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The impact of adipokines on vascular networks in adipose tissue

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ABSTRACT

Adipose tissue (AT) is a highly active and plastic endocrine organ. It secretes numerous soluble molecules known as adipokines, which act locally to AT control the remodel and homeostasis or exert pleiotropic functions in different peripheral organs. Aberrant production or loss of certain adipokines contributes to AT dysfunction associated with metabolic disorders, including obesity. The AT plasticity is strictly related to tissue vascularization. Angiogenesis supports the AT expansion, while regression of blood vessels is associated with AT hypoxia, which in turn mediates tissue inflammation, fibrosis and metabolic dysfunction. Several adipokines can regulate endothelial cell functions and are endowed with either pro- or anti-angiogenic properties. Here we address the role of adipokines in the regulation of angiogenesis. A better understanding of the link between adipokines and angiogenesis will open the way for novel therapeutic approaches to treat obesity and metabolic diseases.

1. Introduction

Obesity, defined as a body mass index (BMI) ≥ 30 kg/m^2 is a chronic, multifactorial disease associated with various life-threatening chronic diseases (https://www.who.int). Thus, prevention and treatment of obesity are key challenges, which are directly linked with the biology and physiology of adipose tissue (AT) [1]. The AT is highly dynamic and comprises multiple cells, including adipocytes, mesenchymal and endothelial cells (ECs), fibroblasts, and immune cells surrounded by extracellular matrix (ECM) [2]. Obesity induces AT expansion and remodeling, characterized by adipocyte hypertrophy and hyperplasia, accumulation of immune cells, hypoxia, and EC activation. This dysfunction is accompanied by lesser vascular density and the consequent development of obesity related metabolic diseases [3,4].

Recently, an endocrine role has been attributed to AT in addition to its ability to regulate energy expenditure. AT secretes several nervous and endocrine factors identified as adipokines [5] which sustain a cross-communication between numerous organs within the body. The production of adipokines is altered by AT hypertrophy and hyperplasia in obese patients, supporting detrimental metabolic alterations leading to insulin resistance, dyslipidemia, and an increased risk of cardiovascular diseases [6].

The expansion and remodeling of AT is regulated by the vascular system, which maintains cellular homeostasis throughout the body via a complex network of capillaries, arteries, and veins [7]. In this narrative review, we describe the available evidence regarding the effects of adipokines on the angiogenic process leading to AT remodeling. We also discuss the cross-communication between AT and angiogenesis and how anti- and pro-angiogenic approaches could be employed to impair the progression of obesity, as well as whether AT engineering can improve AT dysfunction in patients with metabolic disorders.

2. The adipose organ

The AT is an organ specialized in energy storage, endocrine regulation of energy, homeostasis, and thermoregulation. It consists of mature

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adipocytes surrounded by a stromal vascular cell fraction (SVF) containing pre-adipocytes, macrophages, smooth muscle cells, immune cells, vessels, and a rich innervation of both sensory and sympathetic fibers. The SVF controls the dynamics of AT development, homeostasis, and inflammation [8]. Extracellular matrix (ECM) provides mechanical support and adsorbs cytokines and growth factors, thus regulating physiological/pathological processes within AT [9]. In mammals, two major types of AT have been observed: white AT (WAT) and brown AT (BAT) [10]. WAT composes around 20–25 % of the total body weight in humans [11]. WAT stores energy in the form of triacylglycerols that are hydrolyzed, releasing fatty acids when the organism needs fuel [12]. White adipocytes have a round shape, a large diameter and are characterized by the presence of a big lipid droplet which pushes all other components close to the membrane. Few mitochondria can be observed next to the nucleus and the ribosomes [11].

In humans, the WAT exists in different depots, characterized by typical patterns of gene expression and, thus, by distinct functions [13]. Indeed, each fat depot differs in the size of adipocytes, ECM composition and mechanical properties [14]. The BAT is mainly composed of brown adipocytes that derive from $Myf5^{+}$ precursors and are characterized by many small lipid droplets and a high number of mitochondria, responsible for their brown color [15]. Their nucleus occupies a central position, and the endoplasmic reticulum is not highly developed. BAT regulates thermogenesis, a function that explains the multilocular arrangement of lipids that amplify exponentially the number of fatty acids that can enter the beta-oxidation [16]. Upon sympathetic activation, brown adipocytes release chemical energy as heat. Consistent with this, in brown adipocytes there is a high expression of thermogenin (uncoupling protein 1; UCP1). UCP1 is a fatty acid anion/H^{+} symporter in the inner membrane of mitochondria. It dissipates the respiration proton gradient by uncoupling cellular respiration and mitochondrial ATP synthesis, thus inducing thermogenesis [17].

Several depots of active BAT have been identified in adult humans [18,19], including shoulder blades, around the kidneys, neck, supraclavicular area, and along the spinal cord [20–22]. Importantly, the localization of BAT and WAT is not exclusive; for example, subcutaneous and visceral depots contain both tissues. Due to its high metabolic activity, the BAT should be considered an organ of pharmaceutical and physiological importance in the adult [23,24].

Recently, “beige” or “brite” adipocytes have been identified [25] at anatomical sites that correspond to WAT after thermal stimulation [26,27]. These cells have characteristics of both brown and white adipocytes. In the basal state, they display the morphology of white adipocytes while after stimulation, they acquire intermediate morphology with multilocular lipid droplets, higher number of mitochondria, and express BAT markers, including UCP1 [10,27,28]. In addition, they express typical beige markers, such as CD137, Tbx1, and Cited-1 [29]. Different developmental lineages have been suggested for beige adipocytes: the transdifferentiation of mature white adipocytes [30,31] and the maturation of brown or white preadipocytes that are both present in WAT [32,33]. All these processes could contribute to beige adipocyte development, depending on tissue depot and stimuli [34,35].

3. Angiogenesis in AT

Contrarily to other organs, the AT can also expand in adulthood, up to comprising more than 40 % of the total body composition in obese patients [36]. This high plasticity is paralleled by a coordinated vascular network growth, which provides AT with oxygen and nutrients and drains waste products [4]. The continuous growth, regression, and remodeling of blood vessels is regulated by metabolites and growth factors known as adipokines, which are secreted by adipocytes [37].

Angiogenesis is a multistep process, regulated by pro- and anti-angiogenic factors. This process can be triggered in response to proliferating and enlarging adipocytes and/or precedes adipocyte proliferation and enlargement [38], but, of course, it is essential in modulating AT physiopathology [39,40]. Adipocytes and other stromal cell types release pro- or anti- angiogenic factors in the microenvironment to maintain vascular homeostasis and induce vascular increase or regression [37]. In expanding WAT, the switch toward an angiogenic phenotype facilitates energy deposition and vascular density [41]. Instead, in metabolically active BAT, the same angiogenic phenotype may facilitate energy consumption [42]. Also, WAT transition to brite phenotype is associated with an angiogenic switch with a consequent increase in vascular density. Moreover, blood vessels provide a protective niche for adipocyte progenitors that can differentiate into pre-adipocytes and adipocytes [42,43].

Importantly, angiogenesis can be altered in pathological conditions like obesity, metabolic syndrome, cancers and cardiovascular pathologies [44], characterized by abnormal expression of angiogenic factors and/or by other angiogenic-related conditions including hypoxia, oxidative stress, hormone imbalance, and hyperglycemia [45].

4. Angiogenic modulators released by adipose tissue

Adipokines, which include hormones, free fatty acids, growth factors, and cytokines, act either locally or systemically to regulate a wide range of physiological and pathological processes such as immune-system modulation, inflammation, cell differentiation, and angiogenesis [1]. Novel pro/anti-angiogenic adipokines are continuously identified and characterized. AT dysfunction leads to changes in cellular composition, inability to store the surplus lipids, alteration of insulin sensitivity, and in the secretion of pro-inflammatory and diabetogenic adipokines and cytokines [46,47].

Surprisingly, dysfunctional AT in patients with obesity and metabolic syndrome often displays increased expression of anti-angiogenic factors. This suggests that the high expression of factors that restrict blood vessel growth is meant to avoid abnormal vessel outgrowth when an AT becomes stabilized. In the next sections we discuss the role of main adipokines known to regulate EC functions, and potentially involved in the remodeling of AT vasculature. Also, we address the effects of metalloprotease enzymes that indirectly modulate AT angiogenesis (Fig. 1).

4.1. ECM remodeling factors

The ECM of AT is continuously remodeled to accommodate changes in adipocyte size and AT composition during tissue turnover [48]. Proteases and inhibitors of such proteases are locally produced to guide AT remodeling. Among these, metalloproteinases (MMPs) are pivotal enzymes produced by mature adipocytes (especially MMP-12) and by the SVF in a depot-dependent manner [48]. Metalloproteases are a protease family involved in the turnover of connective tissue during morphogenesis, development, wound healing, reproduction, and neovascularization. Also, the activity of MMPs contributes to allow the release of basement membrane components or the activation of latent growth factors [49,50]. MMPs promote angiogenesis by regulating EC proliferation, migration, and attachment to the ECM, either directly or by releasing growth factors sequestered in the ECM [51,52]. The proteolytic activity of MMPs is controlled by a family of proteins called tissue inhibitors of metalloproteinases (TIMPs). The imbalance of MMPs vs TIMPs is implicated in many pathological processes and may contribute to altered angiogenesis and AT dysfunction in metabolic disorders and obesity [53].

MMPs are modulated during adipogenic differentiation of 3T3-L1 cells in vitro. In addition, pro-inflammatory adipokines upregulate MMP levels during obesity, with a shift toward increased matrix degradation [54]. Accordingly, MMP pharmacological inhibition leads to a collagen-rich matrix cap around the treated tissue thus restraining AT development in mice [55]. Several studies confirm the role of MMP inhibitors on AT homeostasis in vivo. The administration of specific or broad-spectrum MMP inhibitors reduces the subcutaneous or gonadal

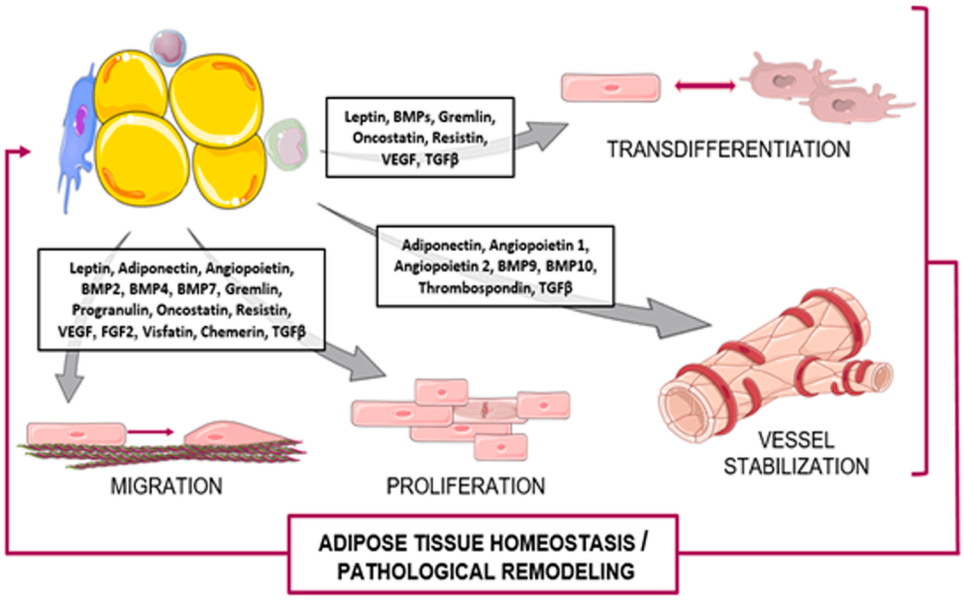

Fig. 1. Differential roles of adipokines on endothelial cells in the remodeling of adipose tissue vascular network.

AT deposits. In this case, MMP inhibitors do not affect the number of adipocytes, but increase significantly the amount of collagen in treated animals. Importantly, MMP inhibition results in a higher blood vessel density in AT [56,57].

