [41,42] |
| MMP9 | (HFD) | (HFD) | [37,41] |
| MMP15 | (HFD) | (HFD) | [37] |
| TIMP-1 | (HFD) | (HFD) | [41] |
| TIMP-2 | (HFD males) | (HFD males) | [64] |
| TIMP-3 | (ob/ob, db/db) | (ob/ob, db/db) | [42] |
| TIMP-4 | (HFD) | (HFD) | [41] |
| **ECM receptor** | **J2 integrin (αXβ2, αMβ2, αXJ2, and αDβ2)** | **CD44** | **CD36** |
| | (HFD) | (HFD) | (HFD) |

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and influences cellular responses such as proliferation and migration [23]. HA content is increased in hypertrophic 3T3-L1 cells and in adipose tissues of diabeticogenic LDL receptor-deficient and ob/ob mice, possibly due to an increased expression of HA syn-thase 2 [24]. Increased HA content has been demonstrated to facilitate monocyte adhesion and chemotaxis [24]. In contrast, the reduction of HA by exogenous hyaluronidase inhibits adipogenesis of 3T3-L1 cells [25]. Moreover, chronic treatment of HFD-fed obese mice with a PEGylated human recombinant hyaluronidase PH-20 decreases adiposity and adipose inflammation to prevent insulin resistance [26].

2.4. Thrombospondins

Thrombospondin 1 (THBS1) is a large adhesive ECM glycoprotein expressed predominantly in visceral adipose tissues and its expression is elevated in insulin-resistant, obese humans [27,28]. In mice, HFD acutely induces Thbs1 expression in visceral adipose tissues and increases the circulating THBS1 level [29]. The genetic deletion of Thbs1 renders mice protected from adipose tissue inflammation and insulin resistance [29,30]. Most importantly, a recent study suggests that circulating THBS1 may induce fibrotic damage to skeletal muscle and insulin resistance as Thbs1-null skeletal muscles are protected from HFD-induced collagen deposition [29]. This is the first study that suggests a potential role of circulating ECM protein in the crosstalk between the adipose tissue and the skeletal muscle in obesity and insulin resistance. Despite the important role played by THBS1 in adipose tissue inflammation and insulin resistance, THBS2 does not seem to play a substantial role in adipose tissue development and HFD-induced obesity, at least in mice [31].

3. ECM modifiers in the adipose tissue

3.1. MMPs

Matrix metalloproteinases (MMPs), a family of calcium-dependent and zinc-containing endopeptidase, are responsible for the degradation of virtually all ECM proteins [32,33]. MMPs play an essential role in regulating ECM remodelling in both normal physiology and diseases [33,34]. MMP family members are categorized into soluble collagenase (MMP1, -8, -13), gelatinase (MMP2, -9), stromelysin (MMP3, -10, -11), matrilysin (MMP7, -12), membrane-type MMPs (MT-MMPs) (MMP14, -15, -16, -17, -24, -25), and elastase (MMP12) [34]. Dysregulation of MMPs are implicated in the pathophysiology of obesity and diabetes in humans [35–37]. Plasma concentrations of gelatinases (MMP2 and -9), two major circulating MMPs, are increased in obese [38] and diabetic humans [39,40]. The adipose expression of MMP9 positively correlates with the homoeostasis model assessment index of insulin resistance (HOMA-IR) in obese humans [37].

The specific role played by each MMP in the pathogenesis of obesity and insulin resistance has not been fully defined. MMP expression in the adipose tissue is differentially regulated in HFD-fed obese mice [41,42]. A series of MMP gene targeting were tested in mice to determine the role of each MMP in obesity and diabetes, and the results have been variable. The genetic deletion of MMP3 (stromelysin-1) causes hyperphagia and obesity in HFD-fed mice [43]. The responsible substrate or the site of action of MMP3 in metabolism is unknown. MMP3 cleaves OPN [44]; therefore, the loss of MMP3 may exacerbate OPN-dependent adipose inflammation. Similarly, MMP11 (stromelysin-3)-null mice are more prone to HFD-induced obesity [45]. The gene targeting of MMP10 (stromelysin-2) did not cause any significant changes in adipose tissue size and function after 15-week HFD [46].

