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Blood vessels in fat tissues and vasculature-derived signals in controlling lipid metabolism and metabolic disease

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Metabolic disorders, including endocrine disorders, obesity, diabetes, cerebrocardiovascular disease, and even cancer, are the most common and lethal diseases with the leading all-cause mortality around the globe.[1] For example, according to the World Health Organization, type 2 diabetes mellitus (T2DM) as a chronic disease owing to insulin resistance became the ninth leading cause of death with 1.5 million deaths in 2019.[2] Currently, there are approximately 422 million people worldwide suffering from diabetes, with the majority living in low- and middle-income countries.[3] High T2DM prevalence has been associated with obesity and lifestyle factors such as lack of physical exercise, although genetic factors are linked to a subpopulation of T2DM patients.[4]

Unlike most other tissues in the body, adipose tissues, in particular white adipose tissues (WATs), experience expansion and shrinkage throughout the entire adult life.[5-8] While WATs store excessive energy as lipid droplets within adipocytes, adipocytes in brown adipose tissue (BAT) are engaged in energy dissipation by generating heat.[8,9] Accumulating evidence shows that WATs can be converted into a BAT-like phenotype and participate in energy expenditure.[10-12] In addition to deposition and expenditure of energy, adipose tissues are probably the largest endocrine organ in the body, which produce a myriad of endocrine hormones and adipokines.[13,14] These adipocyte-derived factors regulate global metabolisms and other systemic functions through endocrine, paracrine, and even autocrine mechanisms.[14,15]

Both WAT and BAT are highly vascularized and each adipocyte is engulfed by several capillaries.[16-18] Among all known tissues, adipose tissues, especially BAT, probably contain the highest density of microvessels.[16-18] In metabolically active adipose tissues such as thermogenically active BAT, angiogenesis concomitantly occurs to cope with metabolic alterations. Consequently, stimulation or inhibition of angiogenesis alters metabolic functions of adipose tissues and provides a promising opportunity for treatment of obesity and metabolic disease.[16] Moreover, obesity- and diabetes-associated clinical complications such as diabetic retinopathy (DR) and chronic leg ulcers also entail excessive or insufficient angiogenesis.[16] In fact, drugs targeting angiogenesis have been successfully used for treatment of DR in human patients.[19-21]

This editorial provides updated knowledge and understanding of vascular roles in regulating adipose tissue functions. In particular, therapeutic opportunities and challenges that are involved in treating metabolic diseases by targeting the adipose vasculature are discussed.

Angiogenesis and vasculatures in adipose tissues

During embryonic development, the formation of blood vessel networks occurs prior to any other specialized tissue formation and organogenesis, owing to their prerequisite roles in supplying nutrients and factors for cell growth and differentiation.[22] Without exception, the formation and maturation of adipose tissues are also dependent on angiogenesis.[17,23] Emerging experimental evidence shows that vasculatures display multifarious functions in controlling adipose tissue functions [Figure 1],[16-18] including: (1) Providing nutrients, oxygen, and factors for adipocyte survival and homeostasis; (2) Formation for the initial adipose niche and adipose development during embryogenesis; (3) Removal of metabolites from adipose tissues; (4) Controlling metabolic status of adipocytes. Energy deposition and expenditure in WAT and BAT are tightly regulated by the number and function of microvessels; (5) Transporting hormones, growth factors, and cytokines to distal tissues to exert their endocrine functions; (6) Regulation of adipose inflammation by recruiting inflammatory cells and producing inflammatory

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cytokines; (7) Production of paracrine factors by vascular cells; (8) Regulation of thermogenesis by browning adipose tissues; (9) Homeostasis of adipose tissue mass and physiological functions; (10) Modulation of interactions between adipocytes and stromal cells; and (11) Serving as a stem cell/preadipocyte reservoir. Based on their diverse functions, targeting the vascular vasculature, especially the angiogenic vessels, provides an attractive approach for treating metabolic disease.[16]