4.2. Leptin

Leptin is a 16 kDa protein encoded by obese (Ob) gene [58,59]. It is mainly secreted by WAT and, at lower levels, by other tissues such as muscle, stomach, and mammary gland. Leptin is an endocrine hormone with multiple properties including the regulation of appetite. For this reason, leptin is also known as the "satiety hormone" [60]. It controls energy expenditure, body weight, thermogenesis, fertility, and immune functions [59] and its serum levels positively correspond with the energy stored in the fat mass [61,62]. A reduction of circulating leptin follows food restriction. Leptin expression is associated with hypertension, atherosclerosis, myocardial infarction, and stroke [63]. The functions of leptin are mediated by the leptin or obesity receptor (Ob-R), a single membrane-spanning receptor belonging to the class I cytokine receptor family, which is mainly expressed in the hypothalamus and immune cells The JAK/STAT signaling pathway modulates the intracellular cascades activated by leptin in target cells. Loss-of-function mutations in the leptin or Ob-R genes result in severe, early-onset obesity and are associated with altered hematopoiesis, immunity, blood pressure, and angiogenesis [64]. Leptin is a pro-atherogenic, pro-thrombotic molecule and controls vasodilation. In ECs, leptin promotes a pro-inflammatory response, the expression of endothelial nitric oxide synthase (eNOS), and the production of reactive oxygen species (ROS), leading to EC dysfunction [65], proliferation, and survival [65,66]. In ECs, by binding Ob-R, leptin activates the p38 (MAPK)/Akt/-COX-2 and Wnt axes [67,68]. Moreover, leptin supports angiogenesis in several in vivo models [66,69], upregulating MMP-2/9 and pro-angiogenic factors like fibroblast growth factor-2 (FGF-2), vascular endothelial growth factor A (VEGF-A) and its receptor VEGFR-1 [70]. Also, leptin induces the mobilization of vascular progenitor cells from the bone marrow, through a Ob-R/NOX2/MMP-9 mechanism [71] and boosts up the angiogenic potential of circulating angiogenic cells through a Ob-R/Src/alphavbeta5 cross talk [72]. Under other experimental conditions, leptin inhibits EC inflammation, and the endothelial-to-mesenchymal transition (EndMT), thus exerting protective effects on vessel endothelium.

The observation that leptin regulates angiogenesis opens the way to using anti-leptin approaches to treat angiogenic-dependent pathologies. Preclinical studies confirm the effects of therapeutic strategies targeting leptin, such as leptin mutants/antagonists, or neutralizing antibodies in several pathological conditions, including cancers. However, a deeper characterization of leptin antagonists is needed to ameliorate the major drawback of most anti-leptin strategies, including their transport to the hypothalamic nuclei [73]. The fine elucidation of endothelial-specific molecular mechanisms involved in leptin response could contribute to the design of pharmacological approaches to target leptin-driven pro-angiogenic effects without the unwanted associated weight-gain.

4.3. Angiogenin

Angiogenin was originally identified in the culture medium of human colon adenocarcinoma cells [74]. As the name suggests, angiogenin is a potent inducer of angiogenesis. Upon receptor binding on the EC surface, angiogenin is internalized and translocated to the nucleus, where it regulates the expression of several pro-angiogenic genes, including MMPs [75]. Its ribonucleolytic activity makes angiogenin unique among the angiogenic factors. The inhibition of its enzymatic activity or the prevention of its internalization pathway ameliorate the angiogenin pro-angiogenic activity [76]. Several inhibitors of angiogenin including the anti-human monoclonal antibody, small chemical compounds, neomycin and neamine, siRNA, antisense, soluble binding proteins, and enzymatic inhibitors have been developed and exert anti-angiogenic/anti-tumor effects in various animal models [77,78].

Within AT, angiogenin is expressed by both adipocytes and non-adipocyte stromal cells. It is upregulated in cultured AT explants by PPAR agonists [79] and can be used in regenerative fat grafts to improve tissue vascularization [80]. Remarkably, angiogenin levels have been positively correlated with BMI [81]. The reduction of angiogenin expression in the elderly [82] is associated with an impaired angiogenic potential of adipose-derived mesenchymal stromal cells and with coronary artery disease [83] This data suggests a role of angiogenin in the regulation of AT expansion, further confirming the pivotal role of angiogenesis during AT remodeling in obese patients. On these bases, inhibitors of angiogenin (i.e. monoclonal antibodies, small chemical compounds, neamine and neomycin, enzymatic inhibitors, receptor antagonists [77,84–86] may have the potential to block angiogenesis in AT, thus restraining its expansion during obesity.

4.4. Bone morphogenetic proteins (BMPs)

The bone morphogenetic proteins (BMPs) are small secreted proteins belonging to the transforming growth factor-beta (TGF-β) superfamily [87]. Originally studied as inducers of bone formation, they are now widely known for their involvement in various morphogenetic and differentiative processes during development, including the development of AT [88–91]. BMPs are produced by human and mouse adipocytes. In particular, BMP4 and BMP6 control white and brown adipogenesis, respectively. BMPs activate canonical SMAD protein signaling through activation of their cognate serine-threonine kinase receptors. In addition, BMP can also signal through the mitogen-activated protein kinase (MAPK) pathway [92]. The acknowledged role of BMPs in vascular homeostasis derives from the strong connection existing between obesity and cardiovascular diseases. During the angiogenic process, BMPs intervene in both EC sprouting and vessel maturation steps (reviewed in [92]). BMP2, BMP4, and BMP6 have been clearly shown to trigger the pro-angiogenic effect on ECs through the differential activation of their BMP type I receptors ALK3 and ALK2 [93,94]. BMP2 and BMP6 coordinate tip vs stalk identity of ECs during sprouting angiogenesis. BMP4 stimulates the formation of micro-blood vessels, which serve as stem cell niches during expanding WAT [95]. Meanwhile, BMP4, recruits and commits stem cells to differentiate into preadipocytes. These processes are part of the remodeling of white adipocytes into beige as demonstrated by the expression of Tbx1, Tbx15, Hoxc9, PGC1α, and PRDM16 [88].

Mechanistically, BMP4 elicits a pro-angiogenic responses in ECs through a src-dependent transactivation of VEGFR-2 [96]. BMP7 induces the expansion of BAT, increases the expression of UCP1, the activity of the hormone-sensitive lipase, and energy expenditure [97]. In other words BMP7 modulates the “browning” of WAT. On the contrary, BMP9 and BMP10 mostly have homeostatic effects on ECs, being involved in the regulation of vessel maintenance and remodeling [92, 98]. BMP7 downregulates and BMP9 upregulates the EndMT process respectively [99,100]. Considering the multiple roles of BMPs in AT, genetic variations, small molecule inhibitors of BMPs, including dorsomorphin and its derivatives, should be considered to influence the plasticity, the systemic metabolic phenotypes, and the vascularization of AT [101].

4.5. Gremlin-1

The activity of BMPs is regulated by extracellular antagonists that sequester BMPs in inactive complexes [102,103]. Among these, gremlin-1 by binding BMP2/4/7 regulates organogenesis and cancer [104–106]. More recently, gremlin-1 was recognized as an adipokine produced by the human AT [107–109]. It is downregulated during adipogenesis [110] and limits the BMP2/4-dependent brown adipogenesis [109]. Gremlin-1 is more expressed in omental fat than in its subcutaneous counterpart [111]. Local and circulating gremlin-1 is increased in obesity (in human AT from bariatric surgery) and in metabolic diseases, such as type 2 diabetes and non-alcoholic fatty liver disease [107]. Remarkably, gremlin-1 antagonizes insulin action in adipose, skeletal muscle, and liver cells, suggesting a pivotal and detrimental endocrine function of gremlin-1 *in vivo* during obesity [107]. Finally, gremlin-1 levels are normalized by physical exercise, which correlates with reduced cardio-metabolic risk in obese patients [112]. Together, these data indicate a possible role of gremlin-1 as a biomarker and therapeutic target in metabolic disorders.

Gremlin-1 exerts pro-inflammatory and angiogenic responses in ECs both *in vitro* and *in vivo* [113,114]. The pro-angiogenic activity of gremlin-1 is mediated by the interaction with both low- and high-affinity to heparan sulfate proteoglycans and VEGFR2 receptors, respectively [103,115,116]. Remarkably, gremlin-1 induces EndMT in human pulmonary artery endothelial cells, confirming its involvement in endothelial dysfunction [117]. Also, inhibitors of VEGFR2 block gremlin-1-driven angiogenesis and fibrosis in kidney disease [115,118]. These findings should stimulate future research on the role of gremlin-1 in AT angiogenesis, which remains largely unexplored.

4.6. Progranulin

Progranulin (PGRN), also known as granulin (GRN)-epithelin precursor, is a secreted glycoprotein which can be fragmented by some matrix metalloproteinases (MMPs) into small homologous subunits, granulins/epithelins [119]. PGRN is a pluripotent growth factor that promotes cell proliferation and tumorigenesis [120]. PGRN is an adipokine and its overexpression is linked to high fat diet (HFD)-induced adipocyte hypertrophy, obesity, insulin resistance, and liver disease [121,122]. The level of PGRN is higher in obese and diabetic patients and correlates with lipodystrophy syndrome [122–124]. In vivo evidence suggests a sexual dimorphism for PGRN, as female mice exhibit higher PGRN expression than males both in subcutaneous and epididymal AT [123]. Taken together, the evidence indicates that PGRN is a promising target for treating HFD-induced obesity [125,126]. However, it is important to note that AT is not the main source of PGRN in obesity [127].

PGRN is associated with systemic inflammatory markers like C-reactive protein and with AT macrophage infiltration [123]. A recent study showed that PGRN is an inducible protein in response to hypoxia [128]. Accordingly, PGRN is a pro-angiogenic factor for blood and lymphatic vessels under physiological and pathological conditions [128–130]. It has been found to bind to Ephrin type A receptor 2 receptor with high affinity, prolonging receptor activation and the downstream stimulation of MAPK and Akt, and promotion of capillary morphogenesis [131]. In contrast, its interaction with perlecan may inhibit its function [132]. Based on these findings, the regulation of PGRN expression is of high interest in obesity and metabolic research.

4.7. Oncostatin M

Oncostatin M (OSM) is a pleiotropic cytokine produced by several tissues, including AT [133]. Within AT, OSM is not expressed in adipocytes but, instead, is produced by the SVF compartment. Adipocytes are responsive to OSM as they express the OSM receptor (OSMr), a heterodimeric complex formed by the OSM receptor beta and gp130 monomers. OSM regulates AT metabolic homeostasis, as OSM and OSMr are highly induced in the AT of diabetic and obese patients [134] while loss of OSM leads to insulin resistance and AT inflammation in a mouse model [135]. OSM induces EC activation *in vitro,* paralleled by an increase in the expression of the pro-angiogenic molecule FGF-2 [136]. OSM is active also in *in vivo* models [137] suggesting its role in pathological angiogenesis in different contexts, like after myocardial infarction and cancers [133,137]. Moreover, OSM induces the expression of EndMT markers [138], of VEGF, cyclooxygenase-2 (COX2), urokinase-type plasminogen activator (uPA), and angiopoietin 2 (ANG-2) [139], indicating that OSM contributes to the vascularization of growing AT [140]. Inhibition of OSM signaling via anti-receptor antibodies or genetic deletion improves the outcome of heart failure [141], while the potential role of these approaches in AT angiogenesis remains unclear.

4.8. Resistin

Resistin is an adipokine secreted by adipocytes and monocytes, implicated in inflammatory processes including atherosclerosis, non-alcoholic fatty liver disease, and malignancies [142]. In human serum, the physiological concentration of resistin is in a range of 7–22 ng/mL, and higher circulatory levels correlate with autoimmune disorders, as well as metabolic disorders [143–145]. The high levels of resistin in obese patients suggest a non-redundant role in energy homeostasis and AT dysfunction [146,147]. Indeed, high concentration of resistin is often

associated with chronic low-grade sub-clinical inflammation accompanied with obesity, which involves macrophage infiltration in the AT. In mice, resistin is a late marker of adipocyte differentiation and its accumulation is necessary for adipogenesis [148]. By binding the adenylyl cyclase-associated protein 1 (CAP1), resistin impairs insulin signaling and oxidative stress response via MAPK pathway [149].

