OPINION

Adipose tissue angiogenesis as a therapeutic target for obesity and metabolic diseases

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Abstract | Current pharmacotherapeutic options for treating obesity and related metabolic disorders remain limited and ineffective. Emerging evidence shows that modulators of angiogenesis affect the expansion and metabolism of fat mass by regulating the growth and remodelling of the adipose tissue vasculature. Pharmacological manipulation of adipose tissue neovascularization by angiogenic stimulators and inhibitors might therefore offer a novel therapeutic option for the treatment of obesity and related metabolic disorders. This Perspective discusses recent progress in understanding the molecular mechanisms that control adipose tissue angiogenesis and in defining potential new vascular targets and approaches for the treatment of this group of diseases.

Obesity and related disorders constitute the greatest threat to global human health. According to a recent report by the World Health Organization, there are >1 billion overweight adults worldwide, and at least 300 million of these individuals are clinically obese[1]. Approximately two-thirds of US adults and the majority of the rest of the Western adult population are overweight or obese. Obesity is a complex metabolic disorder linked to an increased risk of the most common and severe human diseases, including type 2 diabetes, hypertension, cardiovascular diseases, stroke and certain types of cancer such as colorectal, breast and prostate cancers[2]. Additionally, obese individuals of all ages often suffer from social and psychological problems such as depression and low self-esteem.

Non-pharmacological management of obesity, including lifestyle changes and physical exercise, is recommended as first-line treatment, and gastrointestinal and fat elimination surgical procedures provide alternative options for reducing the body burden of obesity. However, with the exception of the gastric bypass operation, these methods are often insufficient to normalize body weight and prevent life-threatening complications[3]. Thus, effective drugs are urgently needed for the treatment of obesity and related disorders.

Angiogenesis — the process of new blood vessel formation — is crucial for all tissue growth, expansion and repair[4]. Adipose tissue, and in particular brown adipose tissue (BAT), is probably the most highly vascularized tissue in the body, as each adipocyte is encircled by capillaries[2]. Indeed, angiogenesis has been shown to have a crucial role in the modulation of adipogenesis and obesity[2,5]. Molecular mechanisms of switching on angiogenic phenotypes in both healthy and pathological tissues involve an imbalanced production of overlapping angiogenic factors and inhibitors, including vascular endothelial growth factor A (VEGFA), fibroblast growth factor (FGF), adiponectin and thrombospondin 1 (REFS 6–10). Anti-angiogenic drugs, such as those targeting VEGFA pathways, are key components of first-line therapy for various human cancers[11–14]. Similarly, VEGFA blockade is used to treat non-malignant diseases such as choroidal neovascularization in age-related macular degeneration[15,16]. The clinical success of anti-angiogenic drugs in these otherwise clinically unrelated diseases shows that pathological angiogenesis is regulated by common molecular mechanisms. Given that obesity and almost all obesity-associated disorders — including diabetic complications, cardiovascular disorders and malignancies — are associated with pathological angiogenesis[2,17,18], modulating angiogenesis could be a novel therapeutic approach[2,5]. In metabolically active BAT, stimulation of angiogenesis may facilitate energy expenditure and could therefore be beneficial against obesity[19–21]. However, as adipose tissue is one of the largest tissues in the body, effective angiogenesis-targeted therapy would probably require systemic delivery of angiogenesis modulators, which may be associated with various adverse effects. In addition, the metabolic state of adipose tissue must be considered.

This Perspective highlights recent advances in understanding of the role of adipose vasculature in modulating adipose tissue development, growth and metabolism, revealing its potential to be therapeutically modulated as a possible future treatment approach for obesity and associated disorders.

Vascular functions in adipose tissues

The key role of the vasculature in the modulation of adipogenesis and the development of obesity are being increasingly recognized and understood[2]. In growing adipose tissue, angiogenic vessels contribute to adipogenesis by numerous mechanisms (FIG. 1). First, they supply nutrients and oxygen in the blood, which adipocytes, like most other tissues in the body, require for growth and maintenance[2]. In particular, increased vascular perfusion in BAT can further increase metabolic rates by providing oxygen molecules to burn fuels. Second, the vessels supply plasma, which is enriched in growth factors and cytokines. These trigger growth and survival signals in adipocytes to maintain their physiological functions[2]. Third, the vessels supply circulating stem cells, derived from bone marrow and other tissues, that are capable of differentiating into preadipocytes, adipocytes and vascular cells[22,23]. Fourth, the vessels facilitate the infiltration