Blood vessels in WATs and BATs

For decades, it was believed that WATs simply served as an inert energy storage depot, and their role as an active participant in energy consumption and global metabolism was never considered.[5,11] Recent studies, however, demonstrate that WAT is a multifunctional organ that exerts broad biological functions, including: (1) Storage of excessive energy as lipid droplets[5,11]; (2) Production of endocrine hormones such as leptin and adiponectin[13]; (3) Secretion of cytokines and adipokines[24]; (4) Release of exosomes and nucleotides[25]; (5) Expenditure of energy[10-12]; and (6) Regulation of glycolysis and insulin sensitivity.[26] These diverse functions are accomplished by vasculature-dependent mechanisms.[18] For example, the expansion of the WAT mass is dependent on microvessels to transport energy and hormonal molecules for lipid deposition.[16] Adipose vasculatures contain

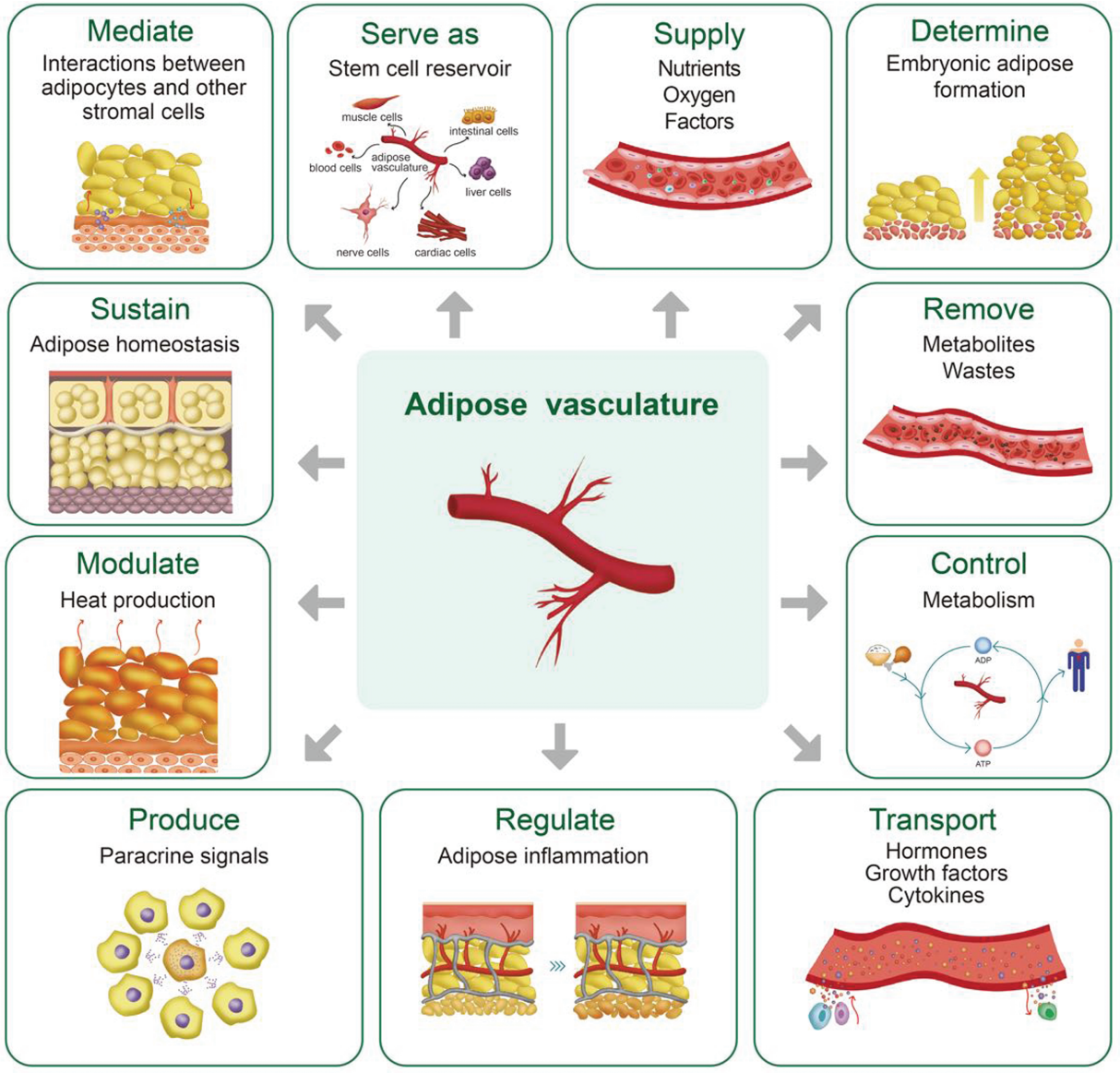

Figure 1: Vascular functions in adipose tissues and metabolism. Cells in the vessel wall serve as a stem cell reservoir to provide progenitor cells and preadipocytes that can differentiate into mature adipocytes. Blood vessels supply nutrients, oxygen, growth signals necessary for adipose homeostasis, metabolism, and endocrine functions. During embryogenesis, the formation of vascular networks is a prerequisite for adipose tissue formation and development. Blood vessels remove metabolites and wastes in adipose tissues. The vasculature controls global metabolism by transporting adipose-derived hormones, growth factors, and other signaling molecules. Vasculatures in adipose tissues regulate inflammation by recruiting or disseminating inflammatory