Most of the available literature on the pro-angiogenic role of resistin has focused on cancerous contexts where it often promotes the expression of VEGF [142,150]. Despite the presence of CAP1 and TLR4 receptors on ECs, resistin's mechanism of action remains to be elucidated [151–153]. If this mechanism is elucidated, resistin may become a prognostic biomarker linking obesity, inflammation, and angiogenesis in dysfunctional AT.

4.9. Vascular endothelial growth factors (VEGFs)

Vascular endothelial growth factor (VEGF) is a family of master regulators of blood vessel growth in various physiological and pathological contexts. VEGF family comprises seven members: VEGF-A to -F and PlGF [154]. VEGF expression is influenced by a number of factors including hypoxia, insulin, growth factors, and several cytokines.

VEGF-A promotes sprouting angiogenesis by inducing vascular permeability, EC migration and proliferation, as well as vessel maturation, in both *in vitro* and *in vivo* angiogenesis models. Accordingly, loss of VEGF-A is embryonically lethal due to severe defects in vascular development. The activity of VEGFs is mediated by three transmembrane tyrosine kinase receptors (VEGFR-1, −2, −3). VEGFR-3 is mainly expressed in lymphatic vessels, VEGFR2 is the main pro-angiogenic receptor, while VEGFR-1 sequesters VEGFs, thus, limiting the activation of VEGFR-2 [155]. In AT, VEGF is produced by mature adipocytes and the SVF [156] where it regulates adipogenesis and angiogenesis [38]. VEGF overexpression in mouse AT increases tissue vascularization and improves insulin sensitivity and glucose tolerance, protecting mice from diet-induced obesity [157]. Accordingly, AT-specific loss of VEGF impairs AT angiogenesis and promotes AT hypoxia, inflammation, and apoptosis in a mouse model [158]. Moreover, inhibition of VEGFR-2 restrains diet-induced AT expansion by decreasing angiogenesis [159]. Finally, genetic ablation or pharmacological inhibition of VEGFR-1 increases angiogenesis and browning in AT, protecting mice from diet-induced obesity. These results confirm the role of VEGFR-1 as a decoy receptor sequestering VEGF from binding pro-angiogenic VEGFR-2 [160]. Together these findings suggest that the role of VEGF in AT may be beneficial, limiting AT dysfunction and obesity. This opens a path for future anti-angiogenic approaches to prevent AT expansion. Numerous inhibitors of the VEGF/VEGFR-2 axis are used in clinics to treat tumors or ocular diseases (i.e., bevacizumab or tyrosine kinase inhibitors). Preclinical studies have suggested that targeting this axis may improve obesity and metabolic diseases [161]. However, future clinical trials should assess the potential of these drugs in the treatment of AT angiogenesis and remodeling [161].

4.10. Fibroblast growth factors (FGFs)

Fibroblast growth factors are multifunctional secreted growth factors expressed by many cell types. They regulate a plethora of physiological and pathological processes. Among 22 members of the FGF family, FGF-1, FGF-10, and FGF-21 have been recognized as AT-derived adipokines. In light of this role, FGF-1 (regulated by PPARγ) and FGF-10 are essential modulators of white adipogenesis, while FGF-21 activates BAT and promotes the accumulation of brown adipocytes within BAT during cold-exposure. FGF-1 loss leads to aberrant AT expansion in mice fed with HFD [162]. Also, FGF-21 protects AT from acquiring a dysfunctional state during HFD as demonstrated by resistance to diet-induced obesity of FGF-21 transgenic mice [163]. FGF-10, instead, is a paracrine stimulus which activates PPARγ expression and adipogenesis in pre-adipocytes [164]. FGFs are key regulators of angiogenesis [165]. Among FGF adipokines, FGF-21 has been recently classified as a pro-angiogenic stimulus able to induce the pro-angiogenic activation of ECs [166–168], while the angiogenic potential of FGF-1 and FGF-10 needs to be elucidated to reveal whether they could contribute to angiogenesis during AT remodeling. Inhibitors of the FGF/FGFR system are available and widely used in preclinical and clinical studies [168–170]. Once the role of FGFs is clear, these drugs could be validated for their effects on FGF-driven AT vascular remodeling.

4.11. Visfatin

Visfatin/extracellular-nicotinamide-phosphoribosyltranferase-(eNampt) is a multifaceted adipokine produced preferentially by visceral depots and exerts paracrine pro-adipogenic functions increasing AT mass [170]. Visfatin expression increases in parallel with obesity [171], thus it is not surprising that its plasmatic levels correlate with intra-abdominal fat mass. Also, visfatin may promote insulin resistance in peripheral organs [172]. Visfatin promotes EC proliferation, migration, and sprouting by activating classical ERK1/2 signaling pathway and induces the expression of VEGF and MMPs [173–176]. *In vivo*, visfatin promotes vascular dysfunction and inflammation via TLR4 receptor, the activation of the nod-like-receptor-protein-3 (NLRP3) inflammasome complex, and the release of IL-1β, the final mediator of EC damage. Accordingly, treatment with MCC 950 (NLRP3-inflammasome inhibitor), or anakinra (interleukin(IL)− 1-receptor antagonist) reduces the release of IL-1β and the vessel dysfunction [175]. Thus, those targets may become therapeutic strategies for attenuating the adipokine-mediated vascular dysfunction associated with obesity and/or type-2-diabetes. In the future, the molecular basis of visfatin activity on EC should be explored in more detail to better assess its potential role as a therapeutic target for the treatment of AT-related disorders.

4.12. Chemerin

Chemerin is a multifunctional adipokine, expressed both by WAT and BAT, that modulates adipogenesis, inflammation, and energy metabolism [177,178]. Its plasmatic levels correlate with the BMI [179]. *In vitro*, chemerin is overexpressed in differentiated adipocytes compared to pre-adipocytes and promotes the expression of VEGF [180]. Chemerin may contribute to browning of adipocytes, as high levels of chemerin in the BAT of ob/ob mice is associated with BAT "whitening" [178].

Chemerin induces a pro-inflammatory phenotype in ECs [181] *in vitro* and promotes neo-vessel formation in murine models [182,183]. However, a recent study showed opposite results demonstrating that chemerin inhibits both physiological and pathological angiogenesis through its main functional receptor CMKLR1 [184]. Also, chemerin binds to two other receptors, namely GPR1 and CCRL2, suggesting novel possible functions [185]. The LRH7-G5 peptide antagonist hampers chemerin/GPR1 signaling and has anti-cancer activity in triple-negative breast cancer [186]. Also, the chemokine-like receptor 1 (CMKLR1) antagonist α-NETA counteracts chemerin direct action on ECs [187]. Further studies need to clarify whether chemerin may become a target for the modulation of AT vasculature in metabolic disorders.

4.13. Adiponectin

Adiponectin is the most abundant circulating plasma adipokine secreted by mature adipocytes. Adiponectin is widely recognized for its insulin-sensitizing, anti-diabetic, anti-inflammatory, anti-atherogenic, and cardio-protective effects [188]. Consistent with its beneficial effects, adiponectin is abundant in the plasma of lean individuals, while it is downregulated in obese patients [189]. Adiponectin acts through two major functionally distinct ubiquitously expressed G-protein coupled receptors, AdipoR1 and AdipoR2. In the liver, adiponectin activates

glucose transport and inhibits gluconeogenesis via activation of AMPK. On the other hand, it activates fatty acid oxidation and decreases inflammation through the PPARα pathway. Together, these metabolic changes contribute to adiponectin-driven increased insulin sensitivity. In addition, in vitro studies demonstrated that adiponectin regulates fat lipid metabolism inhibiting lipolysis [188].

Adiponectin plays a crucial role in the regulation of EC homeostasis, by increasing nitric oxide (NO) production through the PI3K/Akt pathway and suppressing ROS generation. Also, it induces VEGF-A expression and enhances EC proliferation, migration and morphogenesis [190–192].

In addition, adiponectin counteracts the vascular inflammatory response by interfering with NF-κB signaling and by down-modulating the expression of EC adhesion molecules ICAM-1, VCAM-1, and E-selectin [193]. Low plasmatic concentration of adiponectin is an independent risk factor for endothelial dysfunction [194]. Consistent with this observation, adiponectin loss is associated with impaired angiogenesis after ischemic stress and its replacement restores post-ischemic angiogenesis [195]. However, a considerable body of literature describes the anti-angiogenic properties of adiponectin [196,197]. These studies have shown that adiponectin inhibits EC proliferation, migration, and survival and promotes cell apoptosis via MAPK and cAMP-PKA pathways [196,65,198]. The different biological activities of adiponectin across different studies may depend on the type of adiponectin employed in each study [199]. Indeed, globular adiponectin, a result of proteolytic cleavage of the full-length protein, strongly induces pro-angiogenic activation of EC, with increased VEGF and MMP2/9 expression. On the other hand, full-length adiponectin promoted a negligible angiogenic response [200]. Various adiponectin mimetics, adiponectin receptor agonists, such as AdipoRon, have been developed and tested in a wide spectrum of animal models [201,202]. On the other hand, very few antagonists of AdipoR including the ceramidase inhibitor, 1 S,2R-D-erythro-2-N-myristoylamino-1-phenyl-1-propanol (MAPP) and TNF-α are available at present but their pharmacological translational potential remains to be assessed [203].

4.14. Angiopoietin 2

Angiopoietin 1 and 2 (ANG-1 and ANG-2), the agoniztic and antagonistic TIE-2 ligands, respectively, are involved in the maintenance of vessel stability [204]. During vessel remodeling, ECs release a high level of ANG-2, which competes with ANG-1 and reduces TIE-2 phosphorylation in the cell-cell junctions. In quiescent vessels, the specific activation of TIE-2 by ANG-1 reduces endothelial permeability and promotes vessel stabilization [205]. ANG modulates the EC responses to other stimuli. In the presence of VEGF, ANG-2 enables EC migration and proliferation and, therefore, angiogenesis; alternatively ANG-2 induces EC death and vessel regression [206].

In AT, the functions of the ANGs are poorly defined. In ob/ob mice, the expression of ANG-1 in AT is reduced, while ANG-2 is overexpressed [40]. The expression of ANG-2 is differentially regulated under different metabolic stimuli, including HFD, fasting, cold exposure, and exercise [207]. ANG-2 regulates the alpha5-beta1-dependent transport of fatty acids through the endothelium in subcutaneous AT [208]. ANG2 deletion leads to ectopic fat accumulation in mouse liver and muscle, leading to increased insulin resistance. Within AT, ANG-2 results in increased vascularization and reduced inflammation of AT conferring to these animals resistance to diet-induced obesity and improving their metabolic health [209]. Inhibition of endogenous ANG-2 via administration of neutralizing antibodies has opposite effects with decreased vascularization, increased inflammation and fibrosis, and exacerbation of HFD-induced metabolic. Together, these changes link ANG-2 to angiogenesis during AT expansion and indicate that it plays a role in AT dysfunction *in vivo* [207].

4.15. Thrombospondin-1

Thrombospondin-1 (TSP1) is a matricellular protein well characterized for its anti-angiogenic function [210]. TSP-1, by binding the CD36 receptor or the VLDL receptor, inhibits intracellular signaling and cell cycle progression, inducing EC apoptosis [211]. TSP-1 is normally produced by differentiated adipocytes while it is downregulated in preadipocytes, indicating that *in vivo* it may negatively regulate angiogenesis during AT stabilization. Remarkably, TSP-1 high levels correlate with obesity, chronic inflammation, and insulin resistance [212,213]. Consistent with its anti-angiogenic properties, TSP-1 sustains HFD-induced muscle fibrosis, suggesting that TSP-1 may promote the acquisition of a fibrotic/mesenchymal phenotype in AT cells. However, loss of TSP-1 expression in mice does not cause AT defects [214]. Thus, further studies are warranted to clarify its function in the regulation of AT vascularization.