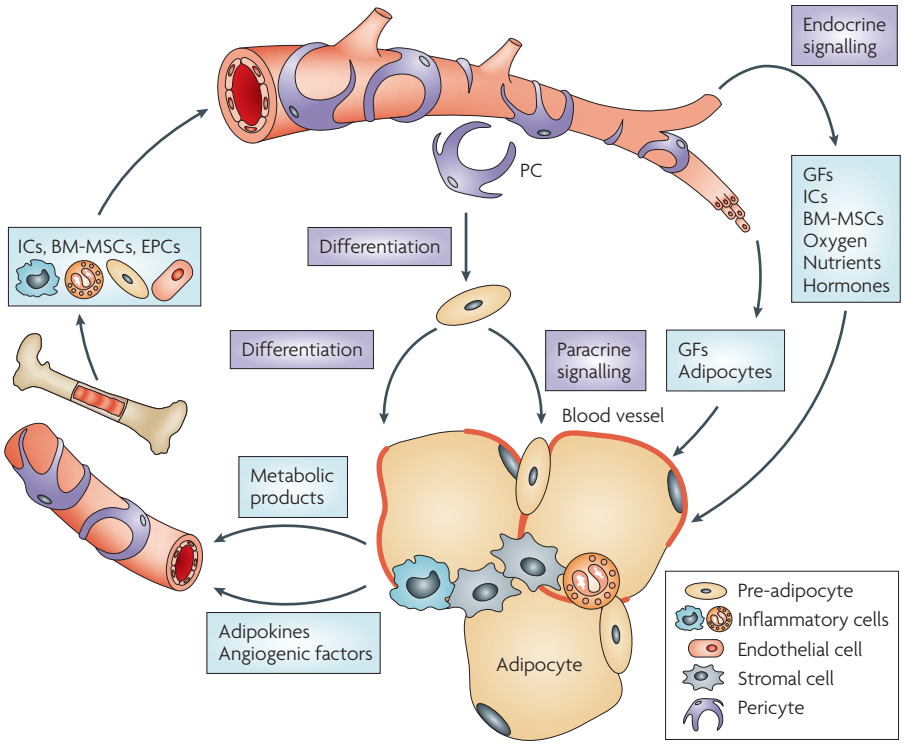

Figure 1 | **Functions of adipose tissue vasculature.** Outgrowth of blood vessels in adipose tissue provides oxygen, nutrients, growth factors (GFs), hormones, inflammatory cells (ICs) and bone marrow-derived mesenchymal stem cells (BM-MSCs) for maintaining homeostatic functions of adipocytes and expanding adipose tissue. Adipose tissue vasculature also removes metabolic products from the adipocytes. In the circulation, bone marrow-derived ICs, BM-MSCs and endothelial progenitor cells (EPCs) actively participate in adipogenesis and angiogenesis. Endothelial cells in angiogenic vessels produce growth factors and adipokines to maintain homeostatic functions and expand adipose tissue. Perivascular cells such as pericytes (PCs) can differentiate into white adipose tissue preadipocytes that become adipocytes. Adipocytes also produce angiogenic factors and adipokines that induce angiogenesis.

of monocytes and neutrophils into the adipose tissue, which augments the high numbers of inflammatory cells, originating from the bone marrow, that are observed in obese individuals[24,25]. Fifth, activated endothelial cells in angiogenic vessels produce various growth factors and cytokines that communicate with adipocytes in a paracrine fashion to promote their growth and expansion[2]. Sixth, a recent study shows that mural cells including vascular pericytes have stem cell features and can be differentiated into preadipocytes and adipocytes[23]. The plasticity feature of pericytes further increases the complex interplay between the vascular and adipose compartments. Seventh, the angiogenic vessels remove waste products from the adipose tissue which, in metabolically active BAT, is as important as supplying nutrients and oxygen. Eighth, recent studies show that adipose tissue vasculature consists of fenestrated microvessels that might play essential parts in determining local or systemic effects of adipokines[26,27]. Hypervascularization of adipose tissue might also contribute substantially to pathological angiogenesis in other tissues and organs.

Adult adipose tissue is probably one of the most plastic tissues in the body, and it expands and shrinks throughout adulthood[2]. The vasculature might have a causal role in determining adipocyte growth, regression and physiological functions by controlling the number of microvessels and by remodelling existing vessels. For example, vascular remodelling may alter blood perfusion, which could control the numbers and sizes of adipocytes, leading to expansion or shrinkage of adipose depots. Alteration of the adipose tissue mass would alter adipocyte functions considerably in relation to endocrine signalling and metabolism, as well as secretion of proangiogenic factors[2]. Expression levels of several adipokines including leptin and adiponectin are either positively or negatively correlated with the adipose mass[28,29]. Similarly, adipocytes may communicate directly with endothelial cells by producing proangiogenic factors and cytokines, which determine vessel growth and remodelling (discussed below).

Reciprocal interplay between endothelial cells and adipocytes suggests that dysfunction of either compartment would have a substantial impact on the other system. For example, endothelial dysfunction in obese individuals makes an important contribution to the development and progression of type 2 diabetes[30]. Functional alterations of the vascular endothelium in adipose tissues include impaired vasodilation, changes in angiogenic capacity, hypoxia-induced angiogenic responses and inflammation-induced vascular damage[31]. Impaired vascular functions in the adipose tissues could lead to alteration of lipid metabolism and the development of insulin resistance[30]. Conversely, certain adipokines produced by expanding adipose tissues cause endothelial dysfunction[32]. It seems that endothelial dysfunction in obese individuals affects multiple tissues and organs, leading to the development of commonly associated disorders of cardiovascular disease, diabetes and cancer[33]. Thus, normalization of endothelial function in adipose tissues of obese individuals is an important approach for the prevention and treatment of many human diseases.

Angiogenic modulators

To adapt to changes in the size and metabolic rate of adipose depots, adipose vasculature requires constant regulation by several angiogenic modulators. In metabolically quiescent adipose tissues, maintenance of the vasculature might be achieved by certain endothelial cell survival factors. Indeed, several adipokines, including leptin, resistin and visfatin, modulate angiogenic and vascular survival activities[2,26,34] (FIG. 2). Angiogenic adipokines and classical angiogenic factors such as VEGFA and FGF can synergistically induce angiogenesis[26]. Leptin might also upregulate the expression of VEGFA and synergistically induce angiogenesis[35]. In addition, certain adipocyte lipids such as monobutyrin induce angiogenesis[36]. Adipose tissue also produces several endogenous angiogenesis inhibitors to prevent further neovascularization, including thrombospondin 1 and plasminogen activator inhibitor[21,37–41]. Adiponectin has also been described as an endogenous angiogenesis inhibitor[37,38], although it has also been reported to have pro-angiogenic activity[42,43]. These findings suggest that switching on an angiogenic phenotype in the adipose tissue may require both upregulation of

proangiogenic factors and downregulation of endogenous inhibitors. Indeed, in a cold-induced adipose angiogenesis mouse model, simultaneous upregulation of VEGFA and downregulation of thrombospondin were observed[21].