cells. Vascular cells including endothelial cells and perivascular cells produce paracrine factors to modulate preadipocyte differentiation and metabolic functions in mature adipocytes. Blood vessels control thermogenesis in metabolically active browning white adipocytes and brown adipocytes. Vasculatures modulate complex interactions between adipocytes and other stromal cells such as mesenchymal stromal cells and inflammatory cells.

fenestrated capillaries that warrant delivery of adipocyte-secreted hormones to distal tissues and organs.[27,28] The fenestrated endothelium commonly exists in nearly all endocrine organs such as adrenal glands, insulin-producing pancreatic islets, thyroid, and ovary.[27,29-31]

It has been reported that angiogenesis occurs in expanding WAT masses to justify the energy and oxygen demands of growing adipocytes.[6,7] Expansion of the WAT mass is primarily achieved by increasing the adipocyte size owing to upsurge of intracellular lipid droplets, although increases of adipocyte numbers by differentiation of preadipocytes into mature adipocytes may also participate in this process.[32-34] Consequently, antiangiogenic treatments with generic inhibitors suppress WAT expansion and obesity.[6,7] Despite the existence of exceptionally high density of capillaries in adipose tissues, it is likely that only a fraction of microvessels is perfused to sustain physiological functions, especially under metabolically inert WATs.[17] BAT is probably the most vascularized tissue in the adult body and hypervascularization copes with specialized BAT functions, including thermogenesis, lipid mobilization, endocrine hormone secretion, and coordination of global metabolism.[9]