Mice lacking a gelatinase, MMP2 (gelatinase A), are resistant to obesity induced by HFD feeding, displaying smaller fat pads and smaller adipocytes [47]. The genetic deletion of another gelatinase, MMP9 (gelatinase B), however, did not demonstrate a significant change in weight, fat mass, fasting blood glucose and insulin levels after 15 weeks of HFD [48]. As MMP9 is highly expressed by adipose tissue macrophages [49], a further study should be needed to fully define the impact of genetic deletion of MMP9 on adipose inflammation and metabolism. Interestingly, a pharmacological inhibition of MMPs with a relative specificity to MMP2 and MMP9 reduces weight gain and fat pad weights in ob/ob mice [50].

Among MT-MMPs, MMP14 (MT1-MMP) and MMP15 (MT2-MMP) act as major pericellular collagenases [51]. The loss of MMP14 causes severe lipodystrophic phenotype, underscoring its dominant role in adipose tissue development in mice [52]. MMP14 haploinsufficiency confers mice a protection from diet-induced obesity and a genetic variance in human MMP14 gene is associated with obesity and diabetes [36]. While MMP14 is the major regulator of MMP2 activation [53], the gene deletion of both MMP2 and MMP14 causes a synthetic lethality, underscoring the critical biological pathways regulated through the interplay between MMP2 and MMP14 [54]. In humans, MMP15 (MT2-MMP) is down-regulated in white adipose tissues of obese humans [37]. The exact role of MMP15 in regulating adipose tissue size and function is unknown. Unlike MMP14, the gene deletion of MMP15 alone does not cause a significant developmental defect; however, the loss of both MMP14 and -15 causes embryonic lethality due to the defective development of the placenta [55]. As such, the functional interplay of MMP14 with MMP2 and/or MMP15 may play a synergistic role in regulating adipose tissue function as well. The roles played by other MT-MMPs (MMP16, -17, -24, -25) in the regulation of obesity and diabetes are unknown.

Elastin is another major component of adipose ECM [56]. The expression of elastin in adipose tissues was found to be less abundant in obesity [14]. MMP12 (macrophage elastase) is the major MMP that degrades elastin in mice [57]. In HFD (60% fat)-induced obesity, adipose macrophages, particularly CD11c+ resident macrophages (M2-like) express a high level of MMP12 [58,59]. In their study, the loss of MMP12 exacerbated HFD-induced adipose hypertrophy but improved insulin sensitivity [58]. The loss of MMP12 alone, however, did not change elastin content in adipose tissues under either normal or HFD condition [59]. Another group reported that the loss of MMP12 did not exert any significant effects on HFD (42% fat)-induced obesity [60]. It is unclear whether a difference in dietary fat content or genetic background may account for the difference in the reported obesity phenotypes.

Together, these data suggest that MMPs play important but diverse roles in regulating adipose tissue homoeostasis in obesity; however, the exact substrates of each MMP responsible for the regulation of obesity and diabetes phenotypes have not been fully defined. The functional interplays between MMPs, e.g. MMP2 and -14, MMP14 and -15, in the regulation of adipose tissue homoeostasis and metabolism should require further investigation.

3.2. TIMPs

The TIMPs are inhibited by specific endogenous tissue inhibitors of metalloproteinases (TIMPs), which comprise a family of four protease inhibitors: TIMP-1, -2, -3 and -4 [61]. Circulating levels of TIMP-1 and -2 are increased in patients with metabolic syndrome and diabetes [40]. Hypothalamic TIMP-1 expression is regulated by an adipose-derived hormone, leptin, and the gene deletion of TIMP-1 causes increased food intake and obesity in female mice [62]. The overexpression of TIMP-1 in pancreatic β-cells protects...
mice from streptozotocin-induced β-cell death and diabetes [63]. While TIMP-1 mostly inhibits soluble MMPs alone, TIMP-2 can inhibit both soluble and MT-MMPs [51]. The genetic deletion of TIMP-2 in mice exacerbates HFD-induced obesity and diabetes [64]. TIMP-2 gene deletion impairs MMP14 (MT1-MMP)-dependent MMP2 activation [65]; therefore, the phenotype of TIMP-2-null mice might be partly modified by the impaired MMP2 activation. TIMP-3 expression is reduced in the adipose tissue of mouse obesity models [42]. The genetic deletion of TIMP-3 in mice causes hepatic steatosis and adipose tissue inflammation [66], whereas TIMP-3 overexpression in macrophages protects mice from insulin resistance, adipose inflammation, and hepatic steatosis [67].

