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Review

Adipose tissue angiogenesis: Impact on obesity and type-2 diabetes ☆

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ABSTRACT

The growth and function of tissues are critically dependent on their vascularization. Adipose tissue is capable of expanding many-fold during adulthood, therefore requiring the formation of new vasculature to supply growing and proliferating adipocytes. The expansion of the vasculature in adipose tissue occurs through angiogenesis, where new blood vessels develop from those pre-existing within the tissue. Inappropriate angiogenesis may underlie adipose tissue dysfunction in obesity, which in turn increases type-2 diabetes risk. In addition, genetic and developmental factors involved in vascular patterning may define the size and expandability of diverse adipose tissue depots, which are also associated with type-2 diabetes risk. Moreover, the adipose tissue vasculature appears to be the niche for pre-adipocyte precursors, and factors that affect angiogenesis may directly impact the generation of new adipocytes. Here we review recent advances on the basic mechanisms of angiogenesis, and on the role of angiogenesis in adipose tissue development and obesity. A substantial amount of data points to a deficit in adipose tissue angiogenesis as a contributing factor to insulin resistance and metabolic disease in obesity. These emerging findings support the concept of the adipose tissue vasculature as a source of new targets for metabolic disease therapies. This article is part of a Special Issue entitled: Modulation of Adipose Tissue in Health and Disease.

1. Introduction

The growth and function of all tissues and organs are critically dependent on their appropriate vascularization. Blood flow is important for providing the correct oxygen tension in individual tissues, for the delivery and removal of nutrients and waste products, and for the transit of cells involved in tissue immune surveillance. In addition to being critical for the health of individual tissues, blood flow delivers hormones and growth factors that insure the inter-tissue and inter-organ communication necessary for whole body homeostasis. Thus, the growth of any organ or tissue must be accompanied by parallel growth of its vascular network. Most of the growth of organs and tissues occurs during development, and their final size remains relatively constant through adulthood. In contrast, adipose tissue is unique in that it can expand many-fold, to comprise more than 40% of total body composition in obese individuals, defined as a body mass index of 30 or higher. The ability of adipose tissue to expand has clear evolutionary advantages, enabling survival in times of nutrient scarcity; however, concomitant with adipose tissue expansion are metabolic alterations that enhance risk of metabolic disease. The cellular and molecular mechanisms by which adipose tissue growth is coordinated with the expansion of its capillary network are unknown. As these mechanisms may underlie the basis for adipose tissue dysfunction in metabolic disease, they comprise a fertile and exciting area of research.

While the close association between weight gain and heightened risk of type 2 diabetes (T2DM) is well established, not all individuals with obesity become diabetic, and certain individuals become diabetic after very minor weight gain [1]. This paradox is explained by the large individual variation in the size and expandability of different adipose tissue depots in humans, as expansion of some depots is associated with increase risk, while expansion of others is associated with decreased risk [2]. Strikingly, each standard deviation (SD) increase in subcutaneous adipose tissue mass decreases the odds of insulin resistance by 48%. In contrast, each SD increase in visceral adipose tissue mass increases the odds of insulin resistance by 80% [3]. The protective effect of expandable subcutaneous fat depots during weight gain is likely to be due to their capacity to properly store excess calories in the form of triglycerides, thus preventing ectopic lipid deposition into muscle, liver and visceral fat depots. Such ectopic deposition and inappropriate lipid metabolism are thought to cause insulin resistance and result in a greatly increased risk of T2DM [4,5]. Thus, understanding the specific mechanisms by which the subcutaneous adipose tissue expands is of particular interest, as these could provide new approaches for therapeutic intervention in metabolic disease. Several lines of evidence indicate that adipose tissue growth can be limited by its vascular supply [6–8], raising the possibility that the angiogenic potential of specific depots might be critical in limiting their maximal expandability. Testing this hypothesis will require a deep understanding of the basic mechanisms

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of vascularization in expanding adult tissues, and the specific regulatory factors that operate in different adipose tissue depots.

2. Basic molecular and cellular mechanisms of angiogenesis

The de-novo formation of blood vessels during the development of the embryo occurs through the process of vasculogenesis, in which mesoderm-derived precursors, called angioblasts, organize into the first primitive blood vessels. All further vessel growth during organ and tissue development, as well as during tissue repair in adult organism, takes place through the process of angiogenesis, in which new vessels sprout from pre-existing vasculature. It is likely therefore that the vascularization of adipose tissue depots in adults proceeds through angiogenic expansion of the existing vasculature, as has been shown to occur during the formation of fat pads from implanted cells [9]. The last few years have brought great insight into the basic molecular and cellular mechanisms of angiogenesis [10–14], setting the stage for the identification of factors that regulate this process to fulfill tissue and developmental stage specific functions. Key insights into the cellular and molecular bases for angiogenesis, derived from experimental models such as the developing zebrafish embryo and the mouse retina, are very briefly summarized below.

The cardinal features of angiogenesis comprise the proliferation of endothelial cells, their directed migration through the extracellular matrix, the establishment of intercellular junctions, the formation of a lumen, the organization of perivascular supporting cells, the anastomosis with existing vessels, and the establishment of circulation. The cardinal initiating event is the stimulation of endothelial cell proliferation, which is mediated by the VEGF family of growth factors. These growth factors and their receptors have been established as master regulators of endothelial cell growth. In particular, VEGF-A, acting through the VEGFR2 (VEGF receptor 2, also known as KDR in humans or Flk1 in mice) represents the most potent mitogenic and chemo attractant signal for endothelial cells. In response to VEGF-A gradients, endothelial cells divide, and acquire a specific phenotype (tip cell phenotype) characterized by the formation of branches and numerous filopodia, which extend towards the direction in which the endothelial cell migrates. The action of VEGFs and their receptors are critically controlled by the Notch signaling pathway, which modulates the responsiveness of endothelial cells to VEGF, and their subsequent specialization. Thus, tip cells are characterized by high levels of expression of Delta-like 4 (Dll4), which is a ligand for Notch. The stimulation of Notch signaling by Dll4 in the tip cell suppresses VEGF signaling in adjacent cell, resulting in the acquisition of a stalk-cell phenotype. The continuous dynamic interaction between VEGF, Notch and Dll4 results in the development of angiogenic sprouts. Newly formed sprouts are then stabilized by interactions with smooth muscle cells and pericytes, and become lumenized, through processes that appear to involve junctional trans-membrane proteins such as VE-cadherin, as well as matrix proteins which are broken down and reorganized dynamically during vessel growth [14]. Newly formed sprouts anastomose with existing vessels, thus extending tissue microcirculation.

While the basic steps of angiogenesis outlined above are expected to operate, it is likely that the vascular network of each organ and tissue will be established through key tissue-specific mechanisms. A prominent example is the regulation of angiogenesis in the central nervous system, where specific G-protein coupled receptors are uniquely expressed and play dominant roles in angiogenic vascularization of the developing brain [15,16]. What mechanisms operate in adipose tissue, and how they modulate the basic steps of angiogenesis described above, are outstanding questions in adipose tissue biology.

3. Adipose tissue angiogenesis; what are the triggers?

One of the guiding questions for understanding angiogenic growth in adipose tissue is whether the mechanisms involved during embryonic and early postnatal development are similar to those involved in response to excess calorie consumption in adults. In both cases, two broad possibilities can be considered: First, angiogenic expansion may be triggered in response to signals emanating from proliferating and enlarging adipocytes. The second possibility is that angiogenic growth is triggered by developmental and/or metabolic signals, and parallels or precedes adipocyte proliferation and enlargement (Fig. 1). These two possibilities are not mutually exclusive, and in all likelihood tissue expansion involves both local cues arising from expanding adipocytes, as well as distant cues reflecting the developmental and metabolic states of the whole organism.

The first option, in which vascular growth ensues secondarily to parenchymal growth is the canonical model for oncogenic vascularization [17–19]. In this model, the rapid growth of tumor cells and the formation of a tumor mass elicit regions of hypoxia. Hypoxia is sensed through multiple mechanisms, prominent amongst which is the inactivation of oxygen-dependent prolyl-hydroxylases. Inactivation of these enzymes results in the protection of HIF-1α from proteolytic degradation, allowing its dimerization with constitutively expressed HIF-1β to form the functional transcription factor HIF1. This transcription factor potently activates a program of hypoxia adaptation, which includes decreased transcription and translation and increased VEGF-A expression. The angiogenic expansion of the vasculature in response to VEGF-A enhances blood flow and relieves hypoxia, allowing further tumor growth. This model, in which tumor growth is absolutely dependent on stimulation of angiogenesis, forms the basis for the development and use of anti-angiogenic therapies in cancer [11].

4. Role of hypoxia in adipose tissue angiogenesis

The most relevant evidence consistent with a possible role for hypoxia in adipose tissue angiogenesis are the findings that adipose tissue in rodents becomes hypoxic in response to obesity that is rapidly induced by high fat diet (HFD). This finding has been documented repeatedly, using both chemical indicators of hypoxia, as well as direct monitoring of tissue oxygen tension using microelectrodes [20–22]. Using directly placed microelectrodes, adipose tissue in obese humans has been found to be hypoxic [23]. Other findings consistent with a role for hypoxia are that the expression and secretion of pro-angiogenic factors by cultured adipocytes are strongly stimulated under low oxygen culture conditions [24]. These results suggest that, in a manner analogous to that occurring during tumor growth, adipose tissue hypoxia might be a driver for angiogenesis. However, the reported levels of hypoxia in human adipose tissue are relatively small, and one study actually finds increased oxygen tension in adipose tissue of obese subjects [25]. Moreover, it has been previously noted that expansion of adipose tissue in response to HFD is not accompanied by a corresponding increased blood flow [26]. Collectively, these results suggest that the response to hypoxia in adipose tissue may be insufficient to elicit sufficient compensatory angiogenic expansion.