Angiogenic switch during browning of adipose tissues

Activation of thermogenesis in BAT and browning WAT (bWAT) concurrently occurs with a robust angiogenic phenotype, which participates in modulating adipocyte metabolism.[35-37] Angiogenic vessels are originally believed to play adaptive roles in supplying sufficient oxygen for energy consumption. According to this assumption, metabolic reprograming in browning adipocytes occurs prior to angiogenesis and new blood vessels may simply accelerate the fueling process of energy dissipation.[35,36] Indeed, metabolically active adipocytes, together with other stromal cells such as inflammatory cells and mesenchymal stromal cells, produce numerous angiogenic factors and cytokines to augment angiogenesis.[17] However, recent time-course studies of bWAT show that angiogenesis may occur prior to adipose browning, indicating that switching to an angiogenic phenotype is a prerequisite for activation of thermogenesis.[35,36] For example, in a cold-induced mouse WAT browning model, time-course analysis demonstrates that increases of microvascular density take place already within 3 days before adipocyte browning.[35,36] Independent studies show that vascular endothelial growth factor receptor (VEGFR) 2 expressed in vascular endothelial cells, but not in adipocytes, is essentially required for WAT browning.[36,38] Pharmacological blocking of VEGFR2 by a specific neutralizing antibody nearly completely ablates cold- or the β-adrenergic agonist CL316,243-induced WAT browning through inhibition of angiogenesis.[36,38] Similarly, genetic deletion of VEGFR2 in endothelial cells also abrogates WAT browning and non-shivering thermogenesis (NST), providing compelling evidence of vascular endothelial cell-driven activation of WAT browning and metabolism.[36] In another experimental setting, inhibition of VEGFR1 alone induces a browning phenotype in WAT.[35] Although VEGFR1 expression is not exclusively restricted in vascular endothelial cells, adipocytes lack detectable levels of this receptor.[35] Additionally, VEGFR1 is generally considered to act as a decoy receptor that negatively regulates angiogenesis, and its tyrosine kinase activity remains in an inert state even in the presence of ligands.[39] Consistent with this notion, vascular endothelial growth factor (VEGF)-B and placental growth factor (PlGF) as two VEGFR1 exclusive binding ligands are unable to induce angiogenesis in various *in vivo* animal models.[40-49] Blocking VEGFR1 allows more VEGF molecules to bind VEGFR2 and subsequently triggers the VEGF-dependent angiogenic response.[35,39] Thus, VEGF expression levels and balance between VEGFR1 and VEGFR2 in adipose tissues are tightly regulated under physiological conditions. Excessive VEGF molecules or mitigated VEGFR1 expression in adipose tissues may tip the balance toward an angiogenic phenotype,[35,39] which augments WAT browning and NST even under thermoneutrality. In addition to the VEGF-VEGFR2 signaling, other proangiogenic factors may also significantly contribute to modulation of adipose angiogenesis and metabolism. However, in various experimental settings of adipose angiogenesis and thermogenesis, VEGF appears to be the crucial regulator in controlling adipocyte metabolic activity.[18,50]

Vasculature-derived paracrine signals in controlling adipocyte metabolism

Given pivotal roles of the adipose vasculature in regulation of metabolic functions, tremendous efforts have been focused on studying signaling pathways that mediate the crosstalk between vessel wall cells and adipocytes.[17,18,51] What are the key paracrine signaling molecules released by angiogenic endothelial cells to modulate adipocyte metabolism? Through what mechanisms do these factors regulate adipocyte activity? Would these potential signaling components be therapeutic targets for treatment of metabolic diseases? At the time of this writing, these important questions remain unresolved.

In response to VEGF stimulation, vascular endothelial cells in bWAT express high levels of platelet-derived growth factors (PDGFs) and PDGF-C is identified as one of the paracrine factors responsible for thermogenesis.[36] PDGF-C and PDGF-B become upregulated in angiogenic endothelial cells in response to VEGF stimulation.[36] In response to PDGF stimulation, activation of PDGFRs in adipocyte progenitors and preadipocytes undergo differentiation toward mature WAT adipocytes[52] [Figure 2].

Under browning conditions such as cold exposure, PDGF-C induces differentiation of preadipocytes into metabolically active browning adipocytes.[36] Fibroblast growth factor (FGF)-10 is another stromal-vascular fraction-derived differentiation factor that induces progenitor cell differentiation into browning adipocytes.[53,54] FGF-10 may stimulate differentiation through an autocrine mechanism.[53] Additionally, FGF-21 has been described as a potent browning factor that possibly mediates endothelial cell–adipocyte crosstalk.[55] Members in the epidermal growth factor family also participate in

paracrine regulation of adipose browning through modulation of endothelial cell–adipocyte interactions.[56] In addition to differentiation, conversion of mature adipocytes into brown-like adipocytes may also simultaneously occur during adipose browning. Factors that control conversion of white adipocytes into browning adipocytes remain to be identified.

Therapeutic implications

Targeting angiogenic vessels in the adipose tissue provides a promising and attractive approach for treating metabolic diseases such as T2DM.[16] The original idea for this therapeutic approach is that expansion of the adipose tissue mass and deposition of energy, similar to tumor growth, are dependent on angiogenesis.[6,7] Inhibition of angiogenesis offers an anti-obesity strategy by restricting adipose tissue expansion and energy deposition. In support of this concept, inhibition of angiogenesis by TNP-470, a generic angiogenesis inhibitor, prevents obesity in high-fat-diet-fed and genetic mouse obese models.[6,7] TNP-470-provoked anti-obesity is dependent on angiogenesis, but not due to decrease of food intake and direct impacts on adipocytes.[7] Importantly, reduction of body weight by TNP-470 results in improvement of insulin sensitivity in obese animals.[7] Some of these findings are reproduced by treatment of obese animals with endogenous angiogenesis inhibitors such as angiostatin.[6] If these preclinical data can be successfully translated in humans, anti-angiogenic therapy would be potentially used for treatment of obesity and metabolic diseases.