These data may suggest that increased activities of TIMPs in tissues are protective in metabolic regulation, but in a tissue- and context-dependent manner. While TIMPs are endogenous inhibitors of MMPs that are responsible for degrading excess ECM, it is unclear whether the beneficial effects of increased TIMP activities is solely due to the suppressed activity of MMPs and increased ECM stability or through different target molecules, including ADAM (a disintegrin and metalloproteinase) and ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) [68].

4. ECM receptors in the adipose tissue

4.1. Integrins

Integrins are heterodimeric transmembrane receptors ensuring the communication between ECM and the intracellular environment. In mammals, there are eighteen α and eight β integrin subunits that can be non-covalently assembled into 24 heterodimeric combinations [69]. The specific integrin expression patterns determine which ECM substrate can bind to the cell and further regulate the downstream signalling events. In brief, integrins are classified into several subfamilies including collagen receptors, laminin receptors, Arg-Gly-Asp (RGD) receptors and leucocytes-specific receptors [69]. Collagen and laminin receptor integrins share common β1 subunit and leucocyte-specific receptor integrins share common β2 subunit. It has been shown that integrin β1 is critical in regulating HFD-induced insulin resistance in skeletal muscles [70,71]; however, its role in adipose tissues has not been studied. On the other hand, leucocyte-derived β2 integrin has been associated with HFD-induced obesity and insulin resistance in the adipose tissue. Under a HFD condition, mutated β2-integrin knockin mice display increased neutrophil numbers in white adipose tissues and show significantly increased peripheral insulin resistance [72]. The β2 integrin subfamily is comprised of 4 members, αLβ2 (CD11a/CD18), αMβ2 (CD11b/CD18), αXβ2 (CD11c/CD18), and αDβ2 (CD11d/CD18). CD11b, CD11c and CD11d expression is increased in the adipose tissue and circulating monocytes of obese humans and rodents [73–75]. The majority of macrophages infiltrated in white adipose tissue in obesity co-express CD11b and CD11c [76]. Moreover, CD11b deficient mice are protected from development of HFD-induced insulin resistance through reduction of alternative activation and proliferation of adipose tissue macrophages [77]. CD11c-positive adipose tissue macrophages are identified as markers of insulin resistance in human obesity [78]. These studies are consistent and may suggest a contributing role of β2 integrin expressed by neutrophils and macrophages in diet-induced insulin resistance. Integrin α4 associates with either β1 or β2 subunit to form an integrin that may play a role in cell motility and migration [79]. Although inhibiting α4 integrin function and signalling has been shown to block inflammatory responses associated with mononuclear cell-mediated diseases such as multiple sclerosis and Crohn’s disease [80,81], their role in low-grade chronic inflammatory conditions, such as obesity-induced insulin resistance is not well studied. However, it is shown that mice bearing an P (Y991A) mutation are protected from development of HFD-induced insulin resistance through mediating the trafficking of monocytes into adipose tissues [82].

4.2. CD44

CD44 is a multifunctional cell membrane receptor for ECM components, mainly HA and OPN [83]. CD44 transcripts are subject to alternative splicing, resulting in the expression of CD44 standard isoform (CD44s) and multiple CD44 variants (CD44v) [84]. CD44s is ubiquitously expressed in most tissues, whereas the larger variant isoforms are expressed only in a few epithelial tissues and several cancers [85]. The expression of CD44v in adipose tissues has not been identified and studied. Current studies of CD44 in the adipose tissue in the context of obesity and diabetes have focused on the standard form of CD44. CD44s is associated with type 2 diabetes from expression-based genome-wide association studies [86]. CD44s expression level in the adipose tissue is positively correlated with adipose inflammation and an index of insulin resistance, HOMA-IR in obese individuals and HFD-fed obese mice [86–88]. Serum CD44s levels are positively correlated with insulin resistance and glycemic control in human subjects [86]. HFD-fed CD44 knockout mice remain considerably more insulin sensitive and glucose tolerant than HFD-fed wildtype control mice and exhibit lower blood insulin levels [89]. Treatment of CD44 monoclonal antibody suppresses visceral adipose tissue inflammation and reduces fasting blood glucose levels, weight gain, liver steatosis, and insulin resistance in a HFD-fed mouse model [88]. These of course cannot rule out the potential expression and importance of CD44v in the adipose tissue of obesity and insulin resistance.