In addition to adipocytes, other cell types such as inflammatory cells and stromal cells in the adipose tissue contribute substantially to angiogenesis (BOX 1). Hypoxia in adipose tissue of obese individuals also has a causal role in triggering inflammation and angiogenic responses. It induces high levels of hypoxia-inducible transcription factor 1 (HIF1) and HIF2, which increases the expression of certain angiogenesis-related factors and downregulates several endogenous angiogenesis inhibitors[26,44–46].

Vascular–adipose cell type switching

Two types of bone marrow-derived stem cells might contribute substantially to adipose tissue angiogenesis. Bone marrow-derived circulating endothelial progenitor cells participate in neovascularization in adipose tissue[47–50]. Bone marrow also contains multipotent mesenchymal stem cells (BM-MSCs), which can differentiate into cells and tissues of mesenchymal origin, including adipocytes, cartilage, bone and muscles[51,52]. BM-MSCs can also differentiate into endothelial cells, which might actively participate in adipose tissue angiogenesis[53] (FIG. 3).

Similar to BM-MSCs, pluripotent adipose-derived stromal cells (ADSCs) also differentiate into various cell types including endothelial and perivascular cells[54]. Based on their angiogenic properties and stem cell potential, ADSCs have been used for tissue repair and regeneration, such as in the treatment of ischaemic myocardium after an infarction[55]. Adipose tissue contains resident endothelial precursors that express endothelial markers including CD34, CD31, VEGF receptor 2 (VEGFR2), tyrosine kinase with immunoglobulin-like and EGF-like domains 1 (TIE1) and vascular endothelial cadherin[56]. When needed, these cells can be quickly mobilized and differentiated into mature endothelial cells in the angiogenic vessels.

Although mesenchymal stem cells that originate from the mesoderm are generally thought to give rise to preadipocytes, markers to trace the commitment and differentiation of these cells have been lacking. Using a mouse model with genetic lineage tracing, a recent study has shown that adipose progenitor cells reside in the mural cell compartment in the blood vessel wall of the adipose tissue, together with pericytes and vascular smooth muscle cells[23,57] (FIG. 3). Furthermore, these

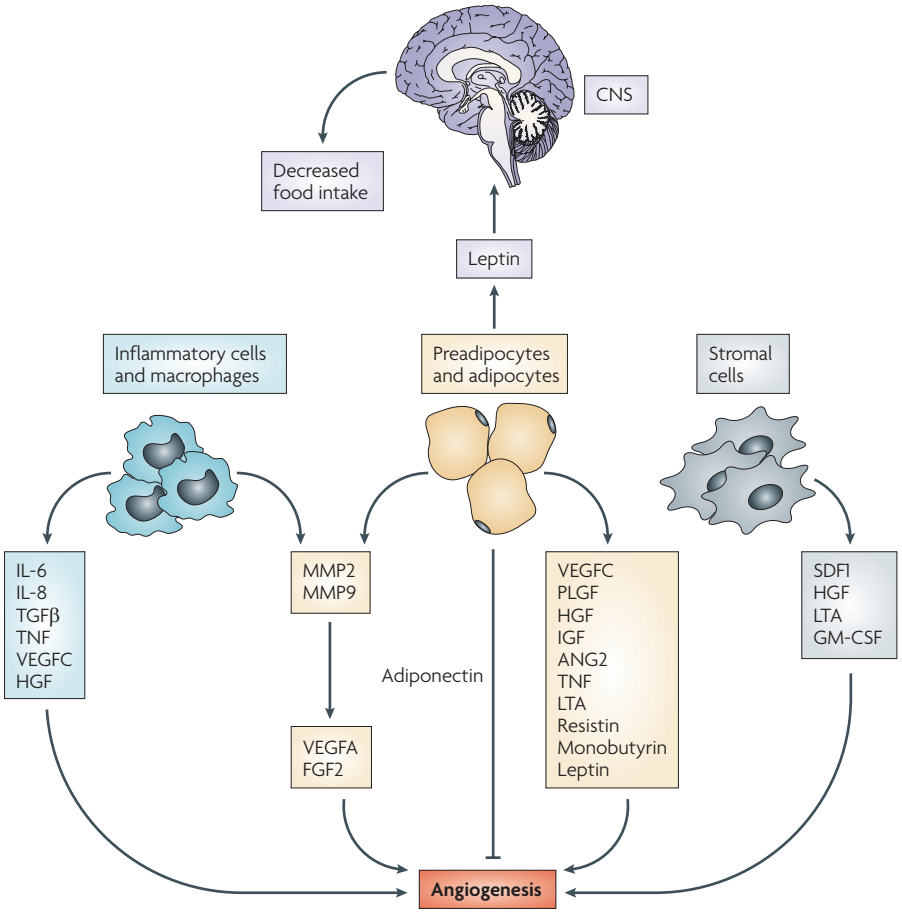

Figure 2 | **Mechanisms and molecular mediators of adipose tissue angiogenesis.** Adipocytes, adipose stromal cells and inflammatory cells produce multiple angiogenic factors, adipokines and cytokines that stimulate angiogenesis. Adipocytes also produce endogenous angiogenesis inhibitors that suppress vessel growth. Reciprocal interactions of various angiogenic factors in the adipose environment might lead to angiogenic synergism. Multifunctional leptin suppresses food intake through the central nervous system (CNS) and locally stimulates angiogenesis in the adipose tissue. ANG2, angiotensin 2; GM-CSF, granulocyte–macrophage colony-stimulating factor; HGF, hepatocyte growth factor; IGF, insulin-like growth factor; IL, interleukin; LTA, lymphotoxin-α (also known as TNFβ); MMP, matrix metalloproteinase; PLGF, placental growth factor; SDF1, stromal cell-derived factor 1; TGFβ, transforming growth factor-β; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.

adipose progenitor cells are located in the vasculature of only adipose tissue and not in that of non-adipose tissues[23]. Thus, adipose vasculature not only supplies oxygen, nutrients, inflammatory cells and paracrine factors for adipogenesis, but also provides a progenitor niche for adipose tissue development. Brown and white adipocytes originate from distinct cell precursors[58,59]. Maintenance of the brown fat phenotype requires persistent expression of PR domain zinc finger protein 16 (PRDM16)[60].