Paradoxically, angiogenesis is also essentially required for energy consumption in metabolically active adipose tissues such as BAT and bWAT.[18] Instigation rather than inhibition of angiogenesis may provide a therapeutic option for treatment of obesity and metabolic diseases. Indeed, delivery of VEGF that specifically targets vascular endothelial cells, but not adipocytes, mitigates the adipose tissue mass by inducing a browning phenotype of WATs and NST.[35,36,38] In several experimental settings, VEGF is identified as the key angiogenic factor for augmenting adipose browning.[35,36,38,50] The paradox of angiogenesis in regulating energy deposition and consumption can be explained through context-dependent mechanisms. Metabolically inert WAT adipocytes rely on angiogenic vessels for energy deposition, whereas metabolically active adipocytes are dependent on angiogenesis for energy consumption.[16] Thus, stimulation or inhibition of angiogenesis for treatment of metabolic diseases may be dependent on the metabolic status of adipose tissues.

A similar paradoxical therapy may also apply to clinical complications of metabolic diseases. For example, neovascularization and vascular leakiness are key pathological processes for causing DR, and inhibition of VEGF, the crucial factor responsible for these retinal pathologies, is beneficial for treatment of patients with DR.[20,21] In fact, several agents targeting the VEGF–VEGFR2 axis have been approved for treatment of patients with DR and diabetic macular edema.[20,21] By contrast, stimulation of angiogenesis by delivery of proangiogenic factors offers an opportunity for treatment of diabetic foot ulcers that lack