A powerful, direct approach to defining the role of hypoxia in adipose tissue growth has been the tissue-specific overexpression and ablation of both HIF-1α and HIF-1β. Overexpression of a constitutively active form of HIF-1α in adipose tissue failed to induce a pro-angiogenic response; rather, it resulted in a fibrotic response and an increase in local inflammation [27]. Conversely, ablation of HIF-1α or HIF-1β (ARNT) in adipose tissue reduced fat formation, and protected from HFD-induced obesity and insulin resistance [28,29]. Furthermore, anti-sense mediated depletion of HIF-1α in obese mice resulted in amelioration of HFD-induced insulin resistance [30], as did pharmaceutical inhibition of HIF-1α, as well as inducible expression of a dominant negative form [31]. Overall, these results are consistent with a model where adipose tissue hypoxia induces HIF-1α, which induces a fibrotic and inflammatory response rather than a compensatory pro-angiogenic response. Nevertheless, HIF-1α may be relevant for the growth and maintenance of brown

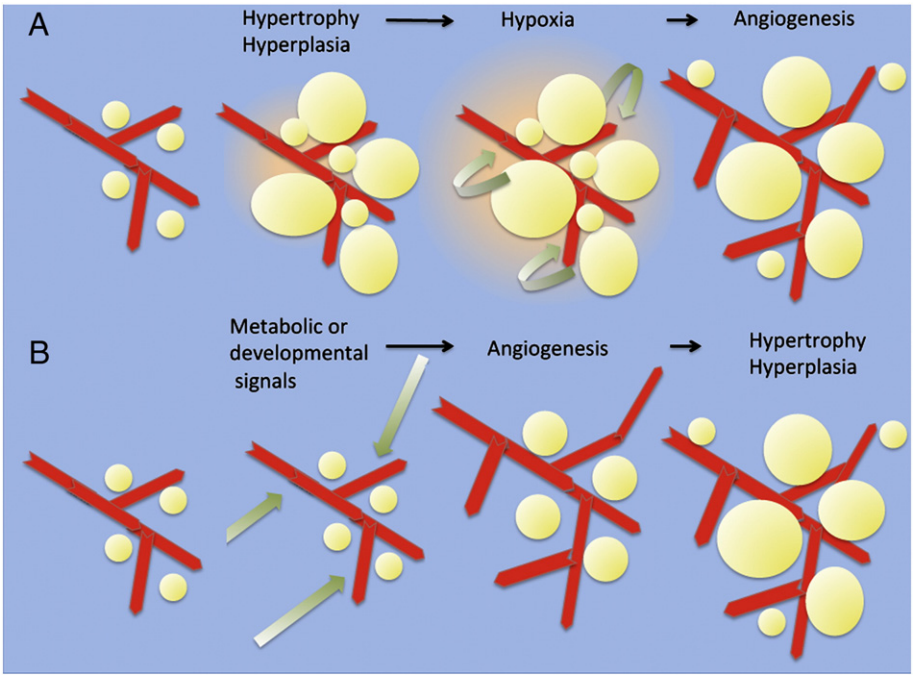

Fig. 1. Two possible models for the stimulation of angiogenesis during adipose tissue growth. A. Increased calorie consumption results in adipocyte hypertrophy and hyperplasia, generating areas of tissue hypoxia. Hypoxia, and/or other factors released from the tissue stimulate angiogenesis. Angiogenesis results in mitigation of hypoxia and appropriate tissue architecture and function. B. Increased calorie consumption results in systemic changes in trophic factors such as insulin, which directly stimulate angiogenesis within adipose tissue. Increased angiogenesis facilitates lipid storage in adipocytes and adipocyte hyperplasia. The simultaneous expansion of adipocytes and vasculature prevents development of hypoxia and metabolic stress.

adipose tissue, as expression of dominant-negative form of HIF-1α impairs thermogenesis and energy expenditure [32].

5. Role of VEGF in adipose tissue angiogenesis

In tumor angiogenesis, hypoxia-induced HIF1 stabilization activates VEGF transcription and secretion, which in turn stimulates angiogenesis. The induction of fibrosis and inflammation by HIF-1α in adipose tissue suggests that the stimulation of VEGF production may be controlled by different mechanisms, which are insufficiently activated during the rapid expansion induced by high-fat diets or hyperphagia. Consistent with this notion, transgenic overexpression of VEGF in adipose tissue results in increased vascularization, decreased inflammation, and amelioration of HFD-induced insulin resistance [33–35]. More strikingly, induced expression of VEGF-A in adipose tissue of animals previously rendered obese and insulin resistant reversed the established metabolic defects [33]. Expression of VEGF-A also caused the generation of adipocytes expressing UCP1, which are more similar to brown adipose tissue and have a higher metabolic rate, and result in lower weight gain under conditions of HFD [36].

Conversely, ablation of VEGF in adipose tissue resulted in hypoperfused adipose tissue, which displayed higher levels of inflammatory markers even under normal chow diet. In response to HFD feeding adipose tissue from VEGF-ablated animals developed much greater inflammation compared to controls [33]. This greater inflammation was accompanied by adipocyte death, a net decrease in depot size, and marked deterioration of glucose tolerance and insulin sensitivity. This enhanced inflammatory phenotype is similar to that observed in animals overexpressing HIF-1α. In aggregate, these findings suggest a model where insufficient angiogenesis during high-fat diet leads to hypoxia, HIF-1α expression, inflammation and adipose tissue dysfunction (Fig. 2). In addition, these studies clearly demonstrate that increased VEGF-A production and increased vascularization enable adipose tissue to adapt to rapid expansion caused by acutely increased caloric intake, and protect from the development of insulin resistance and glucose intolerance.

These results raise the questions: what mechanisms limit the expression of VEGF in adipose tissue, and do differences in VEGF production account for the variation in human adipose tissue expandability and subsequent protection from inflammation and metabolic dysfunction? Although some studies report decreased levels of VEGF gene expression in obese humans [23], others report higher levels of expression of VEGF-A in both subcutaneous and omental fat in obese compared to lean subjects, and a higher level in omental adipose tissue from obese insulin-sensitive compared to obese insulin-resistant individuals [37]. Unpublished results from our own group studying obese female subjects undergoing bariatric surgery are consistent with these later findings, suggesting that increased VEGF-A levels in adipose tissue may result in better vascularization and protection from inflammation and insulin resistance. Moreover, capillary density, as well as the capacity of human adipose tissue to produce new capillaries ex-vivo, is correlated with higher VEGF-A levels and increased insulin sensitivity in non-diabetic obese individuals [38]. Thus, as in mouse models, increased levels of VEGF-A may facilitate healthy expansion of adipose tissue and protect from lipotoxicity and metabolic disease.

6. Hypoxia-independent mechanisms of VEGF production

The finding of beneficial effects of VEGF production and adipose tissue vascularization, as opposed to the deleterious effects of hypoxia signaling, suggests that mechanisms that increase VEGF production independently of hypoxia can confer a protective effect from metabolic risk. Several mechanisms can increase VEGF production independently from classical hypoxia signaling [39,40]. These mechanisms are elicited in response to changes in cellular energy demands; for example, the co-activators PGC-1α and PGC-1β induce VEGF expression and angiogenesis in muscle in response to exercise [41–44]. These co-activators act on multiple transcription factors, including ERRs, PPARs and NRFs, to induce a program of adaptation to increased energy demand. The

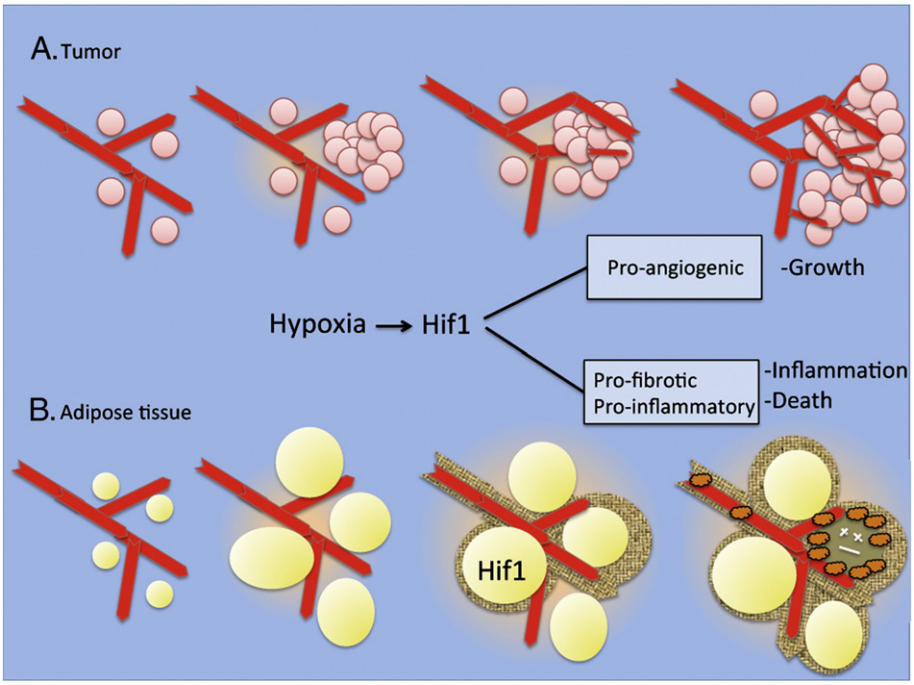

Fig. 2. Different consequences of HIF expression in tumors and adipose tissue. A. Rapid cell proliferation during tumor growth elicits hypoxia, which activates HIF1 signaling, VEGF production and angiogenesis. Increased vascularization allows the tumor to grow. B. HIF1 expression in adipose tissue does not elicit VEGF production, but rather to a pro-fibrotic program, which is followed by inflammation, macrophage infiltration and cell death.

mechanism by which PGC-1α and PGC-1β stimulate VEGF production is complex, and may involve depletion of intracellular oxygen and stabilization of HIF-1α [45], as well as the direct co-activation of ERRα [43,46]. Through a combination of these and possibly other mechanisms, PGC-1α and PGC-1β induce VEGF-A production in-vitro, and in-vivo result in enhanced muscle vascularization. Similar mechanisms may operate in brown adipose tissue, where cold induced capillary expansion is dependent on VEGF-A production. VEGF-A is induced in a hypoxia-independent manner [47,48] through activation of PGC-1α in response to noradrenergic stimulation [47]. White adipose tissue contains detectable levels of PGC-1α [49,50] and its adipose tissue-specific ablation results in insulin resistance [51]. Whether this phenotype is associated with decreased capillary density and angiogenic potential is an interesting question for future study.

Another metabolism-responsive mechanism reported to increase VEGF production is the activation of AMP-dependent protein kinase (AMPK) [52]. AMPK is a central integrator of energy balance, sensing the ratio of AMP/ATP within cells. AMPK is activated by conditions that lower cellular ATP, such as nutritional deprivation or hypoxia, and phosphorylates downstream targets that decrease energy utilization and enhance ATP production. Pharmacologically, AMPK activity can be stimulated in the absence of hypoxia by the AMP mimetic AICAR. AICAR stimulated VEGF mRNA and protein levels in C2C12 myotube cultures, and this effect was blocked by a dominant-negative AMPK [53]. In tumor cells, glucose deprivation caused an increase in VEGF expression, which was also blocked by expression of dominant-negative AMPK, and was not accompanied by changes in HIF-1α levels or transcriptional activity [52]. The mechanism by which AMPK activation results in increased VEGF levels appears to involve stabilization of VEGF mRNA, rather than transcriptional activation of the VEGF gene [52]. More recently, administration of AICAR increased VEGF mRNA in skeletal muscle of wild-type mice, but not in mice expressing dominant-negative AMPK [54]. As AMPK activity is stimulated in adipose tissue of subjects treated with metformin [55], it would be interesting to determine whether the insulin-sensitizing actions of this drug are associated with increased adipose tissue VEGF production.