Angiogenesis as an obesity therapy

The original hypothesis that angiogenesis could be a target for obesity therapy was based on the knowledge that the expansion and growth of white adipose tissue (WAT) is dependent on angiogenesis[61,62]. Thus, as has been proven for tumour growth, inhibition of adipose tissue angiogenesis might inhibit WAT growth and ultimately the development of obesity. Indeed, endogenous angiogenesis inhibitors such as angiostatin[63] and endostatin[64] have been shown to reduce the body weight of obese mice[62]. In addition, angiogenesis inhibitors such as TNP-470 and VEGFR2-specific inhibitors have been shown to prevent the development of obesity in genetic mouse models and studies based on high-fat diets[61,62,65,66] (TABLE 1). Specific inhibition of angiogenesis in the growing adipose tissue and a decrease in the body weight of obese mice

Box 1 | **Role of inflammatory and stromal cells in adipose tissue angiogenesis**

In addition to adipocytes, other cell types such as inflammatory cells and stromal cells in the adipose tissue contribute substantially to angiogenesis. Adipose tissue in obese subjects is a site of chronic inflammation, with infiltration of many macrophages and leukocytes. These cells produce angiogenic factors and cytokines, including vascular endothelial growth factor A (VEGFA), tumour necrosis factor, interleukin-6 (IL-6), IL-8 and chemokines[24,25,117,118]. Deletion of tissue inhibitor of metalloprotease 3, a natural VEGFA antagonist, accelerates inflammation in adipose tissue[119]. Leptin, an adipose tissue-specific hormone that shares structural and functional similarities with the inflammatory cytokine IL-6, may directly and indirectly contribute to inflammation and angiogenesis[120]. Angiogenic macrophages that are positive for lymphatic vessel endothelial hyaluronan receptor 1 are required for angiogenesis in adipose tissue through activation of the hypoxia-dependent VEGFA signalling system[121]. Additionally, various forms of peroxisome proliferator-actived receptor directly participate in the regulation of inflammation and angiogenesis in adipose tissue[122,123]. Mechanistically, it is still unclear why adipose tissue-infiltrating macrophages are increased in obese individuals. One possibility is that angiogenic vessels in adipose tissue might facilitate the infiltration of these cells, which are derived from bone marrow[124].

Another dominant cell type in adipose tissue is adipose-derived stromal cells (ADSCs), which make an important contribution to angiogenesis by producing multiple angiogenic factors including VEGFA, hepatocyte growth factor, fibroblast growth factor 2, transforming growth factor-β and chemokines[55,125,126] (FIG. 3). Importantly, ADSCs have stem or progenitor cell properties that can lead to differentiation into endothelial cells or perivascular pericytes[54,127–131]. $CD34^+$ and $CD34^-$ populations of ADSCs preferentially differentiate into endothelial cells and pericytes, respectively[132,133]. Thus, ADSCs contribute to adipose tissue angiogenesis by producing soluble angiogenic molecules and by supplying vascular cells to the angiogenic vessels.

are associated with a reduction in vascular density and endothelial cell apoptosis[61,62,65]. TNP-470 and its analogues also reduce food intake. These angiogenesis inhibitors seem to specifically target vascular endothelial cells. Capillary endothelial cells are highly sensitive to angiogenesis inhibitors such as TNP-470, whereas preadipocytes remain insensitive[62].

A similar anti-obesity activity by inhibition of angiogenesis was seen for CKD-732, a TNP-470 analogue[67]. Although TNP-470 is considered to be a selective angiogenesis inhibitor, it has other non-vascular effects such as neurotoxicity[68], which may alternatively affect food intake and body weight. However, no other obvious toxicities were observed in mouse models. Thus, the precise mechanisms underlying the anti-obesity activity of TNP-470 remain unclear and warrant further investigation. Notably, mice reduce their body weight while on TNP-470 and regain weight when off schedule[62]. These treatment-regulated cycles can occur several times without causing resistance or other obvious side effects. These findings suggest that anti-angiogenic agents can be used repeatedly for the treatment of obesity without encountering drug resistance. By contrast, preclinical and clinical experiences with anti-angiogenic cancer drugs have shown that malignant tumours develop evasive drug resistance by unconventional mechanisms including compensatory switching to express multiple angiogenic factors[69,70]. Unlike tumour cells, however, adipocytes, stromal cells and inflammatory cells in adipose tissue contain stable genomes, and thus switching between angiogenic pathways may not occur as frequently as it does in malignant tissues.

Nevertheless, it is plausible that chronic activation of different signalling pathways might result in reciprocal switching of angiogenic responses, potentially leading to the development of drug resistance.

Another possible approach to therapeutically target the adipose tissue vasculature is the delivery of a peptide motif that specifically binds to a vascular marker in the adipose tissue. Using an *in vivo* phage display method, a peptide motif specific to the vasculature in WAT (CKGGRAKDC) has been identified, which specifically binds to prohibitin, a multifunctional membrane protein expressed in the adipose tissue vasculature[71]. Coupling this targeting peptide motif with an apoptosis-inducing peptide produced marked anti-obesity effects in mouse obesity models[71]. It would be exciting to see whether such a vascular-targeting approach also has anti-obesity activity in human subjects. Another potential target includes the peroxisome proliferator-activated receptor (PPAR) which, when activated, induces angiogenesis in adipose tissue[72]. For example, the thiazolidinedione rosiglitazone is a PPAR activator which stimulates adipose tissue angiogenesis by increasing expression levels of VEGFA, VEGFB and angiopoietin-related protein 4, leading to accelerated adipose tissue growth[73].