4.16. Transforming growth factor β

The TGF-β superfamily members are locally produced within AT, where they act as regulators of the differentiation of white and brown adipocytes and AT homeostasis (reviewed in [215]). By activating their cognate cell surface serine/threonine kinase receptors, they also activate SMAD proteins that in turn regulate the expression of adipogenic genes. Generally, TGF-β promotes pro-fibrotic events leading to AT metabolic dysfunctions [215]. Thus, a fine tuning of TGF-β levels is necessary for AT homeostasis.

TGF-β elicits dose-dependent and context dependent effects of blood vessel outgrowth. Low levels promote angiogenesis, while high levels of TGF-β have anti-angiogenic effects on ECs. Also, the capacity to promote pericytes and smooth muscle cell differentiation of TGF-β suggests that this factor may be involved in vessel stabilization [216,217]. TGF-β promotes EC transdifferentiation in mesenchymal cells through the EndoMT and in adipocytes through the endothelial-to-adipocyte transdifferentiation. Thus TGF-β is a potential regulator of AT fibrosis and angiogenesis. Antagonists of TGF-β have proven anti-tumor and anti-angiogenic effects in various cancer models [218,219]. Also, the blockade of TGF-β/smad3 signaling enhances WAT browning and prevents HFD-induced obesity and diabetes in mouse models [220].

5. Adipokines orchestrate angiogenesis during AT remodeling driving metabolic syndrome

Adipocytes release a wide number of molecules which collaborate with inflammatory cytokines [221] in the regulation of angiogenesis during AT remodeling (Fig. 2). Also, adipose-derived stromal cells produce VEGF, FGF, and other angiogenic factors, further contributing to angiogenesis [42]. Although the different subsets of angiogenic molecules produced by different AT depots have been characterized, how these differently regulate vessel biology in different AT depots remains to be elucidated. Among others, high amounts of pro-angiogenic leptin and VEGF are secreted during AT expansion while adiponectin, TSP-1, angiopoietin 2, or other negative regulators of angiogenesis are released in the hypo-plastic AT. Therefore, to activate angiogenesis during AT expansion, both overexpression of pro-angiogenic molecules and downregulation of anti-angiogenic ones are required. Consistently, cold exposure in mice leads to the activation of angiogenesis characterized by the simultaneous upregulation of VEGF and downregulation of TSP-1 [37]. Moreover, adiponectin and gremlin-1 can trigger both pro- and anti-angiogenic responses in ECs, suggesting their context-dependent effects. Thus, the final outcome in terms of AT angiogenesis results from a well-balanced integrated action of all different pro- and anti-angiogenic adipokines.

The effects of pro-angiogenic adipokines often converge to the expression of classical angiogenesis inducers such as VEGF and/or FGF-2 [136,139,142,150,180], suggesting that they can synergize with these

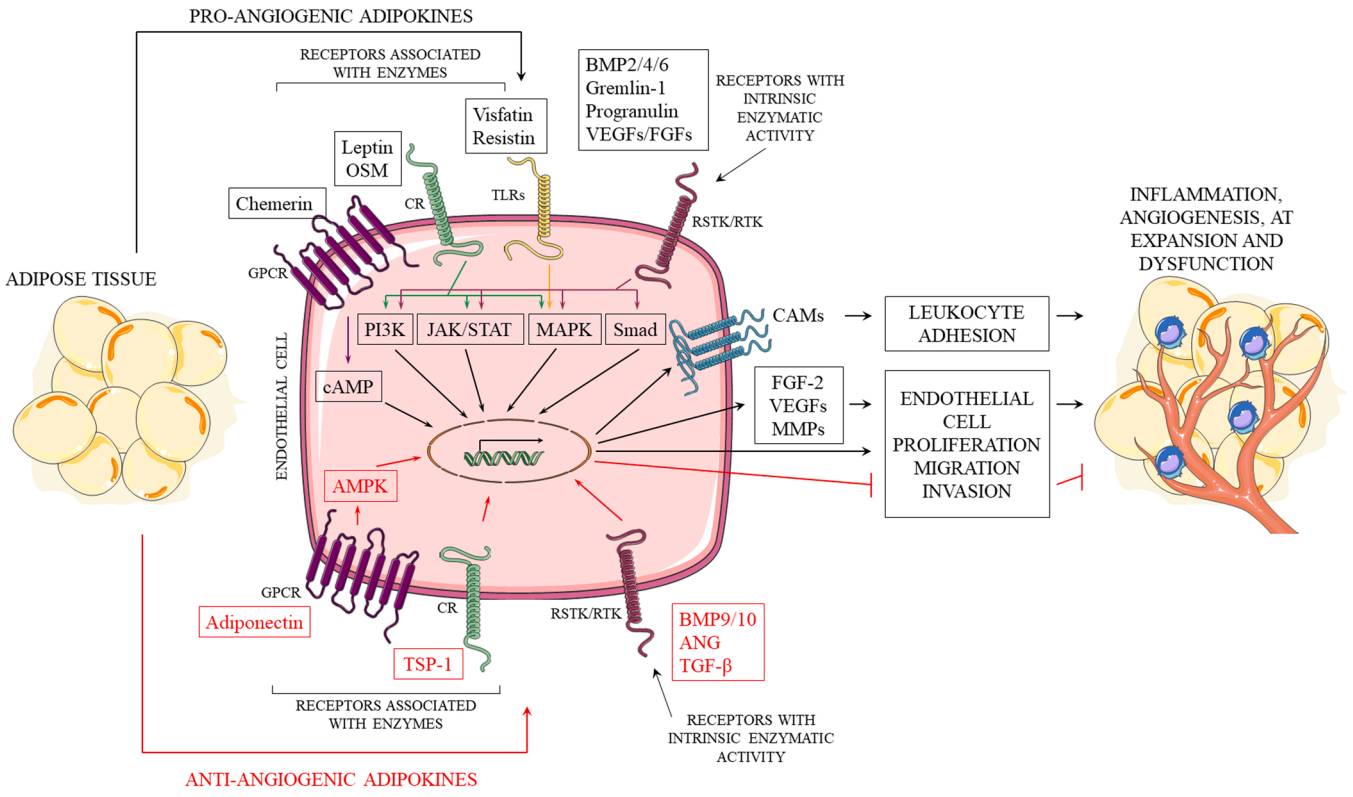

Fig. 2. Molecular mechanisms involved in adipokines mediated angiogenesis during AT dysfunction.

factors to induce AT angiogenesis [222]. In addition, the fact that many different adipokines activate classical angiogenic programs in ECs (i.e. VEGF expression, MMP expression etc.) suggests that redundancy might occur. For example, the overexpression/deletion of adiponectin does not affect body weight, suggesting that the adiponectin system may be redundant [223]. In total, the carefully orchestrated regulation of this diverse adipokine expression in space and time is crucial for a balanced angiogenic process in AT. Perturbations of adipokine expression are indeed hallmarks and biomarkers of AT dysfunction, and are associated with profound alterations in AT angiogenesis.

In obesity, WAT expansion is paralleled by angiogenesis which, through a positive loop, promotes adipocyte differentiation [108] and AT expansion [4]. However, hypertrophic WAT is not always accompanied by increased angiogenesis. Paradoxically, lack of angiogenesis is observed even if overexpression of pro-angiogenic molecules occurs. In this condition, the activation of the hypoxia-inducible factor 1-alpha (HIF1α) recruits inflammatory cells and induces ECM production [224]. This, in turn, leads to metabolic alterations (lipid release) and insulin resistance causing AT dysfunction [42]. In this scenario, EC dysfunction play a major pathogenetic role. Increased vascular permeability as well as reduction of basal lamina [225] enhances inflammation and fibrosis [1,15]. Add to this, leptin, angiogenin, visfatin, and adiponectin regulate the expression of MMPs controlling ECM remodeling. The above demonstrates a crosstalk between adipocytes and EC in AT, with a negative impact on AT functionality in obese patients [4]. A challenge for future research remains to understand how all adipokines together cooperate to control angiogenesis during AT homeostasis and dysfunction.

6. Adipose tissue engineering

As obesity has become an epidemic problem, much of the recent efforts have been spent in the engineering of AT not only for the reconstruction of soft tissue but also for its repair and remodeling after injury/chronic inflammation.

Numerous biocompatible/implantable scaffolds for AT engineering have been developed (Fig. 3).

The synthetic or natural, solid or soft scaffolds should be able to mimic the pre-existing microenvironment of the native ECM, to support cell adhesion, viability and proliferation and to maintain the structural integrity of the implant until it is replaced with newly formed tissue [226,227]. Pre-adipocytes or adipose-derived stem cells have been extensively used as a cell source in combination with different ECM proteins and scaffolds to support the recruitment of vessels [228,229]. Several synthetic polymeric scaffolds, [230] including the poly(lactic-co glycolic) acids (PLGA) [231], the polyethylene tetraphthalate (PET) [232], and the non-degradable polytetrafluoroethylene (PTFE) [233] coated with collagen, albumin or fibronectin have been examined [234]. Natural scaffolds such as collagen, fibrin, and hyaluronic acid-based materials have been extensively used in tissue engineering due to their low cost, biodegradability, and biocompatibility. Given the importance of vascularization in regulating adipogenesis, growth factors have been integrated in scaffolds. Murine models demonstrated that collagen and fibrin matrices induce the regeneration of vascularized AT when implanted in combination with adipose-derived stem cells, and that adipogenesis was further stimulated in presence of pro-agiogenic growth factors (e.i FGF-2). Of note, the exogenous ECMs are fully degraded two weeks post injection.

More recently, decellularized ECM scaffolds from different tissues, including AT, have been tested [235–237]. Characterized by high biocompatibility, AT scaffolds are also composed of all the acellular components of the AT naturally resembling the best environment for cell recruitment, attachment, proliferation and differentiation [237–239]. Different *in vivo* studies mixed AT scaffolds with methylcellulose, methacrylated glycol, chitosan, or chondroitin sulfate, forming injectable hydrogels. In a few weeks adipose lobule-like structures and vessels were observed and the addition of angiogenic growth factors further increased angiogenesis proving their usefulness for the regeneration and functionality of AT [240,241].

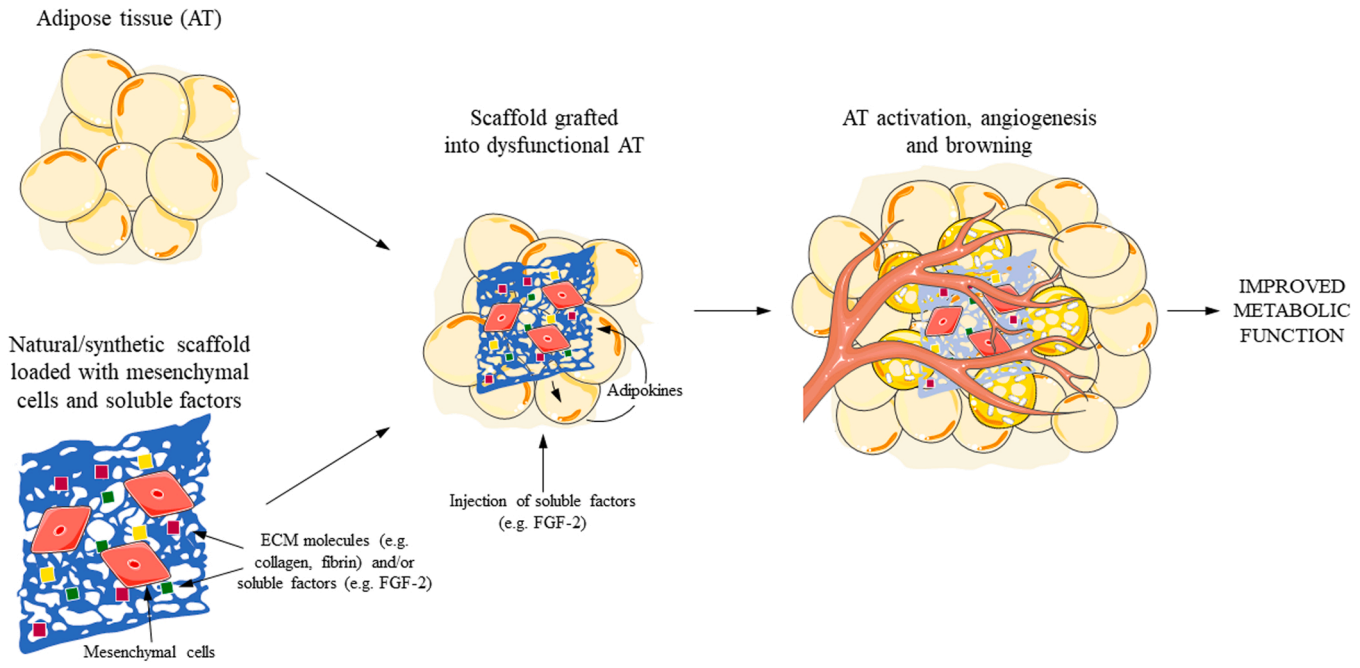

Fig. 3. Scaffold approaches for adipose tissue engineering.