Highly relevant to adipose tissue is the role of the peroxisome proliferator activated receptors (PPARs) in angiogenesis [56]. In particular, the role of PPARγ, a master regulator of adipocyte differentiation, is complex. While PPARγ activation inhibits proliferation of endothelial cells in-vitro [57–59], it has a net pro-angiogenic role in the context of adipose tissue, as determined by the increased capillary density and capillary sprouting capacity of adipose tissue obtained from both mice and humans treated with PPARγ agonist rosiglitazone [59,60]. In addition, increased levels of VEGF are observed in adipose tissue of rodents treated with rosiglitazone [59,61]. Furthermore, inhibition of PPARγ function in pre-adipocytes prevents not only the differentiation of adipocytes, but also the formation of vasculature in-vivo [62]. These results suggest that, while direct activation of endothelial cell PPARγ results in inhibition of angiogenesis, activation of PPARγ in the context of adipose tissue results in a net pro-angiogenic effect. This is likely to be due to the secretion of pro-angiogenic factors from adipocytes in response to PPARγ activation. Indeed, the ability of mature adipocytes to secrete potent pro-angiogenic factors, including VEGF, has been recognized for decades [63–67].

7. Factors other than VEGF involved in adipose tissue angiogenesis

Numerous pro and anti-angiogenic factors secreted by adipocytes are likely to control adipose tissue angiogenesis. A recent proteomic analysis of secreted proteins from adipose tissue depots suggests that as much as 50% of the adipose tissue secretome is comprised of proteins that have been implicated in angiogenesis [68], and various angiogenesis-related factors, shown in Table 1, are reported to be altered in response to obesity and HFD [38,69–73]. One of the barriers in elucidating the specific role for these factors in adipose tissue angiogenesis is their pleiotropic expression and likely important roles in multiple tissues, requiring the generation of tissue-specific models to define their specific roles. Conversely, factors that play important roles in angiogenesis in other tissues may play minor roles in adipose tissue [74,75]. Factors that are increased during adipocyte differentiation, are

Table 1
Factors associated with adipose tissue angiogenesis.

Gene/protein	Association with adipose tissue angiogenesis	References
ANGPTL-4 (Angiopoietin-like 4)	Implicated in angiogenesis, lipid metabolism and glucose homeostasis; transcriptionally activated by PPARγ and hypoxia; highly expressed in adipose tissue, placenta and tumors.	[59,79,85,91,140]
APELIN	Highly expressed in adipose tissue; ligand for G-protein coupled receptor APJ; required for vascular development in frog embryos; pro-angiogenic in human endothelial cells; up-regulated by hypoxia and during pregnancy and lactation.	[35,71,141–143]
PIGF/PLGF (placental growth factor)	Interacts with VEGFR1; Inactivation impairs adipose tissue development.	[144,145]
HGF (hepatocyte growth factor)	Decreased formation of fat pads from 3T3-F442A cells with HGF knockdown.	[72]
FGF-1 (fibroblast growth factor-1)	Pathological adipose tissue vasculature in FGF-1 knockout mice under HFD.	[146]
SPARC/osteonectin/BM40	Enriched in adipose tissue; increased expression in obesity; promotes fibrosis.	[147-149]
Leptin	Produced exclusively by adipocytes; induced vascularization in angiogenic assays; pro-angiogenic on human umbilical vein endothelial cells.	[67,150,151]
Adiponectin	Produced exclusively by adipocytes; chemo-attractant for endothelial progenitor cells; pro-angiogenic in human microvascular and umbilical vein endothelial cells.	[152-154]
Chemerin	Ligand for the G protein-coupled receptor CMKLR1; high level expression in mouse and human adipocytes; pro-angiogenic in human endothelial cells	[155,156]
Ang-2 (angiopoietin-2)	Increased in adipose tissue of obese mice; transcriptionally regulated by FOXC2 in adipose tissue.	[157,158]

greatly overexpressed in adipose tissue, or are direct targets for PPARγ are thus of heightened relevance in this context.

Angiogenesis-related factors directly regulated in response to PPARγ activation, include angiopoietin-like 4 (ANGPTL4) [59,76]. This factor was discovered simultaneously as a fasting-induced adipocyte factor [77], and as a direct target for PPARγ highly expressed in adipose tissue and placenta [78]. ANGPTL4 inhibits lipoprotein lipase, and its expression is correlated with alterations in circulating lipids in mouse models and humans [79–82]. In parallel, ANGPTL4 has been found to be induced in tumors and normal tissues in response to hypoxia [83–87], and to have pro-angiogenic effects that affect tissue vascularization and wound healing [59,88–91]. Overexpression of ANGPTL4 in obese mice ameliorates insulin resistance and glucose intolerance, even while inducing hyperlipidemia [92]. Whether the protective effect of increased ANGPTL4 results from increased adipose tissue vascularization or from inhibition of adipose tissue LPL is not known, but it is interesting to speculate that ANGPTL4 may be important for stimulating angiogenic expansion while preventing excess lipid accumulation in rapidly growing tissues.

In addition to factors secreted from adipocytes, non-adipocyte cells involved in tissue remodeling could induce adipose tissue angiogenesis. Infiltration of adipose tissue by cells of the immune system occurs rapidly in response to HFD in mice, and the visceral adipose depot of insulin-resistant humans is highly inflamed [93,94]. While macrophage infiltration may result in inflammation-induced insulin resistance, these cells may also play a beneficial, trophic role, as has been suggested to occur in other tissues [95]. Indeed, a pro-angiogenic role for LYVE-1 positive macrophages in epididymal fat pad expansion has been shown [6], and a role for macrophages in stimulating tumor angiogenesis is extensively documented [96–100]. The angiogenic role of tissue macrophages has attributed to factors such as TNFα, IL-8, wnt and PDGF signaling [101–103], some of which also have important roles in adipocyte differentiation. Thus, deciphering the relative contribution of factors secreted by adipocytes and immune cells will be important for understanding the mechanisms of adipose tissue angiogenesis under diverse physiological conditions.

8. Developmental mechanisms of adipose tissue angiogenesis

In the paradigm of angiogenic growth described above the critical pro-angiogenic stimuli emanate from adipose cells undergoing hypoxia or energetic stress (Fig. 1A). However, an alternative paradigm is one in which the growth of the vasculature precedes the growth of adipocytes, thus ensuring an adequate blood supply to the expanding tissue (Fig. 1B). This paradigm functions during adipose tissue development in the embryo and early post-natal stages, and the possibility exists that it may also operate in adult tissue. A close association between adipocyte growth and the developing vasculature was noted as far back as 1870, where the emergence of adipocytes from well developed vascular networks led to the suggestion that a robust blood supply was essential for the development of adipose tissue. Extensive morphological analyses of the developing adipose tissue in pig and rodent embryo depots [8] strongly support the concept that the establishment of a capillary network precedes the emergence of adipocytes during embryonic development. Angiogenesis also precedes adipocyte formation during post-natal growth: In mouse epididymal fat, a dense vascular network in the tip of the fat pad expands rapidly during post-natal days 0–5, and new adipocytes arise from within the newly formed vessels [6,104]. The activities of VEGF, VEGFR2, MMPs, and SDF-1 are essential, and administration of antibodies to VEGF inhibited angiogenesis as well as the emergence of adipocytes.

A functional requirement for vascular cells in adipocyte differentiation is also suggested by the experiments of Fukumura et al., mentioned above, in which implantation of pre adipocytes results in vigorous angiogenesis and the formation of fat pads [62]. The formation of the capillary network was dependent on the expression of PPARγ in the implanted cells, consistent with a major role of this transcription factors in regulating the expression of pro-angiogenic factors, as described above. Strikingly, inhibition of VEGF signaling blocked not only angiogenic growth but also the differentiation of the implanted pre-adipocytes, suggesting that direct interaction with endothelial cells, or other cells associated with blood vessels, may be crucial for the differentiation of pre-adipocytes in-vivo. These results are consistent with recent findings that the vasculature of adipose tissue is the niche for pre-adipocyte precursors [105,106]. These precursors, labeled using lineage-specific PPARγ-driven markers, also express smooth muscle actin, PDGFR-β and NG2, which are characteristic markers of mural cells [105].

Cells within human adipose tissue capillaries formed ex-vivo also contain adipocyte precursors [107]; interestingly, these cells contained endothelial cell markers as well as large lipid droplets, glycogen particles and a displaced nucleus, all features of differentiated adipocytes. These results suggest that multi-potent cells with capacity for endothelial and/or adipocyte differentiation exist within the vessel wall. This notion is further supported by the finding that GFP expression driven by the Zfp423 promoter can be localized to cells within the adipose tissue vasculature, including a subset that expresses endothelial cell markers [108]. Because Zfp423 has been identified as a factor enriched in adipocyte precursors, these results are consistent with plasticity in the endothelial-adipose cell lineage, which has been suggested by others [109,110].

The finding that pre-adipocyte precursors reside within the adipose tissue vasculature, and that inhibition of angiogenic growth inhibits pre-adipocyte differentiation, suggests that direct, cell–cell interactions that control angiogenic growth may also be involved in pre-adipocyte proliferation or differentiation in-vivo (Fig. 3). Experiments in which adipose stromal cells co-cultured with endothelial cells display decreased

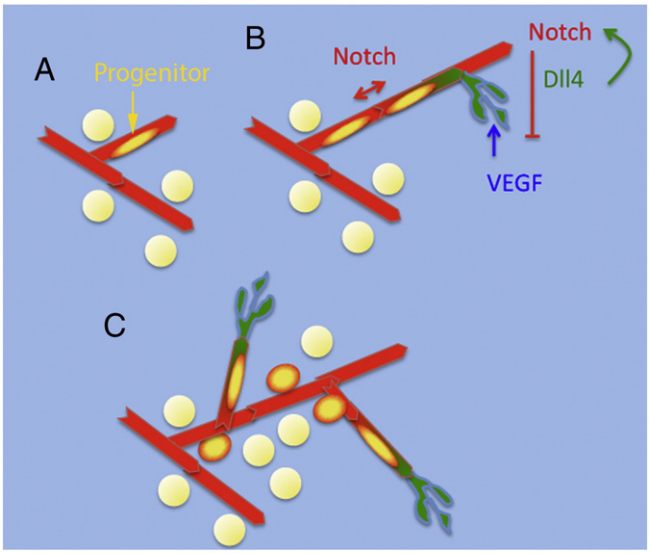

Fig. 3. Hypothetical model for coordination of angiogenesis and adipocyte proliferation. A. Quiescent multi-potent progenitors reside within the adipose tissue vasculature. B. Endothelial cells are stimulated to proliferate by VEGF, resulting in the formation of tip cells (green) expressing Dll4, which suppresses VEGF signaling in adjacent cells via activation of Notch, forming new capillary sprouts. This is accompanied by proliferation of progenitors. C. Progenitors differentiate into adipocytes and/or other cell types such as endothelial or mural cells.

differentiation, possibly due to activation of Wnt1 [111], are consistent with this possibility. In addition to Wnt signaling, Delta (dll4)-Notch signaling, which is crucial in the formation of new vessels, has also been associated with adipocyte differentiation [112–114].