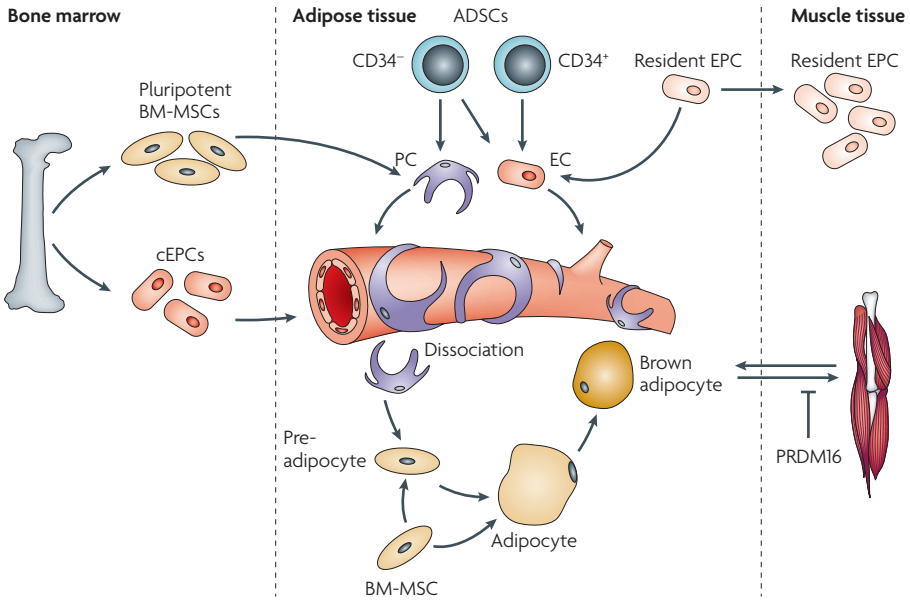

Figure 3 | **Reciprocal switching between various cell types in adipose tissue.** $CD34^-$ and $CD34^+$ populations of adipose-derived stromal cells (ADSCs) can differentiate into pericytes (PCs) and endothelial cells (ECs), respectively. ADSC-derived vascular cells may actively participate in angiogenesis. In addition, endothelial progenitor cells (EPCs) residing in adipose tissue can differentiate into endothelial cells. Bone marrow-derived mesenchymal stem cells (BM-MSCs) and circulating EPCs (cEPCs) may differentiate into vascular cells and adipocytes. Brown adipocytes can differentiate into muscle cells. PRDM16, PR domain zinc finger protein 16.

Table 1 | **Anti-obesity effects of angiogenesis modulators in animal models**

Angiogenesis inhibitor	Mouse model	Body weight	Insulin sensitivity	Angiogenesis	Refs
TNP-470	HFD	Reduced	Increased	Inhibition	61,62
CKD-732 (TNP-470 analogue)	Ob/ob mice	Reduced	ND	Inhibition	67
MMP inhibitors (Galardia and Bay-129566)	HFD	Reduced	ND	Inhibition	62,74–76
Endostatin	Ob/ob mice	Reduced	ND	Inhibition	62
Thalidomide	Ob/ob mice	Reduced	ND	Inhibition	62
Angiostatin	Ob/ob mice	Reduced	ND	Inhibition	62
VEGFR blockade	HFD	No effect	ND	Inhibition	65,66
PLGF blockade	HFD	Reduced	No effect	Inhibition	77,78
EGCG (catechin in tea)	HFD and ob/ob mice	Reduced	ND	Inhibition	81–85
Curcumin (polyphenol)	HFD	Reduced	ND	Inhibition	79
Adiponectin*	Ob/ob mice	Reduced	Increased	Stimulation and inhibition	37,86–88
Leptin	Ob/ob mice	Reduced	Increased	Stimulation	89,90

EGCG, epigallocatechin-3-gallate; HFD, high-fat diet; ND, not determined; PLGF, placental growth factor; VEGFR, vascular endothelial growth factor receptor. *Adiponectin has been reported to be both an anti-angiogenic and a proangiogenic factor (see also REFS 42 and 43).

In addition to specific angiogenesis inhibitors, many nonspecific angiogenesis modulators have been tested in obesity models[28,34,37,62,74–89] (TABLE 1).

Leptin. Whereas results from studies on most of the tested molecules concur with the anti-angiogenesis concept for the treatment of obesity, the actions of leptin remain a paradox. Through a negative feedback system, leptin acts on its target neurons in the hypothalamus to restrict over-eating and obesity[28]. Leptin can, however, induce angiogenesis, suggesting that it might contribute positively to the development of adipose tissue[26,34]. Therefore, if obese individuals received leptin treatment, would this molecule increase or suppress fat development? In genetically obese human individuals carrying homozygous mutations in the leptin gene, administration of recombinant leptin successfully reduces body weight, despite its angiogenic activity[90]. However, the majority of obese humans have unusually high levels of circulating leptin but are leptin-resistant. Therefore, the administration of leptin has no effect on food intake or body weight[91,92]. The complexity of the potential effects of leptin in the treatment of obesity clearly warrants further investigation.