4.3. CD36

CD36 also known as fatty acid translocase is an integral membrane protein, which binds many ligands including collagen, THBS, lipoproteins and fatty acids [90]. CD36 facilitates FFA transport into the adipose tissue in humans [91]. HFD-fed mice harbouring CD36 deletion display improved FFA transport and reduced macrophage infiltration in the adipose tissue compared with wild-type mice, with variable effects on HFD-induced whole-body insulin resistance [92–94]. Genetic variation within the CD36 locus is suggested to contribute to metabolic disease via its effect on body adiposity [95]. Gene expression studies indicate that CD36 is significantly upregulated in the mesenteric adipose tissue of diabetic patients [96]. AP5258, a CD36 specific inhibitor significantly increases cell survival of oleic acid-treated mouse and human adipocytes, and partially restores the transcriptional response to oleic acid in the presence of insulin through JNKs (c-Jun N-terminal kinases) pathway [97]. Although most of these studies of CD36 in adipose tissue in obesity and insulin resistance are attributed to its role as a FFA transporter, the role of ECM binding in the process of FFA uptake is potentially significant. This is evidenced by the fact that an ECM ligand, such as THBS induces the dimerization of membrane-bound CD36, which is proposed to play an important role in signal transduction [98].

5. Proposed model for how ECM-receptor interaction is linked to obesity-associated insulin resistance

Numerous studies have demonstrated that the increased deposition of ECM components and the presence and activation of ECM receptor pathways in the adipose tissue are associated with obesity-associated inflammation and insulin resistance. The under-
Tumour biology. Many of the changes in the ECM, ECM modifiers tissue induces adipocyte death is at odds with its proposed role in regulation that mediates processes that regulate adipocyte necro-
sis or apoptosis. This hypothesis is supported by the fact that receptor pathways (e.g. integrins) would trigger downstream gene
dynamics are highlighted in the following section.

Changes of adipose ECM remodelling in comparison to cancer ECM
of adipose ECM provides structural support but regulates cell proliferation and
and the promotion of inflammatory cytokine production and
macrophage infiltration which culminate in insulin resistance. Potential downstream intracellular
signalling partners of each ECM receptor include FAK for integrin receptors [119],
ERM for CD44 receptor [85] and MAPKs for CD36 receptor [122]. ECM: extracellular
matrix; FAK: focal adhesion kinase; ERM: ezrin–radixin–moesin; MAPKs: mitogen-
activated protein kinases; VEGF: vascular endothelial growth factor; ATM: adipose
tissue macrophase.

Lying mechanisms however, are not fully understood. We propose
the following potential downstream pathways of ECM-receptor
signalling that may mediate the process. These include induction
of adipocyte death, inhibition of angiogenesis in adipose tissues
and the promotion of inflammatory cytokine production and
macrophage infiltration (Fig. 2). It is worth noting that these
pathways share analogies to those leading to pulmonary fibrosis,
wound healing and tumour growth [7–9]. Similarities and differ-
ences of adipose ECM remodelling in comparison to cancer ECM
dynamics are highlighted in the following section.

5.1. Induction of adipocyte death

The ECM in the adipose tissue surrounding adipocytes not only
provides structural support but regulates cell proliferation and
death. Adipocyte death is increased progressively during the develop-
ment of obesity with a frequency of 80% death rate in mice after
16 weeks of HFD feeding, coincident with widespread deposition of
collagen [99]. It is hypothesized that excessive deposition of adi-
pose ECM components physically constraints the expansion of adi-
pocytes and causes adipocyte death [3]. We hypothesize that ECM
receptor pathways (e.g. integrins) would trigger downstream gene
regulation that mediates processes that regulate adipocyte necro-
sis or apoptosis. This hypothesis is supported by the fact that ob/
ob mice that lack collagen VI (Col6a1) display a reduced necrotic
cell death accompanied by enlarged adipocytes and improved sys-
temic insulin resistance [3]. Reduced adipocyte death in these mice
is associated with a significant reduction of spliced form of Xbp1, a
marker for endoplasmic reticulum stress which causes cells to
undergo apoptosis through activation of CHOP and JNK [3]. Adipo-
cyte death may cause adipocyte inflammation and insulin resistance
because necrotic adipocytes become a phagocytic stimulus that
attracts macrophages [99].