7. Conclusion

This review outlines the available evidence regarding the effects of adipokines on the angiogenic process leading to AT remodeling. It also discusses the cross-communication between AT and angiogenesis and how anti- and pro-angiogenic approaches could be employed to impair the progression of obesity. Taken together, the available evidence clearly demonstrates that ECs and blood vessels are directly involved in maintaining the physiological metabolic functions of AT and are pivotal players in AT dysfunction. For this reason, therapeutic intervention on angiogenesis has great potential as a strategy to treat disorders associated with dysfunctional AT such as obesity. Both pharmacological inhibition of angiogenic adipokines and AT engineering represent valuable strategies to improve AT dysfunction in patients with metabolic disorders and may create the potential for novel treatments.

Conflict of interest

All authors declare no Conflict of Interest that are directly or indirectly related to the work submitted for publication.

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References

[1] G. Colleluori, et al., From obesity to diabetes: the role of the adipose organ, Handb. Exp. Pharm. (2022).
[2] F.J. Ruiz-Ojeda, et al., Extracellular matrix remodeling of adipose tissue in obesity and metabolic diseases, Int. J. Mol. Sci. 20 (19) (2019).
[3] P. Nijhawans, T. Behl, S. Bhardwaj, Angiogenesis in obesity, Biomed. Pharm. 126 (2020), 110103.
[4] J. Herold, J. Kalucka, Angiogenesis in adipose tissue: the interplay between adipose and endothelial cells, Front. Physiol. 11 (2020), 624903.
[5] A. Booth, et al., Adipose tissue: an endocrine organ playing a role in metabolic regulation, Horm. Mol. Biol. Clin. Investig. 26 (1) (2016) 25–42.
[6] E.B. Taylor, The complex role of adipokines in obesity, inflammation, and autoimmunity, Clin. Sci. 135 (6) (2021) 731–752.
[7] G. Eelen, et al., Endothelial cell metabolism, Physiol. Rev. 98 (1) (2018) 3–58.
[8] S.Y. Chun, et al., Preparation and characterization of human adipose tissue-derived extracellular matrix, growth factors, and stem cells: a concise review, Tissue Eng. Regen. Med. 16 (4) (2019) 385–393.
[9] K. Sun, C.M. Kusminski, P.E. Scherer, Adipose tissue remodeling and obesity, J. Clin. Investig. 121 (6) (2011) 2094–2101.
[10] A. Valente, et al., Molecular pathways linking non-shivering thermogenesis and obesity: focusing on brown adipose tissue development, Biol. Rev. Camb. Philos. Soc. 90 (1) (2015) 77–88.
[11] A.M. Cypess, et al., Identification and importance of brown adipose tissue in adult humans, N. Engl. J. Med. 360 (15) (2009) 1509–1517.
[12] P. Trayhurn, J.H. Beattie, Physiological role of adipose tissue: white adipose tissue as an endocrine and secretory organ, Proc. Nutr. Soc. 60 (3) (2001) 329–339.
[13] S. Perrini, et al., Fat depot-related differences in gene expression, adiponectin secretion, and insulin action and signalling in human adipocytes differentiated in vitro from precursor stromal cells, Diabetologia 51 (1) (2008) 155–164.
[14] X. Unamuno, et al., Changes in mechanical properties of adipose tissue after bariatric surgery driven by extracellular matrix remodelling and neovascularization are associated with metabolic improvements, Acta Biomater. 141 (2022) 264–279.
[15] S. Cinti, Adipose organ development and remodeling, Compr. Physiol. 8 (4) (2018) 1357–1431.
[16] J.M.A. de Jong, et al., Author correction: human brown adipose tissue is phenocopied by classical brown adipose tissue in physiologically humanized mice, Nat. Metab. 1 (9) (2019) 927.
[17] A. Fedorenko, P.V. Lishko, Y. Kirichok, Mechanism of fatty-acid-dependent UCP1 uncoupling in brown fat mitochondria, Cell 151 (2) (2012) 400–413.
[18] J.M. Heaton, The distribution of brown adipose tissue in the human, J. Anat. 112 (Pt 1) (1972) 35–39.
[19] B.P. Leitner, et al., Mapping of human brown adipose tissue in lean and obese young men, Proc. Natl. Acad. Sci. USA 114 (32) (2017) 8649–8654.
[20] J. Nedergaard, T. Bengtsson, B. Cannon, Unexpected evidence for active brown adipose tissue in adult humans, Am. J. Physiol. Endocrinol. Metab. 293 (2) (2007) E444–E452.
[21] C. Ran, et al., PET imaging of human brown adipose tissue with the TSPO Tracer [(11)C]PBR28, Mol. Imaging Biol. 20 (2) (2018) 188–193.
[22] A.M. Cypess, et al., Anatomical localization, gene expression profiling and functional characterization of adult human neck brown fat, Nat. Med. 19 (5) (2013) 635–639.
[23] M.P.B. Moonen, E.B.M. Nascimento, W.D. van Marken Lichtenbelt, Human brown adipose tissue: underestimated target in metabolic disease? Biochim Biophys. Acta Mol. Cell Biol. Lipids 1864 (1) (2019) 104–112.
[24] P.C. Dinas, et al., Browning formation markers of subcutaneous adipose tissue in relation to resting energy expenditure, physical activity and diet in humans, Horm. Mol. Biol. Clin. Investig. 31 (1) (2017).
[25] J. Wu, et al., Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human, Cell 150 (2) (2012) 366–376.