9. Adipose tissue developmental genes and angiogenesis

Comprehensive analyses of gene expression in human adipose tissue reveal numerous differences related to functions such as lipolysis, fatty acid synthesis and inflammation amongst different depots. These differences in gene expression are consistent with the different functions of adipose tissue in different regions of the body, and with the variance in metabolic disease risk associated with expansion of specific depots [38]. In efforts to elucidate the developmental origins of these depots, and the mechanisms by which they attain specific functions, the expression of genes related to tissue patterning and embryonic development has been studied [115–117]. Importantly, major differences in expression of genes that determine body patterning have been found amongst different adipose depots. These include changes in expression of Hox genes, which are transcription factors that bind DNA through a 60 amino acid helix–turn–helix homeodomain, and control development along the anterior–posterior axis. A large proportion of the HOX gene network is active in adult white adipose tissue [115], and differences are seen in the levels of expression between whole visceral and subcutaneous adipose tissues from non-diabetic male humans [118]. In a comprehensive assessment of developmental gene expression between intra abdominal and subcutaneous depots from mouse and humans, highly significant differences in expression of Hox genes (HOXA5, HOXC8, HOXC9) were found consistently in both species [116]. More recently, differences amongst subcutaneous abdominal and gluteal depots of male and female humans have been reported [117]. Depot-associated variation included HOXA3, HOXA5, HOXB8, HOXC8, which were more highly expressed in abdominal adipose tissue, and HOXA10 and HOXC13, which were highly expressed in the gluteal depot in both genders. Importantly, variances seen in whole tissue are also observed when analyzing the stromovascular fraction, which encompasses a mixed population of endothelial cells, fibroblasts, white blood cells and in all likelihood adipocyte progenitors [116,117].

The finding of significant differences in developmental gene expression in the stromovascular fraction of adipose tissue, together with the possible role for the vasculature as the niche for adipocyte precursors, raises the question of whether the role of these developmental genes is in fact exerted at the level of vascular development. Indeed, the vascular system is the first organ system developed during embryogenesis, and growth of tissues and organs is critically dependent on vascular expansion. Hox genes are important determinants of anterior–posterior development, but act at the cellular level by modulating functions such as cell adhesion, migration and cell cycle control, and are important in the process of angiogenic transcriptional regulation [119].

The developmental genes differentially expressed in adipose tissue depots include several which have been implicated in vascular patterning and endothelial function. Amongst these is HOXC9, which is expressed in different vascular beds, is negatively correlated with growth of human umbilical vein endothelial cells, and impairs vascular development in zebrafish upon endothelial-specific overexpression [119,120]. Another is HOXA9, which is necessary for endothelial cell migration and tube formation [121], and has been reported to be essential for inflammatory activation of endothelial cells [121–123]. Both HOXC9 and HOXA9 are more highly expressed in subcutaneous compared to visceral adipose tissue in mice and lean humans, and HOXA9 is more highly expressed in gluteal compared to abdominal subcutaneous fat [116]. HOXA5 has also been implicated in vasculature development [124,125], while correlating with levels of obesity and fat distribution in humans [117,126]. Distinguishing the relationship between the role of these genes in vascular development and depot-specific adipose tissue growth is an exciting area for future research.

10. Impact of adipose tissue angiogenesis on obesity and insulin resistance

Several lines of evidence indicate that adipose tissue growth can be limited by its vascular supply [6–8], and that rapid adipose tissue expansion, such as that elicited by HFD in mice, is not adequately paralleled by growth of the capillary network, leading to hypoxia [20,22,23,35,127]; hypoxic stress in turn can promote inflammation [21] and insulin resistance. Indeed, recent experiments in mouse models of adipose tissue VEGF over and under expression provide direct and convincing evidence consistent with a critical role for angiogenesis in determining adipose tissue size, as well as impacting the metabolic sequelae associated with impaired adipose tissue growth. As noted above, adipose tissue VEGF-ablated animals display a net decrease in depot size, accompanied by inflammation and marked deterioration of glucose tolerance and insulin sensitivity, most evident in response to HFD. Conversely, overexpression of VEGF in adipose tissue results in increased vascularization, decreased inflammation, and amelioration of HFD-induced insulin resistance [33–35].

Several other instances have been described in which pro- and anti-angiogenic factors impact obesity and/or insulin resistance. For example, overexpression of ANGPTL4 in obese mice ameliorates insulin resistance and glucose intolerance, even while inducing hyperlipidemia [92]. In another example, mice lacking 11β-hydroxysteroid dehydrogenase type 1, which are resistant to HFD-induced metabolic disease even while displaying adipose tissue expansion, have higher adipose tissue vascular density, increased levels of pro-angiogenic factor mRNA levels, and increased secretion of pro-angiogenic factors [35].

While human studies are mostly correlations, existing data indicate that expansion of adipose tissue in adults is accompanied by induction of a pro-angiogenic gene expression profile [70]. Moreover, capillary density, as well as the capacity of human adipose tissue to produce new capillaries ex-vivo, is correlated with higher VEGF-A levels and increased insulin sensitivity in non-diabetic obese individuals [37,38].

Thus, as in mice, increased VEGF-A levels in adipose tissue may result in better vascularization and protection from inflammation and insulin resistance.

11. Is adipose tissue angiogenesis a therapeutic target in Type-2 diabetes?

Initial recognition of a clear association between obesity and insulin resistance suggested that limiting the accretion of fat might also limit the risk of metabolic disease. Knowledge about the absolute requirement for angiogenesis in adipose tissue expansion led to early experiments in which anti-angiogenic compounds were used as possible anti-obesity and anti-diabetes therapeutic approaches [128,129]. These approaches demonstrated decreased fat accumulation; however, their simultaneous effects to decrease food consumption confounded the interpretation of the beneficial results of anti-angiogenic therapy.

Subsequent demonstration that insulin resistance and disease risk most likely stem from insufficient fat storage and ensuing lipotoxicity and inflammation, rather than directly from increased fat accumulation [69,130–132], logically has limited enthusiasm for approaches that focus on deceasing adipose tissue expansion without decreasing caloric input or enhancing energetic output. Indeed, the enhanced risk of diabetes accompanying lipodystrophy [133–135] and, conversely, the improved metabolic state in several models of increased adiposity [136,137], further suggest that impairing adipose tissue growth is not a promising approach for ameliorating metabolic disease.

While anti-angiogenesis approaches in which appropriate adipose tissue vascularization and growth are compromised are unlikely to be of therapeutic benefit, the adipose tissue vasculature remains a promising site for identification of new therapeutic targets. Accumulating evidence for the adipose tissue vasculature as the niche for adipocyte progenitors raises the possibility of vasculature-targeted approaches to enhance the generation of healthy adipocytes, mitigating adipocyte stress and inflammation. Moreover, the vasculature is likely to be the niche for precursor cells giving rise to brite/beige adipocytes, which are metabolically active and may decrease metabolic disease risk [138,139]. Better understanding of the mechanisms that induce adipose tissue angiogenesis, and of the role of the vasculature in adipose tissue function, will in all likelihood provide new and perhaps unexpected insights into ways adipose tissue biology can be targeted to improve human health.