Angiogenesis inhibition or activation? Although the inhibition of adipose tissue angiogenesis had originally been proposed as a means of treating obesity, this concept has now been challenged by the paradox that energy expenditure might also require angiogenesis[2,21]. This is particularly true for the development of BAT for protection against obesity. Therefore, it is uncertain whether a positive or a negative angiogenesis modulator could be used to treat obesity. Based on limited preclinical and clinical findings, it seems that the administration of angiogenesis modulators should depend on the metabolic status of the adipose tissue of a given individual (FIG. 4). Metabolically active adipose tissue (that is, BAT) will have a greater expenditure of energy if its supply of angiogenic vessels is increased. By contrast, in metabolically quiescent obese individuals with a large amount of WAT, it may be therapeutically beneficial to inhibit angiogenesis. This population could also benefit from agents that promote the development of BAT, including BAT angiogenesis, which may be achievable through localized delivery. Interestingly, prolonged exposure to the cold has been associated with increases in BAT stores and BAT activity, which has suggested additional possible therapeutic approaches (BOX 2).

Combination therapies. It is likely that the combination of angiogenesis modulators with other targeted therapies for the treatment of obesity will prove most effective. In principle, combinations of angiogenesis modulators with drugs that target food intake, lipid metabolism or absorption pathways — such as thyroid hormone, sibutramine and orlistat — should produce synergistic anti-obesity effects. It might also be beneficial to combine

Box 2 | **Exposure to the cold may increase BAT**

Whereas white adipocytes store fuel as large lipid droplets, brown adipocytes dissipate energy by a specialized programme that involves activation of uncoupling protein 1 in the inner mitochondrial membrane, which uncouples metabolism from ATP production to produce heat[19,134]. In rodents and humans, prolonged exposure to cold leads to increased depots of brown adipose tissue (BAT)[21,135]. These findings have raised an interesting possibility of switching white adipose tissue to BAT as a therapeutic option. How could angiogenically active BAT be exploited for anti-obesity therapy?

It is probable that the simplest way to lose weight is to chronically expose individuals with metabolically active BAT to cold. Although low temperatures may create discomfort, it would not be difficult to test this hypothesis. Knowledge of BAT metabolism from studies in mice has provided important clues for anti-obesity therapy. For example, thermoneutrality (the environmental temperature at which body temperature is maintained with the lowest expenditure of energy) for mice is at ~30°C; laboratory mice, which are generally kept at 18–22°C are thus under chronic thermal stress. When mice are kept at the thermoneutral temperature of 30°C, however, they become obese when fed their normal diet[19,20]. These findings imply that chronic exposure to low temperature is an effective therapeutic approach against obesity.

Another possibility would be to develop drugs that mimic exposure to cold temperatures by activating the sympathetic nervous system. This approach would be particularly important for generating BAT in obese individuals, who often have BAT with a low metabolic activity. Like most other therapeutic approaches, exposure to cold may potentially cause other pathological responses mediated by sympathetic activation of neuropeptide Y release, including hypertension, hypothermia, abdominal obesity and metabolic syndrome[136]. It is unclear how to avoid these undesirable responses and selectively activate BAT.