[26] M. Giralt, F. Villarroya, White, brown, beige/brite: different adipose cells for different functions? Endocrinology 154 (9) (2013) 2992–3000.
[27] A.C. Pilkington, H.A. Paz, U.D. Wankhade, Beige adipose tissue identification and marker specificity-overview, Front Endocrinology 12 (2021), 599134.
[28] A. Pfeifer, L.S. Hoffmann, Brown, beige, and white: the new color code of fat and its pharmacological implications, Annu Rev. Pharm. Toxicol. 55 (2015) 207–227.
[29] R. Singh, et al., Increased expression of Beige/Brown adipose markers from host and breast cancer cells influence xenograft formation in mice, Mol. Cancer Res. 14 (1) (2016) 78–92.
[30] J. Himms-Hagen, et al., Multilocular fat cells in WAT of CL-316243-treated rats derive directly from white adipocytes, Am. J. Physiol. Cell Physiol. 279 (3) (2000) C670–C681.
[31] A. Vitali, et al., The adipose organ of obesity-prone C57BL/6J mice is composed of mixed white and brown adipocytes, J. Lipid Res. 53 (4) (2012) 619–629.
[32] Q.A. Wang, P.E. Scherer, The AdipoChaser mouse: a model tracking adipogenesis in vivo, Adipocyte 3 (2) (2014) 146–150.
[33] W. Wang, P. Seale, Control of brown and beige fat development, Nat. Rev. Mol. Cell Biol. 17 (11) (2016) 691–702.
[34] J. Sanchez-Gurmaches, D.A. Guertin, Adipocyte lineages: tracing back the origins of fat, Biochim. Biophys. Acta 1842 (3) (2014) 340–351.
[35] M. Harms, P. Seale, Brown and beige fat: development, function and therapeutic potential, Nat. Med. 19 (10) (2013) 1252–1263.
[36] K.L. Spalding, et al., Dynamics of fat cell turnover in humans, Nature 453 (7196) (2008) 783–787.
[37] Y. Xue, et al., Hypoxia-independent angiogenesis in adipose tissues during cold acclimation, Cell Metab. 9 (1) (2009) 99–109.
[38] M. di Somma, et al., Role of VEGFs in metabolic disorders, Angiogenesis 23 (2) (2020) 119–130.
[39] Y. Cao, Angiogenesis modulates adipogenesis and obesity, J. Clin. Investig. 117 (9) (2007) 2362–2368.
[40] G. Voros, et al., Modulation of angiogenesis during adipose tissue development in murine models of obesity, Endocrinology 146 (10) (2005) 4545–4554.
[41] S.M. Dallabrida, M.A. Rupnick, Vascular endothelium in tissue remodeling: implications for heart failure, Cold Spring Harb. Symp. Quant. Biol. 67 (2002) 417–427.
[42] Y. Cao, Adipose tissue angiogenesis as a therapeutic target for obesity and metabolic diseases, Nat. Rev. Drug Discov. 9 (2) (2010) 107–115.
[43] Y. Cao, Angiogenesis and vascular functions in modulation of obesity, adipose metabolism, and insulin sensitivity, Cell Metab. 18 (4) (2013) 478–489.
[44] P. Carmeliet, R.K. Jain, Molecular mechanisms and clinical applications of angiogenesis, Nature 473 (7347) (2011) 298–307.
[45] S. Mahjoub, J. Masrour-Roudsari, Role of oxidative stress in pathogenesis of metabolic syndrome, Casp. J. Intern. Med. 3 (1) (2012) 386–396.
[46] M. Longo, et al., Adipose tissue dysfunction as determinant of obesity-associated metabolic complications, Int. J. Mol. Sci. 20 (9) (2019).
[47] M. Bluher, Adipose tissue dysfunction contributes to obesity related metabolic diseases, Best. Pract. Res. Clin. Endocrinol. Metab. 27 (2) (2013) 163–177.
[48] M. Kim, C. Lee, J. Park, Extracellular matrix remodeling facilitates obesity-associated cancer progression, Trends Cell Biol. (2022).
[49] C. Ravelli, et al., beta3 integrin promotes long-lasting activation and polarization of vascular endothelial growth factor receptor 2 by immobilized ligand, Arterioscler. Thromb. Vasc. Biol. 35 (10) (2015) 2161–2171.
[50] L.A. Zimmermann, et al., Controlling BMP growth factor bioavailability: the extracellular matrix as multi skilled platform, Cell Signal. 85 (2021), 110071.
[51] S. Mitola, et al., IL-12 regulates an endothelial cell-lymphocyte network: effect on metalloproteinase-9 production, J. Immunol. 171 (7) (2003) 3725–3733.
[52] V. Christiaens, H.R. Lijnen, Angiogenesis and development of adipose tissue, Mol. Cell Endocrinol. 318 (1–2) (2010) 2–9.
[53] Q.X. Sang, Complex role of matrix metalloproteinases in angiogenesis, Cell Res. 8 (3) (1998) 171–177.
[54] C. Chavey, et al., Matrix metalloproteinases are differentially expressed in adipose tissue during obesity and modulate adipocyte differentiation, J. Biol. Chem. 278 (14) (2003) 11888–11896.
[55] H.R. Lijnen, et al., Matrix metalloproteinase inhibition impairs adipose tissue development in mice, Arterioscler. Thromb. Vasc. Biol. 22 (3) (2002) 374–379.
[56] D. Demeulemeester, D. Collen, H.R. Lijnen, Effect of matrix metalloproteinase inhibition on adipose tissue development, Biochem. Biophys. Res. Commun. 329 (1) (2005) 105–110.
[57] M.C. Alessi, et al., Production of plasminogen activator inhibitor 1 by human adipose tissue: possible link between visceral fat accumulation and vascular disease, Diabetes 46 (5) (1997) 860–867.
[58] R.C. Gaillard, et al., Cytokines, leptin, and the hypothalamo-pituitary-adrenal axis, Ann. N. Y Acad. Sci. 917 (2000) 647–657.
[59] M. Obradovic, et al., Leptin and obesity: role and clinical implication, Front. Endocrinol. 12 (2021), 585887.
[60] A.N. Comninos, C.N. Jayasena, W.S. Dhillo, The relationship between gut and adipose hormones, and reproduction, Hum. Reprod. Update 20 (2) (2014) 153–174.
[61] M.W. Hulver, J.A. Houmard, Plasma leptin and exercise: recent findings, Sports Med. 33 (7) (2003) 473–482.
[62] T. Thomas, Leptin: a potential mediator for protective effects of fat mass on bone tissue, Jt. Bone Spine 70 (1) (2003) 18–21.
[63] K.L. Meadows, Ischemic stroke and select adipose-derived and sex hormones: a review, Hormones 17 (2) (2018) 167–182.
[64] P. de Candia, et al., The pleiotropic roles of leptin in metabolism, immunity, and cancer, J. Exp. Med. 218 (5) (2021).
[65] R. Adya, B.K. Tan, H.S. Randeva, Differential effects of leptin and adiponectin in endothelial angiogenesis, J. Diabetes Res. 2015 (2015), 648239.
[66] A. Bouloumie, et al., Leptin, the product of Ob gene, promotes angiogenesis, Circ. Res. 83 (10) (1998) 1059–1066.
[67] E. Garonna, et al., Vascular endothelial growth factor receptor-2 couples cyclo-oxygenase-2 with pro-angiogenic actions of leptin on human endothelial cells, PLOS One 6 (4) (2011), e18823.
[68] F. Yu, et al., Leptin-induced angiogenesis of EA.Hy926 endothelial cells via the Akt and Wnt signaling pathways in vitro and in vivo, Front. Pharm. 10 (2019) 1275.
[69] S. Anagnostoulis, et al., Human leptin induces angiogenesis in vivo, Cytokine 42 (3) (2008) 353–357.
[70] R. Cao, et al., Leptin induces vascular permeability and synergistically stimulates angiogenesis with FGF-2 and VEGF, Proc. Natl. Acad. Sci. USA 98 (11) (2001) 6390–6395.
[71] M.R. Schroeter, et al., Leptin promotes the mobilization of vascular progenitor cells and neovascularization by NOX2-mediated activation of MMP9, Cardiovasc. Res. 93 (1) (2012) 170–180.
[72] N.M. Heida, et al., Leptin enhances the potency of circulating angiogenic cells via src kinase and integrin (alpha)vbeta5: implications for angiogenesis in human obesity, Arterioscler. Thromb. Vasc. Biol. 30 (2) (2010) 200–206.
[73] L. Zabeau, F. Peelman, J. Tavernier, Antagonizing leptin: current status and future directions, Biol. Chem. 395 (5) (2014) 499–514.
[74] J.W. Fett, et al., Isolation and characterization of angiogenin, an angiogenic protein from human carcinoma cells, Biochemistry 24 (20) (1985) 5480–5486.
[75] M. Miyake, et al., Angiogenin promotes tumoral growth and angiogenesis by regulating matrix metallopeptidase-2 expression via the ERK1/2 pathway, Oncogene 34 (7) (2015) 890–901.
[76] B.D. Smith, R.T. Raines, Genetic selection for peptide inhibitors of angiogenin, Protein Eng. Des. Sel. 21 (5) (2008) 289–294.
[77] R.Y. Kao, et al., A small-molecule inhibitor of the ribonucleolytic activity of human angiogenin that possesses antitumor activity, Proc. Natl. Acad. Sci. USA 99 (15) (2002) 10066–10071.
[78] J. Sheng, Z. Xu, Three decades of research on angiogenin: a review and perspective, Acta Biochim. Biophys. Sin. 48 (5) (2016) 399–410.
[79] E. Klimcakova, et al., Profiling of adipokines secreted from human subcutaneous adipose tissue in response to PPAR agonists, Biochem. Biophys. Res. Commun. 358 (3) (2007) 897–902.
[80] Y. He, et al., Stromal vascular fraction cells plus sustained release VEGF/Ang-1-PLGA microspheres improve fat graft survival in mice, J. Cell Physiol. 234 (5) (2019) 6136–6146.
[81] J.V. Silha, et al., Angiogenic factors are elevated in overweight and obese individuals, Int. J. Obes. 29 (11) (2005) 1308–1314.
[82] A. Efimenko, et al., Adipose-derived mesenchymal stromal cells from aged patients with coronary artery disease keep mesenchymal stromal cell properties but exhibit characteristics of aging and have impaired angiogenic potential, Stem Cells Transl. Med. 3 (1) (2014) 32–41.
[83] J. Yang, X. Li, D. Xu, Research progress on the involvement of ANGPTL4 and loss-of-function variants in lipid metabolism and coronary heart disease: is the “prime time” of ANGPTL4-targeted therapy for coronary heart disease approaching? Cardiovasc. Drugs Ther. 35 (3) (2021) 467–477.
[84] S. Ibaragi, et al., Neamine inhibits prostate cancer growth by suppressing angiogenin-mediated rRNA transcription, Clin. Cancer Res. 15 (6) (2009) 1981–1988.
[85] Y.S. Gho, C.B. Chae, Anti-angiogenin activity of the peptides complementary to the receptor-binding site of angiogenin, J. Biol. Chem. 272 (39) (1997) 24294–24299.
[86] K. Kishimoto, et al., Endogenous angiogenin in endothelial cells is a general requirement for cell proliferation and angiogenesis, Oncogene 24 (3) (2005) 445–456.
[87] K.C. Kirkbride, et al., Bone morphogenetic proteins signal through the transforming growth factor-beta type III receptor, J. Biol. Chem. 283 (12) (2008) 7628–7637.
[88] S. Qian, Y. Tang, Q.Q. Tang, Adipose tissue plasticity and the pleiotropic roles of BMP signaling, J. Biol. Chem. 296 (2021), 100678.
[89] A.M. Blazquez-Medela, M. Jumabay, K.I. Bostrom, Beyond the bone: bone morphogenetic protein signaling in adipose tissue, Obes. Rev. 20 (5) (2019) 648–658.
[90] A. Margoni, L. Fotis, A.G. Papavassiliou, The transforming growth factor-beta/bone morphogenetic protein signalling pathway in adipogenesis, Int. J. Biochem. Cell Biol. 44 (3) (2012) 475–479.
[91] T.J. Schulz, Y.H. Tseng, Emerging role of bone morphogenetic proteins in adipogenesis and energy metabolism, Cytokine Growth Factor Rev. 20 (5–6) (2009) 523–531.
[92] M.R. Kulikauskas, S. X, V.L. Bautch, The versatility and paradox of BMP signaling in endothelial cell behaviors and blood vessel function, Cell Mol. Life Sci. 79 (2) (2022) 77.
[93] A. Benn, et al., Role of bone morphogenetic proteins in sprouting angiogenesis: differential BMP receptor-dependent signaling pathways balance stalk vs. tip cell competence, FASEB J. 31 (11) (2017) 4720–4733.
[94] W.C. Chen, et al., BMP-2 induces angiogenesis by provoking integrin alpha6 expression in human endothelial progenitor cells, Biochem. Pharm. 150 (2018) 256–266.
[95] Y. Tang, et al., BMP4 mediates the interplay between adipogenesis and angiogenesis during expansion of subcutaneous white adipose tissue, J. Mol. Cell Biol. 8 (4) (2016) 302–312.