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References

[1] T. Nakagami, Q. Qiao, B. Carstensen, C. Nhr-Hansen, G. Hu, J. Tuomilehto, B. Balkau, K. Borch-Johnsen, Age, body mass index and type 2 diabetes—associations modified by ethnicity, Diabetologia 46 (2003) 1063–1070.
[2] S.R. Preis, J.M. Massaro, S.J. Robins, U. Hoffmann, R.S. Vasan, T. Irlbeck, J.B. Meigs, P. Sutherland, R.B. D'Agostino Sr., C.J. O'Donnell, C.S. Fox, Abdominal subcutaneous and visceral adipose tissue and insulin resistance in the Framingham heart study, Obesity (Silver Spring) 18 (2010) 2191–2198.
[3] T. McLaughlin, C. Lamendola, A. Liu, F. Abbasi, Preferential fat deposition in subcutaneous versus visceral depots is associated with insulin sensitivity, J. Clin. Endocrinol. Metab. 96 (2011) E1756–E1760.
[4] S. Virtue, A. Vidal-Puig, Adipose tissue expandability, lipotoxicity and the metabolic syndrome—an allostatic perspective, Biochim. Biophys. Acta 1801 (2010) 338–349.
[5] O.T. Hardy, M.P. Czech, S. Corvera, What causes the insulin resistance underlying obesity? Curr. Opin. Endocrinol. Diabetes Obes. 19 (2012) 81–87.
[6] C.H. Cho, Y.J. Koh, J. Han, H.K. Sung, H. Jong Lee, T. Morisada, R.A. Schwendener, R.A. Brekken, G. Kang, Y. Oike, T.S. Choi, T. Suda, O.J. Yoo, G.Y. Koh, Angiogenic role of LYVE-1-positive macrophages in adipose tissue, Circ. Res. 100 (2007) e47–e57.
[7] V. Christiaens, H.R. Lijnen, Angiogenesis and development of adipose tissue, Mol. Cell. Endocrinol. 318 (2010) 2–9.
[8] D.L. Crandall, G.J. Hausman, J.G. Kral, A review of the microcirculation of adipose tissue: anatomic, metabolic, and angiogenic perspectives, Microcirculation 4 (1997) 211–232.
[9] J.G. Neels, T. Thinnes, D.J. Loskutoff, Angiogenesis in an in vivo model of adipose tissue development, FASEB J. 18 (2004) 983–985.
[10] H.M. Eilken, R.H. Adams, Dynamics of endothelial cell behavior in sprouting angiogenesis, Curr. Opin. Cell Biol. 22 (2010) 617–625.
[11] P. Carmeliet, R.K. Jain, Molecular mechanisms and clinical applications of angiogenesis, Nature 473 (2011) 298–307.
[12] A.S. Chung, N. Ferrara, Developmental and pathological angiogenesis, Annu. Rev. Cell Dev. Biol. 27 (2011) 563–584.
[13] M. Potente, H. Gerhardt, P. Carmeliet, Basic and therapeutic aspects of angiogenesis, Cell 146 (2011) 873–887.
[14] D.R. Senger, G.E. Davis, Angiogenesis, Cold Spring Harb. Perspect. Biol. 3 (2011) a005090.
[15] K.D. Anderson, L. Pan, X.M. Yang, V.C. Hughes, J.R. Walls, M.G. Dominguez, M.V. Simmons, P. Burfeind, Y. Xue, Y. Wei, L.E. Macdonald, G. Thurston, C. Daly, H.C. Lin, A.N. Economides, D.M. Valenzuela, A.J. Murphy, G.D. Yancopoulos, N.W. Gale, Angiogenic sprouting into neural tissue requires Gpr124, an orphan G protein-coupled receptor, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 2807–2812.
[16] F. Kuhnert, M.R. Mancuso, A. Shamloo, H.T. Wang, V. Choksi, M. Florek, H. Su, M. Fruttiger, W.L. Young, S.C. Heilshorn, C.J. Kuo, Essential regulation of CNS angiogenesis by the orphan G protein-coupled receptor GPR124, Science 330 (2010) 985–989.
[17] S.M. Weis, D.A. Cheresh, Tumor angiogenesis: molecular pathways and therapeutic targets, Nat. Med. 17 (2011) 1359–1370.
[18] S. Germain, C. Monnot, L. Muller, A. Eichmann, Hypoxia-driven angiogenesis: role of tip cells and extracellular matrix scaffolding, Curr. Opin. Hematol. 17 (2010) 245–251.
[19] Y. Cao, J. Arbiser, R.J. D'Amato, P.A. D'Amore, D.E. Ingber, R. Kerbel, M. Klagsbrun, S. Lim, M.A. Moses, B. Zetter, H. Dvorak, R. Langer, Forty-year journey of angiogenesis translational research, Sci. Transl. Med. 3 (2011) 114rv113.
[20] M.E. Rausch, S. Weisberg, P. Vardhana, D.V. Tortoriello, Obesity in C57BL/6J mice is characterized by adipose tissue hypoxia and cytotoxic T-cell infiltration, Int. J. Obes. (Lond.) 32 (2008) 451–463.
[21] J. Ye, Z. Gao, J. Yin, Q. He, Hypoxia is a potential risk factor for chronic inflammation and adiponectin reduction in adipose tissue of ob/ob and dietary obese mice, Am. J. Physiol. Endocrinol. Metab. 293 (2007) E1118–E1128.
[22] N. Hosogai, A. Fukuhara, K. Oshima, Y. Miyata, S. Tanaka, K. Segawa, S. Furukawa, Y. Tochino, R. Komuro, M. Matsuda, I. Shimomura, Adipose tissue hypoxia in obesity and its impact on adipocytokine dysregulation, Diabetes 56 (2007) 901–911.
[23] M. Pasarica, O.R. Sereda, L.M. Redman, D.C. Albarado, D.T. Hymel, L.E. Roan, J.C. Rood, D.H. Burk, S.R. Smith, Reduced adipose tissue oxygenation in human obesity: evidence for rarefaction, macrophage chemotaxis, and inflammation without an angiogenic response, Diabetes 58 (2009) 718–725.
[24] K. Lolmede, V. Durand de Saint Front, J. Galitzky, M. Lafontan, A. Bouloumie, Effects of hypoxia on the expression of proangiogenic factors in differentiated 3T3-F442A adipocytes, Int. J. Obes. Relat. Metab. Disord. 27 (2003) 1187–1195.
[25] G.H. Goossens, A. Bizzarri, N. Venteclef, Y. Essers, J.P. Cleutjens, E. Konings, J.W. Jocken, M. Cajlakovic, V. Ribitsch, K. Clement, E.E. Blaak, Increased adipose tissue oxygen tension in obese compared with lean men is accompanied by insulin resistance, impaired adipose tissue capillarization, and inflammation, Circulation 124 (2011) 67–76.
[26] P. Trayhurn, Hypoxia and adipose tissue function and dysfunction in obesity, Physiol. Rev. 93 (2013) 1–21.
[27] N. Halberg, T. Khan, M.E. Trujillo, I. Wernstedt-Asterholm, A.D. Attie, S. Sherwani, Z.V. Wang, S. Landskroner-Eiger, S. Dineen, U.J. Magalang, R.A. Brekken, P.E. Scherer, Hypoxia-inducible factor 1alpha induces fibrosis and insulin resistance in white adipose tissue, Mol. Cell. Biol. 29 (2009) 4467–4483.
[28] C. Jiang, A. Qu, T. Matsubara, T. Chanturiya, W. Jou, O. Gavrilova, Y.M. Shah, F.J. Gonzalez, Disruption of hypoxia-inducible factor 1 in adipocytes improves insulin sensitivity and decreases adiposity in high-fat diet-fed mice, Diabetes 60 (2011) 2484–2495.
[29] K.Y. Lee, S. Gesta, J. Boucher, X.L. Wang, C.R. Kahn, The differential role of Hif1beta/Arnt and the hypoxic response in adipose function, fibrosis, and inflammation, Cell Metab. 14 (2011) 491–503.
[30] M.K. Shin, L.F. Drager, Q. Yao, S. Bevans-Fonti, D.Y. Yoo, J.C. Jun, S. Aja, S. Bhanot, V.Y. Polotsky, Metabolic consequences of high-fat diet are attenuated by suppression of HIF-1alpha, PLoS One 7 (2012) e46562.
[31] K. Sun, N. Halberg, M. Khan, U.J. Magalang, P.E. Scherer, Selective inhibition of hypoxia-inducible factor 1alpha ameliorates adipose tissue dysfunction, Mol. Cell. Biol. 33 (2013) 904–917.
[32] X. Zhang, K.S. Lam, H. Ye, S.K. Chung, M. Zhou, Y. Wang, A. Xu, Adipose tissue-specific inhibition of hypoxia-inducible factor 1{alpha} induces obesity and glucose intolerance by impeding energy expenditure in mice, J. Biol. Chem. 285 (2010) 32869–32877.
[33] H.K. Sung, K.O. Doh, J.E. Son, J.G. Park, Y. Bae, S. Choi, S.M. Nelson, R. Cowling, K. Nagy, I.P. Michael, G.Y. Koh, S.L. Adamson, T. Pawson, A. Nagy, Adipose vascular endothelial growth factor regulates metabolic homeostasis through angiogenesis, Cell Metab. 17 (2013) 61–72.
[34] A. Wree, A. Mayer, S. Westphal, A. Beilfuss, A. Canbay, R.R. Schick, G. Gerken, P. Vaupel, Adipokine expression in brown and white adipocytes in response to hypoxia, J. Endocrinol. Invest. 35 (2012) 522–527.