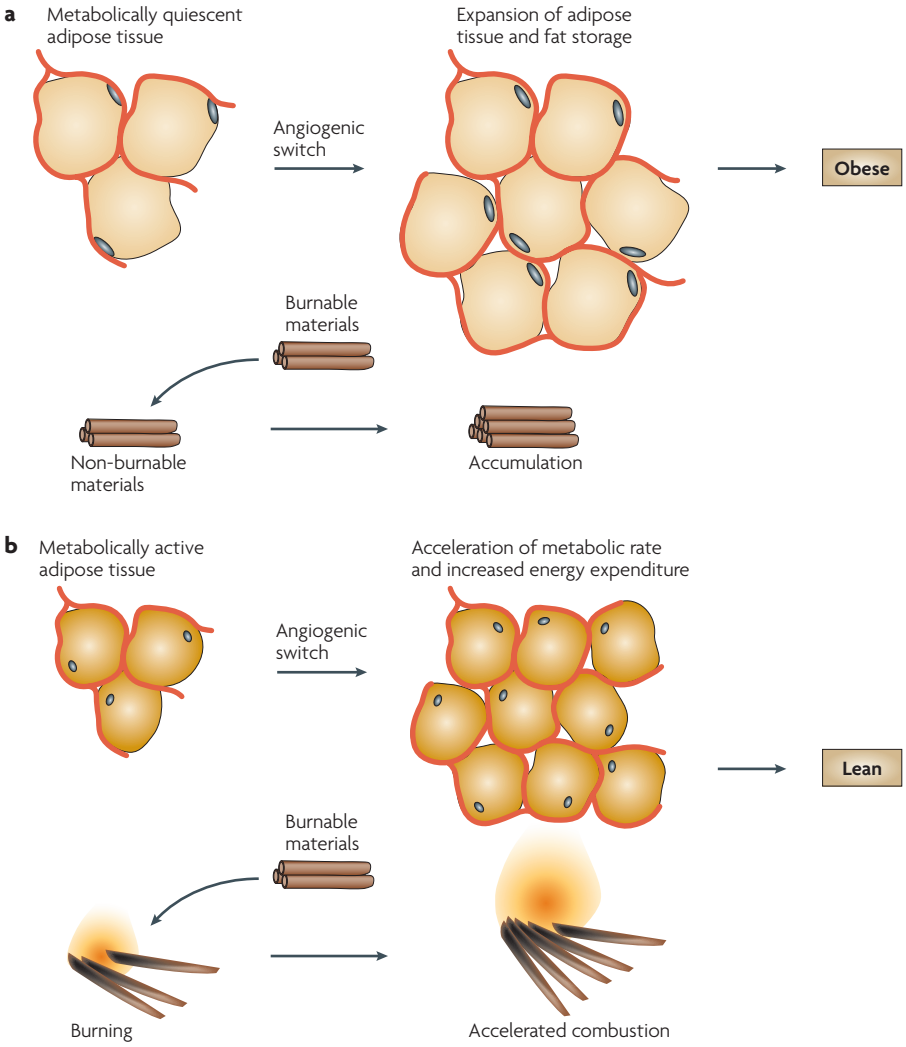

Figure 4 | **Paradoxical relationship between angiogenesis and metabolism in white and brown adipose tissues. a** | In metabolically quiescent white adipose tissue, angiogenesis may facilitate the process of adipogenesis, leading to the development of obesity. An analogous situation would be to accumulate burnable materials in an unlit wood stove, resulting in an increase in the total mass. **b** | In metabolically active brown adipose tissue, active angiogenesis can facilitate energy expenditure and increase the metabolic rate, leading to a lean phenotype. Similarly, addition of oxygen and burnable materials to a lit wood stove would accelerate the burning speed, leading to a decrease in the total mass.

anti-angiogenic agents with multifunctional adipokines such as leptin. For example, whereas other inhibitors could block leptin-induced angiogenesis in adipose tissue, leptin could still control food intake and obesity through the central nervous system (except in leptin-resistant subjects).

Safety. How safe would angiogenesis modulators be for anti-obesity therapy? Clinical experiences with anti-angiogenic drugs for cancer therapy such as bevacizumab, sunitinib and sorafenib show that these drugs are generally safe, but in rare cases can cause fatal cardiovascular disorders[11,12,14]. The cardiovascular disorders triggered by anti-angiogenic drugs are probably further increased by the tendency of these drugs to induce hypertension and proteinuria[12,93]. A reduction in fat mass is achieved by the process of lipolysis, which releases free fatty acids into the circulation. If angiogenesis modulators affect the metabolism of adipocytes in humans, as has been seen in mice[21], their anti-obesity activity might elevate lipolysis to a level that could further increase the cardiovascular risk associated with the formation and decreased stability of atherosclerotic plaques.

Other side effects of angiogenesis inhibition that are not metabolically related might include an impaired process of wound healing and tissue repair, both of which are angiogenesis dependent[4,13,69]. This is particularly important in patients with type 2 diabetes, who often develop chronic ulcers because of impaired wound healing[94]. Angiogenic factors such as VEGFA have broad biological functions even under physiological conditions, including *de novo* formation of the vascular system during embryonic development, neurotrophic and neuroprotective activity, tissue and organ regeneration, maintenance of vascular integrity and maintenance of vascular fenestrations in endocrine glands[95–97]. Thus, long-term systemic delivery of VEGF-targeted drugs for the treatment of obesity may cause a broad range of adverse effects including neurotoxicity[98].

Similarly, if therapies are aimed at stimulating angiogenesis to increase BAT and metabolic rates, their application should be restricted locally within BAT to avoid side effects. Preclinical and clinical experiences of cardiovascular therapy for ischaemic diseases show that gene or protein delivery of pro-angiogenic factors such as VEGFA can cause extremity oedema, haemangioma-like vascular tumours, progression of atherosclerosis and even growth of dormant tumours[99–102], although some of these therapy-related side effects remain controversial. In humans, systemic administration of TNP-470 has resulted in neurotoxic effects[68]. We are clearly at an early stage in the consideration of angiogenesis modulators for the treatment of obesity and related metabolic disorders such as diabetes.

Therapy for obesity complications

The angiogenic switch in adipose tissue might affect several tissues and organs, leading to the development of the most common and lethal human disorders including type 2 diabetes, tumours and cardiovascular disease[57,103,104]. Intriguingly, the onset, development and progression of these diseases are linked to angiogenesis[2] (FIG. 5). Furthermore, complications associated with type 2 diabetes — including retinopathy, neuropathy, nephropathy and chronic inflammation — are accompanied by pathological angiogenesis (FIG. 5). In the case of diabetic retinopathy, pathological angiogenesis is probably triggered by local tissue ischaemia.

In addition to complications associated with abnormal metabolism, it is not surprising that obese individuals develop whole-body angiogenesis-related disorders owing to high levels of angiogenic factors[105,106]. Because adipose tissue is one of the largest tissues in