[96] S. Rezzola, et al., VEGFR2 activation mediates the pro-angiogenic activity of BMP4, Angiogenesis (2019).
[97] S. Saini, et al., Role of BMP7 in appetite regulation, adipogenesis, and energy expenditure, Endocrine 48 (2) (2015) 405–409.
[98] A. Desroches-Castan, et al., BMP9 and BMP10: two close vascular quiescence partners that stand out, Dev. Dyn. 251 (1) (2022) 178–197.
[99] W. Ge, et al., rhBMP7 suppresses TGFbeta1induced endothelial to mesenchymal transition in circulating endothelial cells by regulating Smad5, Mol. Med. Rep. 21 (1) (2020) 478–484.
[100] R. Szulcek, et al., Exacerbated inflammatory signaling underlies aberrant response to BMP9 in pulmonary arterial hypertension lung endothelial cells, Angiogenesis 23 (4) (2020) 699–714.
[101] C.C. Hong, P.B. Yu, Applications of small molecule BMP inhibitors in physiology and disease, Cytokine Growth Factor Rev. 20 (5–6) (2009) 409–418.
[102] L.Z. Topol, et al., Biosynthesis, post-translation modification, and functional characterization of Drm/Gremlin, J. Biol. Chem. 275 (12) (2000) 8785–8793.
[103] S. Mitola, et al., Production and biochemical characterization of dimeric recombinant gremlin-1, Int. J. Mol. Sci. 23 (3) (2022).
[104] D.W. Walsh, et al., Extracellular BMP-antagonist regulation in development and disease: tied up in knots, Trends Cell Biol. 20 (5) (2010) 244–256.
[105] K.S.R. Choudhuri, S. Mishra, Structural basis of BMP-2 and BMP-7 interactions with antagonists Gremlin-1 and Noggin in Glioblastoma tumors, J. Comput. Chem. 41 (30) (2020) 2544–2561.
[106] U. Neckmann, et al., GREM1 is associated with metastasis and predicts poor prognosis in ER-negative breast cancer patients, Cell Commun. Signal. 17 (1) (2019) 140.
[107] S. Hedjazifar, et al., The novel adipokine gremlin 1 antagonizes insulin action and is increased in type 2 diabetes and NAFLD/NASH, Diabetes 69 (3) (2020) 331–341.
[108] A. Hammarstedt, et al., Impaired adipogenesis and dysfunctional adipose tissue in human hypertrophic obesity, Physiol. Rev. 98 (4) (2018) 1911–1941.
[109] B. Gustafson, et al., BMP4 and BMP antagonists regulate human white and Beige adipogenesis, Diabetes 64 (5) (2015) 1670–1681.
[110] F.M. Wade, et al., Differential expression of the peripheral benzodiazepine receptor and gremlin during adipogenesis, Obes. Res. 13 (5) (2005) 818–822.
[111] N. Hoggard, et al., Using gene expression to predict differences in the secretome of human omental vs. subcutaneous adipose tissue, Obesity 20 (6) (2012) 1158–1167.
[112] A. Saeidi, et al., Resistance training, gremlin 1 and macrophage migration inhibitory factor in obese men: a randomised trial, Arch. Physiol. Biochem. (2020) 1–9.
[113] H. Stabile, et al., Bone morphogenic protein antagonist Drm/gremlin is a novel proangiogenic factor, Blood 109 (5) (2007) 1834–1840.
[114] M. Corsini, et al., Cyclic adenosine monophosphate-response element-binding protein mediates the proangiogenic or proinflammatory activity of gremlin, Arterioscler. Thromb. Vasc. Biol. 34 (1) (2014) 136–145.
[115] S. Mitola, et al., Gremlin is a novel agonist of the major proangiogenic receptor VEGFR2, Blood 116 (18) (2010) 3677–3680.
[116] P. Chiodelli, et al., Heparan sulfate proteoglycans mediate the angiogenic activity of the vascular endothelial growth factor receptor-2 agonist gremlin, Arterioscler. Thromb. Vasc. Biol. 31 (12) (2011) e116–e127.
[117] Y. Zhang, et al., Gremlin-1 is a key regulator of endothelial-to-mesenchymal transition in human pulmonary artery endothelial cells, Exp. Cell Res. 390 (1) (2020), 111941.
[118] L. Marquez-Exposito, et al., Gremlin regulates tubular epithelial to mesenchymal transition via VEGFR2: potential role in renal fibrosis, Front. Pharm. 9 (2018) 1195.
[119] T. Zanocco-Marani, et al., Biological activities and signaling pathways of the granulin/epithelin precursor, Cancer Res. 59 (20) (1999) 5331–5340.
[120] Z. He, A. Bateman, Progranulin (granulin-epithelin precursor, PC-cell-derived growth factor, acrogranin) mediates tissue repair and tumorigenesis, J. Mol. Med. 81 (10) (2003) 600–612.
[121] T. Ebert, et al., Relationship between 12 adipocytokines and distinct components of the metabolic syndrome, J. Clin. Endocrinol. Metab. 103 (3) (2018) 1015–1023.
[122] N. Kloting, et al., Insulin-sensitive obesity, Am. J. Physiol. Endocrinol. Metab. 299 (3) (2010) E506–E515.
[123] A. Schmid, et al., Role of progranulin in adipose tissue innate immunity, Cytokine 125 (2020), 154796.
[124] K. Miehle, et al., Progranulin is increased in human and murine lipodystrophy, Diabetes Res. Clin. Pract. 120 (2016) 1–7.
[125] T. Matsubara, et al., PGRN is a key adipokine mediating high fat diet-induced insulin resistance and obesity through IL-6 in adipose tissue, Cell Metab. 15 (1) (2012) 38–50.
[126] M.S. Kraemer, et al., Plasma progranulin levels in obese patients before and after Roux-en-Y gastric bariatric surgery: a longitudinal study, Surg. Obes. Relat. Dis. 16 (11) (2020) 1655–1660.
[127] J. Brock, et al., Progranulin serum levels and gene expression in subcutaneous vs visceral adipose tissue of severely obese patients undergoing bariatric surgery, Clin. Endocrinol. 91 (3) (2019) 400–410.
[128] R.R. Guerra, et al., Progranulin is a stress-response factor in fibroblasts subjected to hypoxia and acidosis, Growth Factors 25 (4) (2007) 280–285.
[129] B. Xu, et al., Abnormal angiogenesis of placenta in progranulindeficient mice, Mol. Med. Rep. 22 (4) (2020) 3482–3492.
[130] G. Li, et al., Progranulin promotes lymphangiogenesis through VEGF-C and is an independent risk factor in human esophageal cancers, Hum. Pathol. 75 (2018) 116–124.
[131] T. Neill, et al., EphA2 is a functional receptor for the growth factor progranulin, J. Cell Biol. 215 (5) (2016) 687–703.
[132] E.M. Gonzalez, et al., A novel interaction between perlecan protein core and progranulin: potential effects on tumor growth, J. Biol. Chem. 278 (40) (2003) 38113–38116.
[133] A.M. Araujo, et al., Stromal oncostatin M cytokine promotes breast cancer progression by reprogramming the tumor microenvironment, J. Clin. Investig. 132 (7) (2022).
[134] D. Sanchez-Infantes, et al., Oncostatin m is produced in adipose tissue and is regulated in conditions of obesity and type 2 diabetes, J. Clin. Endocrinol. Metab. 99 (2) (2014) E217–E225.
[135] C.M. Elks, et al., Loss of oncostatin M signaling in adipocytes induces insulin resistance and adipose tissue inflammation in vivo, J. Biol. Chem. 291 (33) (2016) 17066–17076.
[136] E.S. Wijelath, et al., Oncostatin M induces basic fibroblast growth factor expression in endothelial cells and promotes endothelial cell proliferation, migration and spindle morphology, J. Cell Sci. 110 (Pt 7) (1997) 871–879.
[137] X. Zhang, et al., OSM enhances angiogenesis and improves cardiac function after myocardial infarction, Biomed. Res. Int. 2015 (2015), 317905.
[138] G. Marden, et al., The role of the oncostatin M/OSM receptor beta axis in activating dermal microvascular endothelial cells in systemic sclerosis, Arthritis Res. Ther. 22 (1) (2020) 179.
[139] K. Rychli, et al., The inflammatory mediator oncostatin M induces angiopoietin 2 expression in endothelial cells in vitro and in vivo, J. Thromb. Haemost. 8 (3) (2010) 596–604.
[140] G. Rega, et al., Vascular endothelial growth factor is induced by the inflammatory cytokines interleukin-6 and oncostatin m in human adipose tissue in vitro and in murine adipose tissue in vivo, Arterioscler. Thromb. Vasc. Biol. 27 (7) (2007) 1587–1595.
[141] J. Poling, et al., Therapeutic targeting of the oncostatin M receptor-beta prevents inflammatory heart failure, Basic Res. Cardiol. 109 (1) (2014) 396.
[142] L. Pang, et al., Resistin promotes the expression of vascular endothelial growth factor in ovary carcinoma cells, Int. J. Mol. Sci. 14 (5) (2013) 9751–9766.
[143] P. Raghu, et al., Dimerization of human recombinant resistin involves covalent and noncovalent interactions, Biochem. Biophys. Res. Commun. 313 (3) (2004) 642–646.
[144] P. Malvi, et al., Elevated circulatory levels of leptin and resistin impair therapeutic efficacy of dacarbazine in melanoma under obese state, Cancer Metab. 6 (2018) 2.
[145] A. Deb, et al., Resistin: a journey from metabolism to cancer, Transl. Oncol. 14 (10) (2021), 101178.
[146] K. Makki, P. Froguel, I. Wolowczuk, Adipose tissue in obesity-related inflammation and insulin resistance: cells, cytokines, and chemokines, ISRN Inflamm. 2013 (2013), 139239.
[147] Sadashiv, et al., Over expression of resistin in adipose tissue of the obese induces insulin resistance, World J. Diabetes 3 (7) (2012) 135–141.
[148] B. Sanchez-Solana, J. Laborda, V. Baladron, Mouse resistin modulates adipogenesis and glucose uptake in 3T3-L1 preadipocytes through the ROR1 receptor, Mol. Endocrinol. 26 (1) (2012) 110–127.
[149] C. Chen, et al., Resistin decreases expression of endothelial nitric oxide synthase through oxidative stress in human coronary artery endothelial cells, Am. J. Physiol. Heart Circ. Physiol. 299 (1) (2010) H193–H201.
[150] H.C. Tsai, et al., Resistin enhances angiogenesis in osteosarcoma via the MAPK signaling pathway, Aging 11 (21) (2019) 9767–9777.
[151] H. Mu, et al., Adipokine resistin promotes in vitro angiogenesis of human endothelial cells, Cardiovasc. Res. 70 (1) (2006) 146–157.
[152] S.A. Robertson, C.J. Rae, A. Graham, Induction of angiogenesis by murine resistin: putative role of PI3-kinase and NO-dependent pathways, Regul. Pept. 152 (1–3) (2009) 41–47.
[153] S. Lee, et al., Adenylyl cyclase-associated protein 1 is a receptor for human resistin and mediates inflammatory actions of human monocytes, Cell Metab. 19 (3) (2014) 484–497.
[154] M. Shibuya, VEGF-VEGFR signals in health and disease, Biomol. Ther. 22 (1) (2014) 1–9.
[155] L. Claesson-Welsh, Signal transduction by vascular endothelial growth factor receptors, Biochem. Soc. Trans. 31 (Pt 1) (2003) 20–24.
[156] A.Y. Lemoine, S. Ledoux, E. Larger, Adipose tissue angiogenesis in obesity, Thromb. Haemost. 110 (4) (2013) 661–668.
[157] I. Elias, et al., Adipose tissue overexpression of vascular endothelial growth factor protects against diet-induced obesity and insulin resistance, Diabetes 61 (7) (2012) 1801–1813.
[158] H.K. Sung, et al., Adipose vascular endothelial growth factor regulates metabolic homeostasis through angiogenesis, Cell Metab. 17 (1) (2013) 61–72.
[159] J. Tam, et al., Blockade of VEGFR2 and not VEGFR1 can limit diet-induced fat tissue expansion: role of local versus bone marrow-derived endothelial cells, PLOS One 4 (3) (2009), e4974.
[160] T. Seki, et al., Ablation of endothelial VEGFR1 improves metabolic dysfunction by inducing adipose tissue browning, J. Exp. Med. 215 (2) (2018) 611–626.
[161] H.M. Liu, et al., Losartan attenuates insulin resistance and regulates browning phenomenon of white adipose tissue in ob/ob mice, Curr. Issues Mol. Biol. 43 (3) (2021) 1828–1843.
[162] J.W. Jonker, et al., A PPARgamma-FGF1 axis is required for adaptive adipose remodelling and metabolic homeostasis, Nature 485 (7398) (2012) 391–394.