[35] Z. Michailidou, S. Turban, E. Miller, X. Zou, J. Schrader, P.J. Ratcliffe, P.W. Hadoke, B.R. Walker, J.P. Iredale, N.M. Morton, J.R. Seckl, Increased angiogenesis protects against adipose hypoxia and fibrosis in metabolic disease-resistant 11beta-hydroxysteroid dehydrogenase type 1 (HSD1)-deficient mice, J. Biol. Chem. 287 (2012) 4188–4197.
[36] K. Sun, I. Wernstedt Asterholm, C.M. Kusminski, A.C. Bueno, Z.V. Wang, J.W. Pollard, R.A. Brekken, P.E. Scherer, Dichotomous effects of VEGF-A on adipose tissue dysfunction, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 5874–5879.
[37] F.J. Tinahones, L. Coin-Araguez, M.D. Mayas, E. Garcia-Fuentes, C. Hurtado-Del-Pozo, J. Vendrell, F. Cardona, R.M. Calvo, M.J. Obregon, R. El Bekay, Obesity-associated insulin resistance is correlated to adipose tissue vascular endothelial growth factors and metalloproteinase levels, BMC Physiol. 12 (2012) 4.
[38] O. Gealekman, N. Guseva, C. Hartigan, S. Apotheker, M. Gorgoglione, K. Gurav, K.V. Tran, J. Straubhaar, S. Nicoloro, M.P. Czech, M. Thompson, R.A. Perugini, S. Corvera, Depot-specific differences and insufficient subcutaneous adipose tissue angiogenesis in human obesity, Circulation 123 (2011) 186–194.
[39] P. Fraisl, M. Mazzone, T. Schmidt, P. Carmeliet, Regulation of angiogenesis by oxygen and metabolism, Dev. Cell 16 (2009) 167–179.
[40] J. Aragones, M. Schneider, K. Van Geyte, P. Fraisl, T. Dresselaers, M. Mazzone, R. Dirkx, S. Zacchigna, H. Lemieux, N.H. Jeoung, D. Lambrechts, T. Bishop, P. Lafuste, A. Diez-Juan, S.K. Harten, P. Van Noten, K. De Bock, C. Willam, M. Tjwa, A. Grosfeld, R. Navet, L. Moons, T. Vandendriessche, C. Deroose, B. Wijeyekoon, J. Nuyts, B. Jordan, R. Silasi-Mansat, F. Lupu, M. Dewerchin, C. Pugh, P. Salmon, L. Mortelmans, B. Gallez, F. Gorus, J. Buyse, F. Sluse, R.A. Harris, E. Gnaiger, P. Hespel, P. Van Hecke, F. Schuit, P. Van Veldhoven, P. Ratcliffe, M. Baes, P. Maxwell, P. Carmeliet, Deficiency or inhibition of oxygen sensor Phd1 induces hypoxia tolerance by reprogramming basal metabolism, Nat. Genet. 40 (2008) 170–180.
[41] Z. Arany, S.Y. Foo, Y. Ma, J.L. Ruas, A. Bommi-Reddy, G. Girnun, M. Cooper, D. Laznik, J. Chinsomboon, S.M. Rangwala, K.H. Baek, A. Rosenzweig, B.M. Spiegelman, HIF-independent regulation of VEGF and angiogenesis by the transcriptional coactivator PGC-1alpha, Nature 451 (2008) 1008–1012.
[42] J. Chinsomboon, J. Ruas, R.K. Gupta, R. Thom, J. Shoag, G.C. Rowe, N. Sawada, S. Raghuram, Z. Arany, The transcriptional coactivator PGC-1alpha mediates exercise-induced angiogenesis in skeletal muscle, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 21401–21406.
[43] G.C. Rowe, C. Jang, I.S. Patten, Z. Arany, PGC-1beta regulates angiogenesis in skeletal muscle, Am. J. Physiol. Endocrinol. Metab. 301 (2011) E155–E163.
[44] L. Leick, Y. Hellsten, J. Fentz, S.S. Lyngby, J.F. Wojtaszewski, J. Hidalgo, H. Pilegaard, PGC-1alpha mediates exercise-induced skeletal muscle VEGF expression in mice, Am. J. Physiol. Endocrinol. Metab. 297 (2009) E92–E103.
[45] K.A. O'Hagan, S. Cocchiglia, A.V. Zhdanov, M.M. Tambuwala, E.P. Cummins, M. Monfared, T.A. Agbor, J.F. Garvey, D.B. Papkovsky, C.T. Taylor, B.B. Allan, PGC-1alpha is coupled to HIF-1alpha-dependent gene expression by increasing mitochondrial oxygen consumption in skeletal muscle cells, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 2188–2193.
[46] C. Auxenfans, C. Lequeux, E. Perrusel, A. Mojallal, B. Kinikoglu, O. Damour, Adipose-derived stem cells (ASCs) as a source of endothelial cells in the reconstruction of endothelialized skin equivalents, J. Tissue Eng. Regen. Med. 6 (2012) 512–518.
[47] J.M. Fredriksson, H. Nikami, J. Nedergaard, Cold-induced expression of the VEGF gene in brown adipose tissue is independent of thermogenic oxygen consumption, FEBS Lett. 579 (2005) 5680–5684.
[48] Y. Xue, N. Petrovic, R. Cao, O. Larsson, S. Lim, S. Chen, H.M. Feldmann, Z. Liang, Z. Zhu, J. Nedergaard, B. Cannon, Y. Cao, Hypoxia-independent angiogenesis in adipose tissues during cold acclimation, Cell Metab. 9 (2009) 99–109.
[49] M.E. Patti, S. Corvera, The role of mitochondria in the pathogenesis of type 2 diabetes, Endocr. Rev. 31 (2010) 364–395.
[50] L. Wilson-Fritch, S. Nicoloro, M. Chouinard, M.A. Lazar, P.C. Chui, J. Leszyk, J. Straubhaar, M.P. Czech, S. Corvera, Mitochondrial remodeling in adipose tissue associated with obesity and treatment with rosiglitazone, J. Clin. Invest. 114 (2004) 1281–1289.
[51] S. Kleiner, R.J. Mepani, D. Laznik, L. Ye, M.J. Jurczak, F.R. Jornayvaz, J.L. Estall, D. Chatterjee Bhowmick, G.I. Shulman, B.M. Spiegelman, Development of insulin resistance in mice lacking PGC-1alpha in adipose tissues, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 9635–9640.
[52] H. Yun, M. Lee, S.S. Kim, J. Ha, Glucose deprivation increases mRNA stability of vascular endothelial growth factor through activation of AMP-activated protein kinase in DU145 prostate carcinoma, J. Biol. Chem. 280 (2005) 9963–9972.
[53] N. Ouchi, R. Shibata, K. Walsh, AMP-activated protein kinase signaling stimulates VEGF expression and angiogenesis in skeletal muscle, Circ. Res. 96 (2005) 838–846.
[54] K.A. Zwetsloot, L.M. Westerkamp, B.F. Holmes, T.P. Gavin, AMPK regulates basal skeletal muscle capillarization and VEGF expression, but is not necessary for the angiogenic response to exercise, J. Physiol. 586 (2008) 6021–6035.
[55] J.G. Boyle, P.J. Logan, G.C. Jones, M. Small, N. Sattar, J.M. Connell, S.J. Cleland, I.P. Salt, AMP-activated protein kinase is activated in adipose tissue of individuals with type 2 diabetes treated with metformin: a randomised glycaemia-controlled crossover study, Diabetologia 54 (2011) 1799–1809.
[56] D. Bishop-Bailey, PPARs and angiogenesis, Biochem. Soc. Trans. 39 (2011) 1601–1605.
[57] K.Y. Kim, J.H. Ahn, H.G. Cheon, Anti-angiogenic action of PPARgamma ligand in human umbilical vein endothelial cells is mediated by PTEN upregulation and VEGFR-2 downregulation, Mol. Cell. Biochem. 358 (2011) 375–385.
[58] M.A. Sarayba, L. Li, T. Tungsiripat, N.H. Liu, P.M. Sweet, A.J. Patel, K.E. Osann, A. Chittiboyina, S.C. Benson, H.A. Pershadsingh, R.S. Chuck, Inhibition of corneal neovascularization by a peroxisome proliferator-activated receptor-gamma ligand, Exp. Eye Res. 80 (2005) 435–442.
[59] O. Gealekman, A. Burkart, M. Chouinard, S.M. Nicoloro, J. Straubhaar, S. Corvera, Enhanced angiogenesis in obesity and in response to PPARgamma activators through adipocyte VEGF and ANGPTL4 production, Am. J. Physiol. Endocrinol. Metab. 295 (2008) E1056–E1064.
[60] O. Gealekman, N. Guseva, K. Gurav, A. Gusev, C. Hartigan, M. Thompson, S. Malkani, S. Corvera, Effect of rosiglitazone on capillary density and angiogenesis in adipose tissue of normoglycaemic humans in a randomised controlled trial, Diabetologia 55 (2012) 2794–2799.
[61] K.B. Sotiropoulos, A. Clermont, Y. Yasuda, C. Rask-Madsen, M. Mastumoto, J. Takahashi, K. Della Vecchia, T. Kondo, L.P. Aiello, G.L. King, Adipose-specific effect of rosiglitazone on vascular permeability and protein kinase C activation: novel mechanism for PPARgamma agonist's effects on edema and weight gain, FASEB J. 20 (2006) 1203–1205.
[62] D. Fukumura, A. Ushiyama, D.G. Duda, L. Xu, J. Tam, V. Krishna, K. Chatterjee, I. Garkavtsev, R.K. Jain, Paracrine regulation of angiogenesis and adipocyte differentiation during in vivo adipogenesis, Circ. Res. 93 (2003) e88–e97.
[63] J.J. Castellot Jr., M.J. Karnovsky, B.M. Spiegelman, Differentiation-dependent stimulation of neovascularization and endothelial cell chemotaxis by 3T3 adipocytes, Proc. Natl. Acad. Sci. U. S. A. 79 (1982) 5597–5601.
[64] J. Folkman, Angiogenesis: initiation and control, Ann. N. Y. Acad. Sci. 401 (1982) 212–227.
[65] K.J. Silverman, D.P. Lund, B.R. Zetter, L.L. Lainey, J.A. Shahood, D.G. Freiman, J. Folkman, A.C. Barger, Angiogenic activity of adipose tissue, Biochem. Biophys. Res. Commun. 153 (1988) 347–352.
[66] Q.X. Zhang, C.J. Magovern, C.A. Mack, K.T. Budenbender, W. Ko, T.K. Rosengart, Vascular endothelial growth factor is the major angiogenic factor in omentum: mechanism of the omentum-mediated angiogenesis, J. Surg. Res. 67 (1997) 147–154.
[67] A. Bouloumie, H.C. Drexler, M. Lafontan, R. Busse, Leptin, the product of Ob gene, promotes angiogenesis, Circ. Res. 83 (1998) 1059–1066.
[68] S.L. Hocking, L.E. Wu, M. Guilhaus, D.J. Chisholm, D.E. James, Intrinsic depot-specific differences in the secretome of adipose tissue, preadipocytes, and adipose tissue-derived microvascular endothelial cells, Diabetes 59 (2010) 3008–3016.
[69] A.Y. Lemoine, S. Ledoux, I. Queguiner, S. Calderari, C. Mechler, S. Msika, P. Corvol, E. Larger, Link between adipose tissue angiogenesis and fat accumulation in severely obese subjects, J. Clin. Endocrinol. Metab. 97 (2012) E775–E780.
[70] M. Alligier, E. Meugnier, C. Debard, S. Lambert-Porcheron, E. Chanseaume, M. Sothier, E. Loizon, A.A. Hssain, J. Brozek, J.Y. Scoazec, B. Morio, H. Vidal, M. Laville, Subcutaneous adipose tissue remodeling during the initial phase of weight gain induced by overfeeding in humans, J. Clin. Endocrinol. Metab. 97 (2012) E183–E192.
[71] O. Kunduzova, N. Alet, N. Delesque-Touchard, L. Millet, I. Castan-Laurell, C. Muller, C. Dray, P. Schaeffer, J.P. Herault, P. Savi, F. Bono, P. Valet, Apelin/APJ signaling system: a potential link between adipose tissue and endothelial angiogenic processes, FASEB J. 22 (2008) 4146–4153.
[72] L.N. Bell, L. Cai, B.H. Johnstone, D.O. Traktuev, K.L. March, R.V. Considine, A central role for hepatocyte growth factor in adipose tissue angiogenesis, Am. J. Physiol. Endocrinol. Metab. 294 (2008) E336–E344.
[73] I. Scroyen, F. Jacobs, L. Cosemans, B. De Geest, H.R. Lijnen, Blood vessel density in de novo formed adipose tissue is decreased upon overexpression of TIMP-1, Obesity (Silver Spring) 18 (2010) 638–640.
[74] M. Van Hul, L. Frederix, H.R. Lijnen, Role of thrombospondin-2 in murine adipose tissue angiogenesis and development, Obesity (Silver Spring) 20 (2012) 1757–1762.
[75] H.R. Lijnen, L. Frederix, B. Van Hoef, M. Dewerchin, Deficiency of vascular endothelial growth factor-D does not affect murine adipose tissue development, Biochem. Biophys. Res. Commun. 378 (2009) 255–258.
[76] L. Tian, J. Zhou, M.C. Casimiro, B. Liang, J.O. Ojeifo, M. Wang, T. Hyslop, C. Wang, R.G. Pestell, Activating peroxisome proliferator-activated receptor gamma mutant promotes tumor growth in vivo by enhancing angiogenesis, Cancer Res. 69 (2009) 9236–9244.
[77] S. Kersten, S. Mandard, N.S. Tan, P. Escher, D. Metzger, P. Chambon, F.J. Gonzalez, B. Desvergne, W. Wahli, Characterization of the fasting-induced adipose factor FIAF, a novel peroxisome proliferator-activated receptor target gene, J. Biol. Chem. 275 (2000) 28488–28493.
[78] J.C. Yoon, T.W. Chickering, E.D. Rosen, B. Dussault, Y. Qin, A. Soukas, J.M. Friedman, W.E. Holmes, B.M. Spiegelman, Peroxisome proliferator-activated receptor gamma target gene encoding a novel angiopoietin-related protein associated with adipose differentiation, Mol. Cell. Biol. 20 (2000) 5343–5349.
[79] L. Lichtenstein, F. Mattijssen, N.J. de Wit, A. Georgiadi, G.J. Hooiveld, R. van der Meer, Y. He, L. Qi, A. Koster, J.T. Tamsma, N.S. Tan, M. Muller, S. Kersten, Angptl4 protects against severe proinflammatory effects of saturated fat by inhibiting fatty acid uptake into mesenteric lymph node macrophages, Cell Metab. 12 (2010) 580–592.
[80] S. Romeo, L.A. Pennacchio, Y. Fu, E. Boerwinkle, A. Tybjaerg-Hansen, H.H. Hobbs, J.C. Cohen, Population-based resequencing of ANGPTL4 uncovers variations that reduce triglycerides and increase HDL, Nat. Genet. 39 (2007) 513–516.
[81] U. Desai, E.C. Lee, K. Chung, C. Gao, J. Gay, B. Key, G. Hansen, D. Machajewski, K.A. Platt, A.T. Sands, M. Schneider, I. Van Sligtenhorst, A. Suwanichkul, P. Vogel, N. Wilganowski, J. Wingert, B.P. Zambrowicz, G. Landes, D.R. Powell, Lipid-lowering effects of anti-angiopoietin-like 4 antibody recapitulate the lipid phenotype found in angiopoietin-like 4 knockout mice, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 11766–11771.
[82] K. Yoshida, T. Shimizugawa, M. Ono, H. Furukawa, Angiopoietin-like protein 4 is a potent hyperlipidemia-inducing factor in mice and inhibitor of lipoprotein lipase, J. Lipid Res. 43 (2002) 1770–1772.