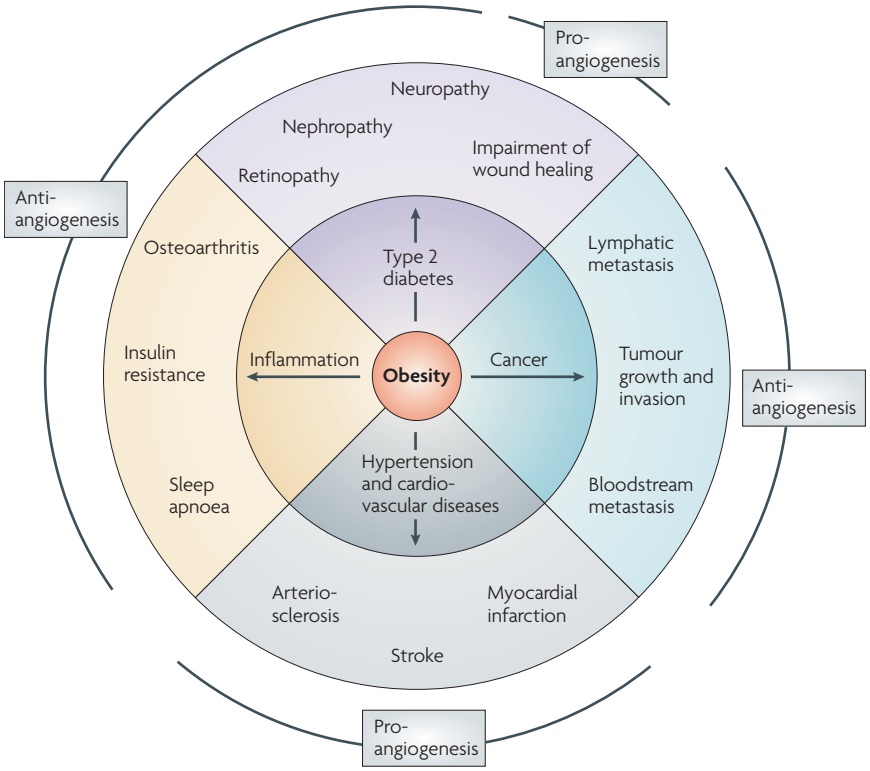

Figure 5 | **Angiogenesis in obesity-associated clinical complications.** Obesity is a pre-disease condition that induces pathological angiogenesis and impaired vascular functions. These changes lead to the onset, development and progression of many diseases such as cancer, cardiovascular disorders, diabetic complications and chronic inflammation. Some of the clinical complications are induced by impaired angiogenesis such as delayed wound healing, myocardial ischaemia and stroke. By contrast, other complications, including cancer metastasis and chronic inflammation, are caused by excessive neovascularization. Thus, therapeutic treatments of these complications should upregulate or downregulate angiogenesis depending on their clinical manifestations.

the body, a subtle elevation of angiogenic factors in this tissue could translate into a substantial increase throughout the body and trigger robust angiogenic responses in many tissues and organs. However, such an effect is also dependent on other environmental factors such as diet and tissue-specific actions of proangiogenic factors. For example, the available angiogenic receptors distributed in the vasculature of a specific tissue determine whether angiogenic factors are able to trigger an angiogenic response.

Angiogenesis-dependent development of obesity-related disorders and complications offers an important opportunity for therapeutic intervention by targeting pathological blood vessels. For example, early clinical studies with bevacizumab have shown promising signs that this anti-angiogenic drug can effectively prevent progression of diabetic retinopathy and diabetic maculopathy[16]. Similarly, pegaptanib and ranibizumab have been used successfully for the treatment of age-related macular degeneration[15,107–109]. The opposite principle has been used for the treatment of diabetic ulcers using platelet-derived growth factor B (PDGFB) as a pro-angiogenic factor[110]. Again, paradoxical mechanisms of modulation of angiogenesis should be considered in the treatment of complications resulting from obesity or diabetes.

Future directions and perspectives

Recent findings have shown that the vasculature has sophisticated functions in controlling adipogenesis, obesity and related complications and have challenged the early concept of simple inhibition of angiogenesis as an anti-obesity therapy. It now seems that the promotion of angiogenesis might, in some cases, be beneficial in obesity because of its ability to accelerate energy expenditure through increases in BAT. How do we relate the paradoxical principle of angiogenesis to anti-obesity and diabetes therapies? This issue may be resolved by systemic delivery of angiogenesis inhibitors to obese individuals who have little metabolically active BAT. In BAT-enriched regions such as the neck, mediastinum and supraclavicular areas, it would be prudent to promote angiogenesis locally to accelerate energy expenditure. The paradoxical regulation of angiogenesis for the treatment of diabetes-related complications has already been used in the clinical setting. For example, anti-angiogenic therapy including VEGF inhibitors has been tested for the treatment of diabetic retinopathy[111–113], and the angiogenic factor PDGFB is currently available for the treatment of ulcers in patients with diabetes[114–116].

Unlike the specific tissue or organ in which tumours are usually found in cancer patients, WAT is the largest tissue in severely obese patients and is distributed all over the body. If angiogenesis modulators are to be considered for therapy, it seems likely that high doses of drugs will be required to target angiogenic vessels in the fat mass, which might increase systemic side effects. In particular, patients who are obese and have already developed complications such as hypertension or cardiovascular disorders might not be recommended for anti-angiogenic therapy. Similarly, angiogenesis inhibitors may further delay wound healing in obese subjects and patients with type 2 diabetes.

In contrast to anti-angiogenic therapy for cancer, such an approach to obesity therapy might not lead to drug resistance because of the genomic stability of adipocytes and endothelial cells. However chronic activation of different signalling pathways may result in reciprocal switching of angiogenic responses. Another advantage of anti-angiogenic obesity treatment is that the timescale is not aimed at a lifetime of treatment. When body weight and metabolism are normalized, anti-angiogenic drugs could potentially be stopped.

Mechanistically, anti-angiogenic agents would target angiogenic vessels to arrest their growth, which would prevent further development of adipose tissue and obesity. In practice, how do we treat those patients who are already severely obese? Can agents that disrupt angiogenesis be used for treatment? This possibility warrants future investigation. In tumour tissues, agents that disrupt angiogenesis preferentially reduce the vasculature in hypoxic regions[49]. It is therefore likely that hypoxia in adipose tissue offers an opportunity for selective therapeutic interventions. Anti-angiogenic agents can affect adipose metabolism and increase insulin sensitivity[21]. These early

findings suggest that angiogenesis modulators may be used for the treatment of metabolic diseases regardless of obesity. In addition, almost all clinical complications related to obesity and diabetes could potentially be treated with angiogenesis modulators (FIG. 5). Following the first clinical success with the delivery of PDGFB for the treatment of chronic ulcers, early clinical evaluation has already shown promising signs that VEGF-targeted drugs might be approved for the treatment of diabetic retinopathy.

Taken together, recent evidence indicates that angiogenesis modulation may offer a tremendous opportunity for the treatment of obesity, metabolic disorders and related clinical complications. Moreover, angiogenesis modulators, in combination with other anti-obesity agents and possibly anti-inflammatory drugs that target different pathways, might synergistically increase the resulting therapeutic efficacy to combat this most common human disorder.

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Competing interests statement

The author declares competing financial interests: see web version for details.

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