The concept that augmented ECM receptor signalling in adipose
tissue induces adipocyte death is at odds with its proposed role in
tumour biology. Many of the changes in the ECM, ECM modifiers
and ECM receptors in expanding adipocytes occur during tumour
cell growth including increased deposition of various collagens
(e.g. I, II, III, V and IX) [9], increased levels of MMPs (e.g. MMP1,
2, 3, 7, 9, 12, 14, 21, 24, 25) and TIMPs (e.g. TIMP 1, 2, 3) [100],
and increased ECM receptor signalling (e.g. hyaluronan and CD44
signalling) [101]. However, it is shown that this ECM remodelling
in cancer facilitates tumour cell growth, invasion, and metastasis
[9,101]. In cancer, activated integrin signalling upon ECM binding
initiates pro-survival signals through increased nuclear factor-κB
(NF-κB) or PI3K-AKT activity, decreased p53 activation and
increased expression of the pro-survival molecules BCL-2 and FLIP
[102]. Although disparate from our proposal that activated ECM
signalling in the adipose tissue would cause adipocyte death and
associated inflammatory response (Fig. 2), research in cancers
would provide insight to our understanding of adipose tissue biol-
ygy in obesity and insulin resistance.

5.2. Inhibition of angiogenesis in the adipose tissue

White adipose tissues are highly vascularised and expansion of
the adipose tissue is necessarily accompanied by angiogenesis. It is
hypothesized that excessive deposition of ECM limits the angiogenic
capacity of white adipose tissue in obesity. It is shown that the
hypoxic response in the adipose tissue of ob/ob mice is para-
doxically associated with decreased gene expression of vascular
endothelial growth factor A (VEGFA), vascular endothelial cell
markers, and decreased vessel density [103]. Overexpression of
dominant active hypoxia inducible factor 1 (HIF1) fail to increase
VEGFA expression but induces the gene expression causal for tissue
fibrosis [103]. Likewise, overexpression of VEGFα leads to increased
adipose vascularity and reduced tissue hypoxia [104]. These find-
ings are in contrast to what is found in cancers wherein hypoxia
stimulates angiogenesis via HIF1α/VEGFA pathway [105], and sug-
gest the presence of an obesity-specific relationship between
hypoxia, fibrosis, and angiogenesis. Moreover, increased collagen
V inhibits endothelial budding, suggesting its inhibitory role in
angiogenesis [14]. As adipose tissue fibrosis inhibits the angiogenic
capacity of the tissue, it is reasonable to propose that the sup-
pressed expression of genes necessary for adipose angiogenesis
(e.g. VEGFA) should be mediated by the activation of ECM receptor
pathways by excess ECM deposition. We have previously showed
that genetic deletion of integrin α2β1, one of the collagen binding
receptors is associated with increased vascularization in muscle of
HFD-induced obese mice [70]. The angiogenic capacity of white
adipose tissues is positively associated with glucose homeostasis.
Mice with adipose-specific deletion of VEGFA display exacerbated
insulin and glucose tolerance on a HFD; in contrast, induction of
VEGFA expression in the adipose tissue reverses glucose intoler-
ance in HFD-induced obese mice [104]. It is hypothesized that
reduced angiogenesis in white adipose tissues leads to reduced
exchange of insulin and other hormones, cytokines and adipokines
from blood to fat, leading to insulin resistance. Although not specif-
ically shown in the adipose tissue, we have successfully demon-
strated such a relationship in an insulin-sensitive metabolic
tissue, i.e., the skeletal muscle. Our previous studies have shown
that defects in recruitment of muscle capillaries contribute to the
development of muscle insulin resistance [106,107]; whereas
improved muscle insulin resistance is associated with increased
muscle capillary density [26,70]. Further studies are needed to
investigate the metabolic impacts of integrin-dependent regula-
tion of angiogenesis in adipose tissues.

Transcriptional co-activators PGC-1α and PGC-1β have been
shown to induce VEGF expression and angiogenesis in muscles
[108–111]. As these two PGC-1 isoforms are operative in white
adipose tissues, it is possible that inhibition of angiogenesis in obese,
expanding adipocytes is due to decreased expression and function
of PGC-1α and PGC-1β. This hypothesis is highly supported by the fact that the expression of both PGC-1α and PGC-1β is decreased in obesity and mice lacking PGC-1α specifically in the adipose tissue develops exacerbated insulin resistance on a HFD [112,113]. However, the role of ECM receptor pathways in the regulation of PGC-1 isoform expression is still unknown and may require further investigations.