[83] L.F. Drager, Q. Yao, K.L. Hernandez, M.K. Shin, S. Bevans-Fonti, J. Gay, T.E. Sussan, J.C. Jun, A.C. Myers, G. Olivecrona, A.R. Schwartz, N. Halberg, P.E. Scherer, G.L. Semenza, D.R. Powell, V.Y. Polotsky, Chronic intermittent hypoxia induces atherosclerosis via activation of adipose angiopoietin-like 4, Am. J. Respir. Crit. Care Med. (2013), (in press).
[84] D. Mazzatti, F.L. Lim, A. O'Hara, I.S. Wood, P. Trayhurn, A microarray analysis of the hypoxia-induced modulation of gene expression in human adipocytes, Arch. Physiol. Biochem. 118 (2012) 112–120.
[85] P. Gonzalez-Muniesa, C. de Oliveira, F. Perez de Heredia, M.P. Thompson, P. Trayhurn, Fatty acids and hypoxia stimulate the expression and secretion of the adipokine ANGPTL4 (angiopoietin-like protein 4/fasting-induced adipose factor) by human adipocytes, J. Nutrigenet. Nutrigenomics 4 (2011) 146–153.
[86] M. Murata, K. Yudo, H. Nakamura, J. Chiba, K. Okamoto, N. Suematsu, K. Nishioka, M. Beppu, K. Inoue, T. Kato, K. Masuko, Hypoxia upregulates the expression of angiopoietin-like-4 in human articular chondrocytes: role of angiopoietin-like-4 in the expression of matrix metalloproteinases and cartilage degradation, J. Orthop. Res. 27 (2009) 50–57.
[87] S. Le Jan, C. Amy, A. Cazes, C. Monnot, N. Lamande, J. Favier, J. Philippe, M. Sibony, J.M. Gasc, P. Corvol, S. Germain, Angiopoietin-like 4 is a proangiogenic factor produced during ischemia and in conventional renal cell carcinoma, Am. J. Pathol. 162 (2003) 1521–1528.
[88] H. Yokouchi, K. Eto, W. Nishimura, N. Takeda, Y. Kaburagi, S. Yamamoto, K. Yasuda, Angiopoietin-like protein 4 (ANGPTL4) is induced by high glucose in retinal pigment epithelial cells and exhibits potent angiogenic activity on retinal endothelial cells, Acta ophthalmol. 91 (4) (June 2013) e289–e297.
[89] E.G. Perdiguero, A. Galaup, M. Durand, J. Teillon, J. Philippe, D.M. Valenzuela, A.J. Murphy, G.D. Yancopoulos, G. Thurston, S. Germain, Alteration of developmental and pathological retinal angiogenesis in angptl4-deficient mice, J. Biol. Chem. 286 (2011) 36841–36851.
[90] B. Mikhak, S. Weinsheimer, L. Pawlikowska, A. Poon, P.Y. Kwok, M.T. Lawton, Y. Chen, J.G. Zaroff, S. Sidney, C.E. McCulloch, W.L. Young, H. Kim, Angiopoietin-like 4 (ANGPTL4) gene polymorphisms and risk of brain arteriovenous malformations, Cerebrovasc. Dis. 31 (2011) 338–345.
[91] Y.Y. Goh, M. Pal, H.C. Chong, P. Zhu, M.J. Tan, L. Punugu, C.K. Tan, R.L. Huang, S.K. Sze, M.B. Tang, J.L. Ding, S. Kersten, N.S. Tan, Angiopoietin-like 4 interacts with matrix proteins to modulate wound healing, J. Biol. Chem. 285 (2010) 32999–33009.
[92] A. Xu, M.C. Lam, K.W. Chan, Y. Wang, J. Zhang, R.L. Hoo, J.Y. Xu, B. Chen, W.S. Chow, A.W. Tso, K.S. Lam, Angiopoietin-like protein 4 decreases blood glucose and improves glucose tolerance but induces hyperlipidemia and hepatic steatosis in mice, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 6086–6091.
[93] J.M. Olefsky, C.K. Glass, Macrophages, inflammation, and insulin resistance, Annu. Rev. Physiol. 72 (2010) 219–246.
[94] J. Ye, Adipose tissue vascularization: its role in chronic inflammation, Curr. Diab. Rep. 11 (2011) 203–210.
[95] J.W. Pollard, Trophic macrophages in development and disease, Nat. Rev. Immunol. 9 (2009) 259–270.
[96] W. Chen, T. Ma, X.N. Shen, X.F. Xia, G.D. Xu, X.L. Bai, T.B. Liang, Macrophage-induced tumor angiogenesis is regulated by the TSC2–mTOR pathway, Cancer Res. 72 (2012) 1363–1372.
[97] A.E. Dirkx, M.G. Oude Egbrink, J. Wagstaff, A.W. Griffioen, Monocyte/macrophage infiltration in tumors: modulators of angiogenesis, J. Leukoc. Biol. 80 (2006) 1183–1196.
[98] M. Arras, W.D. Ito, D. Scholz, B. Winkler, J. Schaper, W. Schaper, Monocyte activation in angiogenesis and collateral growth in the rabbit hindlimb, J. Clin. Invest. 101 (1998) 40–50.
[99] A.E. Koch, P.J. Polverini, S.L. Kunkel, L.A. Harlow, L.A. DiPietro, V.M. Elner, S.G. Elner, R.M. Strieter, Interleukin-8 as a macrophage-derived mediator of angiogenesis, Science 258 (1992) 1798–1801.
[100] S.J. Leibovich, P.J. Polverini, H.M. Shepard, D.M. Wiseman, V. Shively, N. Nuseir, Macrophage-induced angiogenesis is mediated by tumour necrosis factor-alpha, Nature 329 (1987) 630–632.
[101] J.A. Stefater III, S. Rao, K. Bezold, A.C. Aplin, R.F. Nicosia, J. Pollard, N. Ferrara, R.A. Lang, Macrophage Wnt–calcineurin–Flt1 signaling regulates mouse wound angiogenesis and repair, Blood 121 (13) (2013) 2574–2578.
[102] A.C. Newman, C.C. Hughes, Macrophages and angiogenesis: a role for Wnt signaling, Vasc. Cell 4 (2012) 13.
[103] C. Pang, Z. Gao, J. Yin, J. Zhang, W. Jia, J. Ye, Macrophage infiltration into adipose tissue may promote angiogenesis for adipose tissue remodeling in obesity, Am. J. Physiol. Endocrinol. Metab. 295 (2008) E313–E322.
[104] J. Han, J.E. Lee, J. Jin, J.S. Lim, N. Oh, K. Kim, S.I. Chang, M. Shibuya, H. Kim, G.Y. Koh, The spatiotemporal development of adipose tissue, Development 138 (2011) 5027–5037.
[105] W. Tang, D. Zeve, J.M. Suh, D. Bosnakovski, M. Kyba, R.E. Hammer, M.D. Tallquist, J.M. Graff, White fat progenitor cells reside in the adipose vasculature, Science 322 (2008) 583–586.
[106] W. Tang, D. Zeve, J. Seo, A.Y. Jo, J.M. Graff, Thiazolidinediones regulate adipose lineage dynamics, Cell Metab. 14 (2011) 116–122.
[107] K.V. Tran, O. Gealekman, A. Frontini, M.C. Zingaretti, M. Morroni, A. Giordano, A. Smorlesi, J. Perugini, R. De Matteis, A. Sbarbati, S. Corvera, S. Cinti, The vascular endothelium of the adipose tissue gives rise to both white and brown fat cells, Cell Metab. 15 (2012) 222–229.
[108] R.K. Gupta, R.J. Mepani, S. Kleiner, J.C. Lo, M.J. Khandekar, P. Cohen, A. Frontini, D.C. Bhowmick, L. Ye, S. Cinti, B.M. Spiegelman, Zfp423 expression identifies committed preadipocytes and localizes to adipose endothelial and perivascular cells, Cell Metab. 15 (2012) 230–239.
[109] M. Wosnitza, K. Hemmrich, A. Groger, S. Graber, N. Pallua, Plasticity of human adipose stem cells to perform adipogenic and endothelial differentiation, Differentiation 75 (2007) 12–23.
[110] V. Planat-Benard, J.S. Silvestre, B. Cousin, M. Andre, M. Nibbelink, R. Tamarat, M. Clergue, C. Manneville, C. Saillan-Barreau, M. Duriez, A. Tedgui, B. Levy, L. Penicaud, L. Casteilla, Plasticity of human adipose lineage cells toward endothelial cells: physiological and therapeutic perspectives, Circulation 109 (2004) 656–663.
[111] G. Rajashekhar, D.O. Traktuev, W.C. Roell, B.H. Johnstone, S. Merfeld-Clauss, B. Van Natta, E.D. Rosen, K.L. March, M. Clauss, IFATS collection: adipose stromal cell differentiation is reduced by endothelial cell contact and paracrine communication: role of canonical Wnt signaling, Stem cells 26 (2008) 2674–2681.
[112] K. Ba, X. Yang, L. Wu, X. Wei, N. Fu, Y. Fu, X. Cai, Y. Yao, Y. Ge, Y. Lin, Jagged-1-mediated activation of notch signalling induces adipogenesis of adipose-derived stem cells, Cell Prolif. 45 (2012) 538–544.
[113] D. Fukuda, E. Aikawa, F.K. Swirski, T.I. Novobrantseva, V. Kotelianski, C.Z. Gorgun, A. Chudnovskiy, H. Yamazaki, K. Croce, R. Weissleder, J.C. Aster, G.S. Hotamisligil, H. Yagita, M. Aikawa, Notch ligand delta-like 4 blockade attenuates atherosclerosis and metabolic disorders, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) E1868–E1877.
[114] C. Garces, M.J. Ruiz-Hidalgo, J. Font de Mora, C. Park, L. Miele, J. Goldstein, E. Bonvini, A. Porras, J. Laborda, Notch-1 controls the expression of fatty acid-activated transcription factors and is required for adipogenesis, J. Biol. Chem. 272 (1997) 29729–29734.
[115] M. Cantile, A. Procino, M. D'Armiento, L. Cindolo, C. Cillo, HOX gene network is involved in the transcriptional regulation of in vivo human adipogenesis, J. Cell. Physiol. 194 (2003) 225–236.
[116] S. Gesta, M. Bluher, Y. Yamamoto, A.W. Norris, J. Berndt, S. Kralisch, J. Boucher, C. Lewis, C.R. Kahn, Evidence for a role of developmental genes in the origin of obesity and body fat distribution, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 6676–6681.
[117] K. Karastergiou, S.K. Fried, H. Xie, M.J. Lee, A. Divoux, M.A. Rosencrantz, R.J. Chang, S.R. Smith, Distinct developmental signatures of human abdominal and gluteal subcutaneous adipose tissue depots, J. Clin. Endocrinol. Metab. 98 (2013) 362–371.
[118] M.C. Vohl, R. Sladek, J. Robitaille, S. Gurd, P. Marceau, D. Richard, T.J. Hudson, A. Tchernof, A survey of genes differentially expressed in subcutaneous and visceral adipose tissue in men, Obes. Res. 12 (2004) 1217–1222.
[119] S.J. Stoll, J. Kroll, HOXC9: a key regulator of endothelial cell quiescence and vascular morphogenesis, Trends Cardiovasc. Med. 22 (2012) 7–11.
[120] S.J. Stoll, S. Bartsch, H.G. Augustin, J. Kroll, The transcription factor HOXC9 regulates endothelial cell quiescence and vascular morphogenesis in zebrafish via inhibition of interleukin 8, Circ. Res. 108 (2011) 1367–1377.
[121] T. Bruhl, C. Urbich, D. Aicher, A. Acker-Palmer, A.M. Zeiher, S. Dimmeler, Homeobox A9 transcriptionally regulates the EphB4 receptor to modulate endothelial cell migration and tube formation, Circ. Res. 94 (2004) 743–751.
[122] S. Bandyopadhyay, M.Z. Ashraf, P. Daher, P.H. Howe, P.E. DiCorleto, HOXA9 participates in the transcriptional activation of E-selectin in endothelial cells, Mol. Cell. Biol. 27 (2007) 4207–4216.
[123] C.M. Trivedi, R.C. Patel, C.V. Patel, Homeobox gene HOXA9 inhibits nuclear factor-kappa B dependent activation of endothelium, Atherosclerosis 195 (2007) e50–e60.
[124] K. Rhoads, G. Arderiu, A. Charboneau, S.L. Hansen, W. Hoffman, N. Boudreau, A role for Hox A5 in regulating angiogenesis and vascular patterning, Lymphat. Res. Biol. 3 (2005) 240–252.
[125] Y. Zhu, I.C. Cuevas, R.A. Gabriel, H. Su, S. Nishimura, P. Gao, A. Fields, Q. Hao, W.L. Young, G.Y. Yang, N.J. Boudreau, Restoring transcription factor HoxA5 expression inhibits the growth of experimental hemangiomas in the brain, J. Neuropathol. Exp. Neurol. 68 (2009) 626–632.
[126] Y. Yamamoto, S. Gesta, K.Y. Lee, T.T. Tran, P. Saadatirad, C.R. Kahn, Adipose depots possess unique developmental gene signatures, Obesity (Silver Spring) 18 (2010) 872–878.
[127] L. Hodson, S.M. Humphreys, F. Karpe, K.N. Frayn, Metabolic signatures of human adipose tissue hypoxia in obesity, Diabetes 62 (5) (May 2013) 1417–1425.
[128] M.A. Rupnick, D. Panigrahy, C.Y. Zhang, S.M. Dallabrida, B.B. Lowell, R. Langer, M.J. Folkman, Adipose tissue mass can be regulated through the vasculature, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 10730–10735.
[129] A.C. Daquinag, Y. Zhang, M.G. Kolonin, Vascular targeting of adipose tissue as an anti-obesity approach, Trends Pharmacol. Sci. 32 (2011) 300–307.
[130] M. Alligier, L. Gabert, E. Meugnier, S. Lambert-Porcheron, E. Chanseaume, F. Pilleul, C. Debard, V. Sauvinet, B. Morio, A. Vidal-Puig, H. Vidal, M. Laville, Visceral fat accumulation during lipid overfeeding is related to subcutaneous adipose tissue characteristics in healthy men, J. Clin. Endocrinol. Metab. 98 (2013) 802–810.
[131] M. Spencer, R. Unal, B. Zhu, N. Rasouli, R.E. McGehee Jr., C.A. Peterson, P.A. Kern, Adipose tissue extracellular matrix and vascular abnormalities in obesity and insulin resistance, J. Clin. Endocrinol. Metab. 96 (2011) E1990–E1998.
[132] C.Y. Tan, A. Vidal-Puig, Adipose tissue expandability: the metabolic problems of obesity may arise from the inability to become more obese, Biochem. Soc. Trans. 36 (2008) 935–940.
[133] L.R. Strickland, F. Guo, K. Lok, W.T. Garvey, Type 2 diabetes with partial lipodystrophy of the limbs: a new lipodystrophy phenotype, Diabetes Care (2013), (in press).
[134] W.A. Haque, E.A. Oral, K. Dietz, A.M. Bowcock, A.K. Agarwal, A. Garg, Risk factors for diabetes in familial partial lipodystrophy, Dunnigan variety, Diabetes Care 26 (2003) 1350–1355.
[135] B.I. Joffe, V.R. Panz, F.J. Raal, From lipodystrophy syndromes to diabetes mellitus, Lancet 357 (2001) 1379–1381.