[163] H. Ohta, N. Itoh, Roles of FGFs as adipokines in adipose tissue development, remodeling, and metabolism, Front. Endocrinol. 5 (2014) 18.
[164] M. Konishi, et al., Role of Fgf10 in cell proliferation in white adipose tissue, Mol. Cell. Endocrinol. 249 (1–2) (2006) 71–77.
[165] M. Presta, et al., Fibroblast growth factor/fibroblast growth factor receptor system in angiogenesis, Cytokine Growth Factor Rev. 16 (2) (2005) 159–178.
[166] W. Huang, et al., Fibroblast growth factor 21 enhances angiogenesis and wound healing of human brain microvascular endothelial cells by activating PPARgamma, J. Pharm. Sci. 140 (2) (2019) 120–127.
[167] U. Yaqoob, et al., FGF21 promotes endothelial cell angiogenesis through a dynamin-2 and Rab5 dependent pathway, PLOS One 9 (5) (2014), e98130.
[168] Q. Dai, et al., FGF21 promotes ischaemic angiogenesis and endothelial progenitor cells function under diabetic conditions in an AMPK/NAD+-dependent manner, J. Cell. Mol. Med. 25 (6) (2021) 3091–3102.
[169] D. Leali, et al., Fibroblast growth factor 2-antagonist activity of a long-pentraxin 3-derived anti-angiogenic pentapeptide, J. Cell. Mol. Med. 14 (8) (2010) 2109–2121.
[170] Q. Hui, et al., FGF family: from drug development to clinical application, Int. J. Mol. Sci. 19 (7) (2018).
[171] D.G. Haider, et al., Increased plasma visfatin concentrations in morbidly obese subjects are reduced after gastric banding, J. Clin. Endocrinol. Metab. 91 (4) (2006) 1578–1581.
[172] Y.J. Heo, et al., Visfatin induces inflammation and insulin resistance via the NF-kappaB and STAT3 signaling pathways in hepatocytes, J. Diabetes Res. 2019 (2019), 4021623.
[173] D. Chen, et al., Visfatin promotes angiogenesis of RF/6A cells through upregulation of VEGF/VEGFR-2 under high-glucose conditions, Exp. Ther. Med. 21 (4) (2021) 389.
[174] S.R. Kim, et al., Visfatin promotes angiogenesis by activation of extracellular signal-regulated kinase 1/2, Biochem. Biophys. Res. Commun. 357 (1) (2007) 150–156.
[175] T. Romacho, et al., Visfatin/eNampt induces endothelial dysfunction in vivo: a role for toll-like receptor 4 and NLRP3 inflammasome, Sci. Rep. 10 (1) (2020) 5386.
[176] C.H. Tsai, et al., Visfatin increases VEGF-dependent angiogenesis of endothelial progenitor cells during osteoarthritis progression, Cells 9 (5) (2020).
[177] S.D. Parlee, et al., Elastase and tryptase govern TNFalpha-mediated production of active chemerin by adipocytes, PLOS One 7 (12) (2012), e51072.
[178] K.B. Goralski, et al., Chemerin, a novel adipokine that regulates adipogenesis and adipocyte metabolism, J. Biol. Chem. 282 (38) (2007) 28175–28188.
[179] G. Helfer, Q.F. Wu, Chemerin: a multifaceted adipokine involved in metabolic disorders, J. Endocrinol. 238 (2) (2018) R79–R94.
[180] X. Huang, et al., Chemerin-induced angiogenesis and adipogenesis in 3T3-L1 preadipocytes is mediated by lncRNA Meg3 through regulating Dickkopf-3 by sponging miR-217, Toxicol. Appl. Pharm. 385 (2019), 114815.
[181] G.K. Dimitriadis, et al., Chemerin induces endothelial cell inflammation: activation of nuclear factor-kappa beta and monocyte-endothelial adhesion, Oncotarget 9 (24) (2018) 16678–16690.
[182] N. Nakamura, et al., Chemerin promotes angiogenesis in vivo, Physiol. Rep. 6 (24) (2018), e13962.
[183] C. Ben Dhaou, et al., CCRL2 modulates physiological and pathological angiogenesis during retinal development, Front. Cell Dev. Biol. 9 (2021), 808455.
[184] C. Ben Dhaou, et al., Chemerin regulates normal angiogenesis and hypoxia-driven neovascularization, Angiogenesis (2021).
[185] O. De Henau, et al., Signaling properties of chemerin receptors CMKLR1, GPR1 and CCRL2, PLOS One 11 (10) (2016), e0164179.
[186] C. Huang, et al., A screened GPR1 peptide exerts antitumor effects on triple-negative breast cancer, Mol. Ther. Oncol. 18 (2020) 602–612.
[187] L. Tan, et al., Placental trophoblast-specific overexpression of chemerin induces preeclampsia-like symptoms, Clin. Sci. 136 (4) (2022) 257–272.
[188] E. Nigro, et al., New insight into adiponectin role in obesity and obesity-related diseases, Biomed. Res. Int. 2014 (2014), 658913.
[189] T. Yamauchi, et al., The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity, Nat. Med. 7 (8) (2001) 941–946.
[190] N. Ouchi, et al., Adiponectin stimulates angiogenesis by promoting cross-talk between AMP-activated protein kinase and Akt signaling in endothelial cells, J. Biol. Chem. 279 (2) (2004) 1304–1309.
[191] C.C. Huang, et al., Adiponectin promotes VEGF expression in rheumatoid arthritis synovial fibroblasts and induces endothelial progenitor cell angiogenesis by inhibiting miR-106a-5p, Cells 10 (10) (2021).
[192] S. Wang, et al., Adiponectin modulates the function of endothelial progenitor cells via AMPK/eNOS signaling pathway, Biochem. Biophys. Res. Commun. 493 (1) (2017) 64–70.
[193] N. Ouchi, et al., Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF-kappaB signaling through a cAMP-dependent pathway, Circulation 102 (11) (2000) 1296–1301.
[194] H. Okui, et al., Adiponectin is a better predictor of endothelial function of the coronary artery than HOMA-R, body mass index, immunoreactive insulin, or triglycerides, Int. J. Cardiol. 126 (1) (2008) 53–61.
[195] R. Shibata, et al., Adiponectin stimulates angiogenesis in response to tissue ischemia through stimulation of amp-activated protein kinase signaling, J. Biol. Chem. 279 (27) (2004) 28670–28674.
[196] K. Palanisamy, et al., Anti-angiogenic effect of adiponectin in human primary microvascular and macrovascular endothelial cells, Micro Res. 122 (2019) 136–145.
[197] R. Li, et al., Adiponectin inhibits high glucose-induced angiogenesis via inhibiting autophagy in RF/6A cells, J. Cell. Physiol. 234 (11) (2019) 20566–20576.
[198] E. Brakenhielm, et al., Adiponectin-induced antiangiogenesis and antitumor activity involve caspase-mediated endothelial cell apoptosis, Proc. Natl. Acad. Sci. USA 101 (8) (2004) 2476–2481.
[199] M. Fasshauer, R. Paschke, M. Stumvoll, Adiponectin, obesity, and cardiovascular disease, Biochimie 86 (11) (2004) 779–784.
[200] R. Adya, et al., Protective actions of globular and full-length adiponectin on human endothelial cells: novel insights into adiponectin-induced angiogenesis, J. Vasc. Res. 49 (6) (2012) 534–543.
[201] M. Okada-Iwabu, et al., A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity, Nature 503 (7477) (2013) 493–499.
[202] S.J. Wang, W.Y. Lu, K.Y. Liu, Adiponectin receptor agonist AdipoRon suppresses adipogenesis in C3H10T1/2 cells through the adenosine monophosphateactivated protein kinase signaling pathway, Mol. Med. Rep. 16 (5) (2017) 7163–7169.
[203] B.R. Kupchak, et al., Antagonism of human adiponectin receptors and their membrane progesterone receptor paralogs by TNFalpha and a ceramidase inhibitor, Biochemistry 48 (24) (2009) 5504–5506.
[204] H.G. Augustin, et al., Control of vascular morphogenesis and homeostasis through the angiopoietin-tie system, Nat. Rev. Mol. Cell Biol. 10 (3) (2009) 165–177.
[205] P. Saharinen, et al., Angiopoietins assemble distinct Tie2 signalling complexes in endothelial cell-cell and cell-matrix contacts, Nat. Cell Biol. 10 (5) (2008) 527–537.
[206] J.E. Girling, P.A. Rogers, Regulation of endometrial vascular remodelling: role of the vascular endothelial growth factor family and the angiopoietin-TIE signalling system, Reproduction 138 (6) (2009) 883–893.
[207] Y.A. An, et al., Angiopoietin-2 in white adipose tissue improves metabolic homeostasis through enhanced angiogenesis, eLife 6 (2017).
[208] H. Bae, et al., Angiopoietin-2-integrin alpha5beta1 signaling enhances vascular fatty acid transport and prevents ectopic lipid-induced insulin resistance, Nat. Commun. 11 (1) (2020) 2980.
[209] Y. Xue, et al., FOXC2 controls Ang-2 expression and modulates angiogenesis, vascular patterning, remodeling, and functions in adipose tissue, Proc. Natl. Acad. Sci. USA 105 (29) (2008) 10167–10172.
[210] D.J. Good, et al., A tumor suppressor-dependent inhibitor of angiogenesis is immunologically and functionally indistinguishable from a fragment of thrombospondin, Proc. Natl. Acad. Sci. USA 87 (17) (1990) 6624–6628.
[211] P. Bornstein, Thrombospondins function as regulators of angiogenesis, J. Cell Commun. Signal. 3 (3–4) (2009) 189–200.
[212] V. Varma, et al., Thrombospondin-1 is an adipokine associated with obesity, adipose inflammation, and insulin resistance, Diabetes 57 (2) (2008) 432–439.
[213] Y. Matsuo, et al., Thrombospondin 1 as a novel biological marker of obesity and metabolic syndrome, Metabolism 64 (11) (2015) 1490–1499.
[214] G. Voros, H.R. Lijnen, Deficiency of thrombospondin-1 in mice does not affect adipose tissue development, J. Thromb. Haemost. 4 (1) (2006) 277–278.
[215] M.J. Lee, Transforming growth factor beta superfamily regulation of adipose tissue biology in obesity, Biochim. Biophys. Acta Mol. Basis Dis. 1864 (4 Pt A) (2018) 1160–1171.
[216] P. ten Dijke, H.M. Arthur, Extracellular control of TGFbeta signalling in vascular development and disease, Nat. Rev. Mol. Cell Biol. 8 (11) (2007) 857–869.
[217] Z. Wang, et al., Role of endothelial-to-mesenchymal transition induced by TGF-beta1 in transplant kidney interstitial fibrosis, J. Cell Mol. Med. 21 (10) (2017) 2359–2369.
[218] C. Penafuerte, et al., Novel TGF-beta antagonist inhibits tumor growth and angiogenesis by inducing IL-2 receptor-driven STAT1 activation, J. Immunol. 186 (12) (2011) 6933–6944.
[219] J. Liu, et al., TGF-beta blockade improves the distribution and efficacy of therapeutics in breast carcinoma by normalizing the tumor stroma, Proc. Natl. Acad. Sci. USA 109 (41) (2012) 16618–16623.
[220] H. Yadav, et al., Protection from obesity and diabetes by blockade of TGF-beta/Smad3 signaling, Cell Metab. 14 (1) (2011) 67–79.
[221] A.H. Sprague, R.A. Khalil, Inflammatory cytokines in vascular dysfunction and vascular disease, Biochem. Pharm. 78 (6) (2009) 539–552.
[222] R. Cao, et al., Leptin induces vascular permeability and synergistically stimulates angiogenesis with FGF-2 and VEGF, Proc. Natl. Acad. Sci. USA 98 (11) (2001) 6390–6395.
[223] N. Maeda, et al., Diet-induced insulin resistance in mice lacking adiponectin/ACRP30, Nat. Med. 8 (7) (2002) 731–737.
[224] M.K. DeBari, R.D. Abbott, Adipose tissue fibrosis: mechanisms, models, and importance, Int. J. Mol. Sci. 21 (17) (2020).
[225] J. Chudek, A. Wiecek, Adipose tissue, inflammation and endothelial dysfunction, Pharm. Rep. 58 (Suppl) (2006) 81–88.
[226] B.R. Freedman, D.J. Mooney, Biomaterials to mimic and heal connective tissues, Adv. Mater. 31 (19) (2019), e1806695.
[227] N.A. O'Halloran, et al., Hydrogels in adipose tissue engineering-potential application in post-mastectomy breast regeneration, J. Tissue Eng. Regen. Med 12 (12) (2018) 2234–2247.
[228] M. Di Somma, et al., Natural histogel-based bio-scaffolds for sustaining angiogenesis in beige adipose tissue, Cells 8 (11) (2019).
[229] S.V. Koduru, et al., Cellular based strategies for microvascular engineering, Stem Cell Rev. Rep. 15 (2) (2019) 218–240.
[230] A. Bharadwaz, A.C. Jayasuriya, Recent trends in the application of widely used natural and synthetic polymer nanocomposites in bone tissue regeneration, Mater. Sci. Eng. C. Mater. Biol. Appl. 110 (2020), 110698.
[231] P.K. Raghav, et al., Mesenchymal stem cell-based nanoparticles and scaffolds in regenerative medicine, Eur. J. Pharm. 918 (2022), 174657.

[232] S. Dharmadhikari, et al., Deconstructing tissue engineered trachea: assessing the role of synthetic scaffolds, segmental replacement and cell seeding on graft performance, Acta Biomater. 102 (2020) 181–191.
[233] T. Nardo, et al., Mussel-inspired antimicrobial coating on PTFE barrier membranes for guided tissue regeneration, Biomed. Mater. 16 (3) (2021).
[234] J.G. Kral, D.L. Crandall, Development of a human adipocyte synthetic polymer scaffold, Plast. Reconstr. Surg. 104 (6) (1999) 1732–1738.
[235] K. Li, et al., Re-endothelialization of decellularized liver scaffolds: a step for bioengineered liver transplantation, Front. Bioeng. Biotechnol. 10 (2022), 833163.
[236] C. Liu, et al., Decellularized extracellular matrix mediates tissue construction and regeneration, Front. Med. 16 (1) (2022) 56–82.
[237] S. Nellinger, et al., Cell-derived and enzyme-based decellularized extracellular matrix exhibit compositional and structural differences that are relevant for its use as a biomaterial, Biotechnol. Bioeng. 119 (4) (2022) 1142–1156.
[238] Z. Zhu, et al., Construction of adipose tissue using a silica expander capsule and cell sheet-assembled of decellularized adipose tissue, Acta Biomater. 141 (2022) 89–101.
[239] K. Liu, et al., Methoxy polyethylene glycol modification promotes adipogenesis by inducing the production of regulatory T cells in xenogeneic acellular adipose matrix, Mater. Today Bio 12 (2021), 100161.
[240] H.K. Cheung, et al., Composite hydrogel scaffolds incorporating decellularized adipose tissue for soft tissue engineering with adipose-derived stem cells, Biomaterials 35 (6) (2014) 1914–1923.
[241] A. Shridhar, et al., Investigating the effects of tissue-specific extracellular matrix on the adipogenic and osteogenic differentiation of human adipose-derived stromal cells within composite hydrogel scaffolds, Front. Bioeng. Biotechnol. 7 (2019) 402.

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