Angiogenesis is another shared pathway which is proven to be important in both obesity and cancer. Anti-angiogenesis therapy for cancers has been proposed for more than 40 years; however, in both preclinical and clinical settings, the arise of resistance mechanisms limits the long-term benefit of anti-angiogenesis therapy [114]. In obesity, the therapeutic angiogenesis for treatment of obesity and metabolic diseases remains a paradoxically disputed issue [115]. Controversial results exist. For example, early studies using genetic and HFD-induced obese mice show that treatment of generic angiogenesis inhibitors including TNP-470 and angiotatin, suppresses adipose angiogenesis and prevents obesity in mice [116,117]. In contrast, systemic anti-VEGF-A treatment to HFD-fed mice induced weight gain and caused exacerbated systemic insulin resistance [118]. Targeting angiogenesis in white adipose tissues for treating obesity and insulin resistance remains controversial and has been well reviewed previously [115].

5.3. Induction of adipose tissue macrophage infiltration and inflammation

We propose that activation of ECM binding to ECM receptor mediates intracellular signalling to regulate expression of genes that mediate inflammation and adipose tissue macrophage infiltration. Focal adhesion kinase (FAK), a ubiquitously expressed tyrosine kinase, which is essential for development and cellular proliferation, transmits extracellular signals via integrin signalling. Adipocyte-specific deletion of FAK increases adipose tissue inflammation shown by increased macrophage infiltration and adipocyte apoptosis [119]. These results suggest that FAK may be essential for gene expression for adipose tissue remodelling and inflammation. Chronic treatment of human recombinant pegylated hyaluronidase decreases adipose tissue ECM HA and decreases adipocyte size and the gene expression of pro-inflammatory markers (e.g. TNFα) in adipose tissue of HFD-fed mice [26]. Genetic deletion of the main HA receptor CD44 consistently decreases adipose tissue inflammation in mice following a HFD [89]. These results suggest that the activation of HA-CD44 pathway regulates macrophage infiltration and inflammation in the adipose tissue of HFD-fed mice. It has been previously shown that the genetic deletion of β2 integrin CD11b protects mice from development of HFD-induced insulin resistance by suppressing the alternative activation and the proliferation of adipose tissue macrophages [77].

6. Concluding remarks

It is recently ascertained that fibrosis, excess deposition of ECM components, in metabolically active, insulin-sensitive tissues, including the skeletal muscle, adipose tissue and liver has damaging impact on glucose homeostasis [6,120,121]. Obesogenic ECM remodelling of white adipose tissues is closely linked with the increased levels of circulating ECM proteins and ECM-derived peptides in parallel with increased levels of adipose-derived cytokines. These white adipose tissue-derived ECM or ECM-related molecules may exert metabolically deleterious effects on metabolic crosstalk between the adipose tissue, liver, and skeletal muscles (Fig. 3). Despite a recent implication of ECM-receptor pathway in determining glucose homeostasis in the skeletal muscle and liver [6], its role in the adipose tissue has not been fully defined. We postulate that the ECM receptor pathway of adipocytes as well as other cell types found in adipose tissues, i.e. inflammatory monocytes and macrophages and vascular endothelial cells are important in transducing intracellular signalling of adipocyte death, angiogenesis, and the infiltration of inflammatory cells, which culminate in insulin resistance. Tissue-specific mouse models that lack a key ECM, ECM modifier, ECM receptor, or intracellular mediator, will help us decipher the importance of the ECM receptor pathway and its regulators in determining metabolic tissue remodelling, function and glucose homeostasis.

We propose the potential of developing therapeutic strategies that target ECM matrix of metabolically active tissues, including the liver, skeletal muscle and the adipose tissue. Current anti-fibrotic drugs being tested in clinical settings have been focused on cancers (e.g. PEGPH20), heart failure (e.g. FT011) and glaucoma...
surgery (e.g. CLT-28643). The effectiveness of their use in obesity, insulin resistance and type 2 diabetes is unknown and may warrant further investigation.

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