[136] T. Khan, E.S. Muise, P. Iyengar, Z.V. Wang, M. Chandalia, N. Abate, B.B. Zhang, P. Bonaldo, S. Chua, P.E. Scherer, Metabolic dysregulation and adipose tissue fibrosis: role of collagen VI, Mol. Cell. Biol. 29 (2009) 1575–1591.
[137] J.Y. Kim, E. van de Wall, M. Laplante, A. Azzara, M.E. Trujillo, S.M. Hofmann, T. Schraw, J.L. Durand, H. Li, G. Li, L.A. Jelicks, M.F. Mehler, D.Y. Hui, Y. Deshaies, G.I. Shulman, G.J. Schwartz, P.E. Scherer, Obesity-associated improvements in metabolic profile through expansion of adipose tissue, J. Clin. Invest. 117 (2007) 2621–2637.
[138] G.E. Beranger, M. Karbiener, V. Barquissau, D.F. Pisani, M. Scheideler, D. Langin, E.Z. Amri, In vitro brown and "brite"/"beige" adipogenesis: human cellular models and molecular aspects, Biochim. Biophys. Acta 1831 (5) (May 2013) 905–914.
[139] M.L. Bonet, P. Oliver, A. Palou, Pharmacological and nutritional agents promoting browning of white adipose tissue, Biochim. Biophys. Acta 1831 (5) (May 2013) 969–985.
[140] A. Georgiadi, L. Lichtenstein, T. Degenhardt, M.V. Boekschoten, M. van Bilsen, B. Desvergne, M. Muller, S. Kersten, Induction of cardiac Angptl4 by dietary fatty acids is mediated by peroxisome proliferator-activated receptor beta/delta and protects against fatty acid-induced oxidative stress, Circ. Res. 106 (2010) 1712–1721.
[141] F. Xu, D. Burk, Z. Gao, J. Yin, X. Zhang, J. Weng, J. Ye, Angiogenic deficiency and adipose tissue dysfunction are associated with macrophage malfunction in SIRT1-/- mice, Endocrinology 153 (2012) 1706–1716.
[142] C.M. Cox, S.L. D'Agostino, M.K. Miller, R.L. Heimark, P.A. Krieg, Apelin, the ligand for the endothelial G-protein-coupled receptor, APJ, is a potent angiogenic factor required for normal vascular development of the frog embryoc, Dev. Biol. 296 (2006) 177–189.
[143] T. Josephs, H. Waugh, I. Kokay, D. Grattan, M. Thompson, Fasting-induced adipose factor identified as a key adipokine that is up-regulated in white adipose tissue during pregnancy and lactation in the rat, J. Endocrinol. 194 (2007) 305–312.
[144] B. Hemmeryckx, R. van Bree, B. Van Hoef, L. Vercruysse, H.R. Lijnen, J. Verhaeghe, Adverse adipose phenotype and hyperinsulinemia in gravid mice deficient in placental growth factor, Endocrinology 149 (2008) 2176–2183.
[145] H.R. Lijnen, V. Christiaens, I. Scroyen, G. Voros, M. Tjwa, P. Carmeliet, D. Collen, Impaired adipose tissue development in mice with inactivation of placental growth factor function, Diabetes 55 (2006) 2698–2704.
[146] J.W. Jonker, J.M. Suh, A.R. Atkins, M. Ahmadian, P. Li, J. Whyte, M. He, H. Juguilon, Y.Q. Yin, C.T. Phillips, R.T. Yu, J.M. Olefsky, R.R. Henry, M. Downes, R.M. Evans, A PPARgamma-FGF1 axis is required for adaptive adipose remodelling and metabolic homeostasis, Nature 485 (2012) 391–394.
[147] K. Kos, J.P. Wilding, SPARC: a key player in the pathologies associated with obesity and diabetes, Nat. Rev. Endocrinol. 6 (2010) 225–235.
[148] K. Kos, S. Wong, B. Tan, A. Gummesson, M. Jernas, N. Franck, D. Kerrigan, F.H. Nystrom, L.M. Carlsson, H.S. Randeva, J.H. Pinkney, J.P. Wilding, Regulation of the fibrosis and angiogenesis promoter SPARC/osteonectin in human adipose tissue by weight change, leptin, insulin, and glucose, Diabetes 58 (2009) 1780–1788.
[149] J. Nie, E.H. Sage, SPARC inhibits adipogenesis by its enhancement of beta-catenin signaling, J. Biol. Chem. 284 (2009) 1279–1290.
[150] S. Anagnostoulis, A.J. Karayiannakis, M. Lambropoulou, A. Efthimiadou, A. Polychronidis, C. Simopoulos, Human leptin induces angiogenesis in vivo, Cytokine 42 (2008) 353–357.
[151] R. Cao, E. Brakenhielm, C. Wahlestedt, J. Thyberg, Y. Cao, Leptin induces vascular permeability and synergistically stimulates angiogenesis with FGF-2 and VEGF, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 6390–6395.
[152] R. Adya, B.K. Tan, J. Chen, H.S. Randeva, Protective actions of globular and full-length adiponectin on human endothelial cells: novel insights into adiponectin-induced angiogenesis, J. Vasc. Res. 49 (2012) 534–543.
[153] N. Ouchi, H. Kobayashi, S. Kihara, M. Kumada, K. Sato, T. Inoue, T. Funahashi, K. Walsh, Adiponectin stimulates angiogenesis by promoting cross-talk between AMP-activated protein kinase and Akt signaling in endothelial cells, J. Biol. Chem. 279 (2004) 1304–1309.
[154] R. Shibata, C. Skurk, N. Ouchi, G. Galasso, K. Kondo, T. Ohashi, M. Shimano, S. Kihara, T. Murohara, K. Walsh, Adiponectin promotes endothelial progenitor cell number and function, FEBS Lett. 582 (2008) 1607–1612.
[155] K. Bozaoglu, J.E. Curran, C.J. Stocker, M.S. Zaibi, D. Segal, N. Konstantopoulos, S. Morrison, M. Carless, T.D. Dyer, S.A. Cole, H.H. Goring, E.K. Moses, K. Walder, M.A. Cawthorne, J. Blangero, J.B. Jowett, Chemerin, a novel adipokine in the regulation of angiogenesis, J. Clin. Endocrinol. Metab. 95 (2010) 2476–2485.
[156] K.B. Goralski, T.C. McCarthy, E.A. Hanniman, B.A. Zabel, E.C. Butcher, S.D. Parlee, S. Muruganandan, C.J. Sinal, Chemerin, a novel adipokine that regulates adipogenesis and adipocyte metabolism, J. Biol. Chem. 282 (2007) 28175–28188.
[157] G. Voros, E. Maquoi, D. Demeulemeester, N. Clerx, D. Collen, H.R. Lijnen, Modulation of angiogenesis during adipose tissue development in murine models of obesity, Endocrinology 146 (2005) 4545–4554.
[158] Y. Xue, R. Cao, D. Nilsson, S. Chen, R. Westergren, E.M. Hedlund, C. Martijn, L. Rondahl, P. Krauli, E. Walum, S. Enerback, Y. Cao, FOXC2 controls Ang-2 expression and modulates angiogenesis, vascular patterning, remodeling, and functions in adipose tissue, Proc. Natl. Acad. Sci. U. S. A. 105 (2008) 10167–10172.