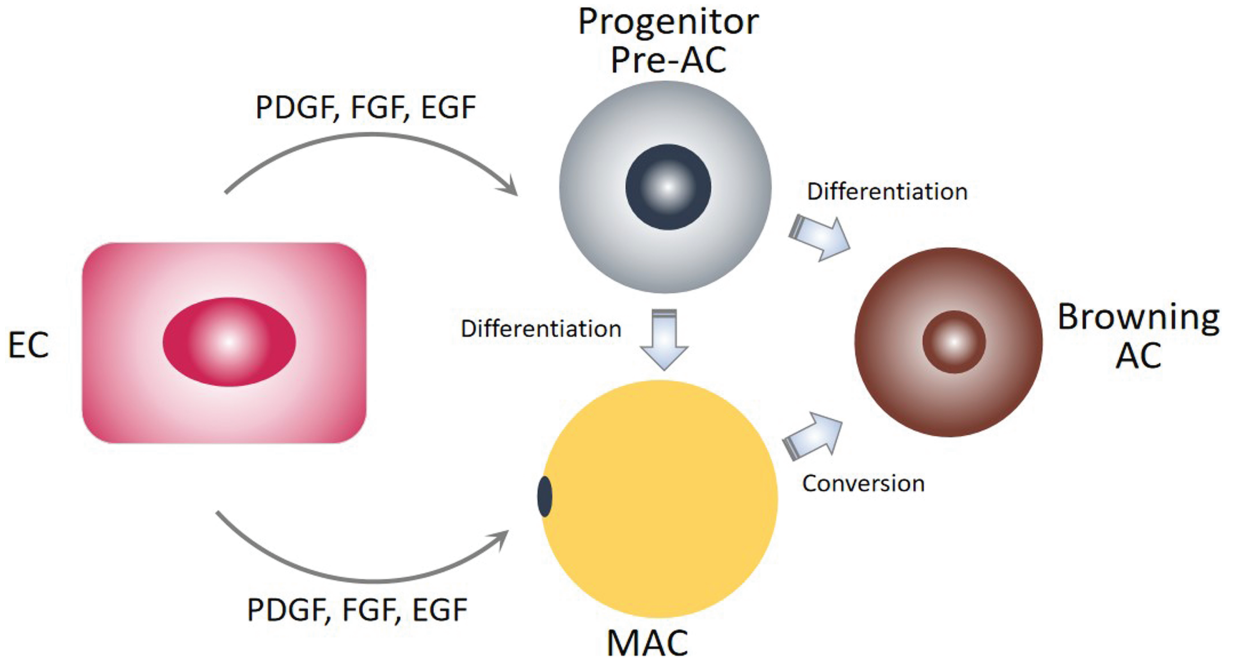

Figure 2: Endothelial cell-derived paracrine signals in controlling progenitor cell differentiation and browning of mature WAT adipocytes. In response to angiogenic stimuli such as VEGF, angiogenic endothelial cells produce high levels of growth factors, including PDGFs, FGFs, and EGFs, which act on adipose progenitor cells and preadipocytes to induce differentiation into mature adipocytes. Differentiation of these progenitor cells into metabolically inert WAT adipocytes or active browning adipocytes is dependent on the microenvironment in an adipose tissue. For example, under thermoneutrality, adipose progenitors differentiate into white adipocytes, whereas under browning conditions such as cold exposure, these progenitors can differentiate into browning adipocytes. In addition to preadipocyte differentiation, the endothelial cell-derived signaling molecules may also participate in conversation of mature WAT adipocytes into metabolically active browning adipocytes. Browning AC: Browning adipocyte; EC: Endothelial cell; EGF: Epidermal growth factor; FGF: Fibroblast growth factor; MAC: Mature adipocytes; PDGF: Platelet-derived growth factor; Pre-AC: Preadipocyte; VEGF: Vascular endothelial growth factor; WAT: White adipose tissue.

sufficient neovascularization. Local delivery of proangiogenic factors to the ulcer bed improves wound healing.[57]

To summarize, we are beginning to learn complex mechanisms that underlie angiogenesis in regulation of adipose and global metabolism. In-depth mechanistic insights into the vasculature–adipocyte crosstalk would inevitably define precision targets for effective treatment of metabolic diseases and their complications. Such angiogenesis-targeted drugs for treatment of metabolic diseases are already available in the clinic and emerging new and more effective drugs are in the pipeline of development.

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Conflicts of interest

None.

References

1. Kaur J. A comprehensive review on metabolic syndrome. Cardiol Res Pract 2014;2014:943162. doi: 10.1155/2014/943162.
2. WHO. 2021. Available from: https://www.who.int/news-room/fact-sheets/detail/diabetes. [Accessed on 2022].
3. WHO. 2022. Available from: https://www.who.int/health-topics/diabetes#tab=tab_1. [Accessed on 2022].
4. Ansari RM. Effect of physical activity and obesity on type 2 diabetes in a middle-aged population. J Environ Public Health 2009;2009:195285. doi: 10.1155/2009/195285.
5. Morigny P, Boucher J, Arner P, Langin D. Lipid and glucose metabolism in white adipocytes: pathways, dysfunction and therapeutics. Nat Rev Endocrinol 2021;17:276–295. doi: 10.1038/s41574-021-00471-8.
6. Rupnick MA, Panigrahy D, Zhang CY, Dallabrida SM, Lowell BB, Langer R, *et al*. Adipose tissue mass can be regulated through the vasculature. Proc Natl Acad Sci U S A 2002;99:10730–10735. doi: 10.1073/pnas.162349799.
7. Brakenhielm E, Cao R, Gao B, Angelin B, Cannon B, Parini P, *et al*. Angiogenesis inhibitor, TNP-470, prevents diet-induced and genetic obesity in mice. Circ Res 2004;94:1579–1588. doi: 10.1161/01.RES.0000132745.76882.70.
8. Saely CH, Geiger K, Drexel H. Brown versus white adipose tissue: a mini-review. Gerontology 2012;58:15–23. doi: 10.1159/000321319.
9. Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. Physiol Rev 2004;84:277–359. doi: 10.1152/physrev.00015.2003.
10. Kajimura S, Spiegelman BM, Seale P. Brown and beige fat: physiological roles beyond heat generation. Cell Metab 2015;22:546–559. doi: 10.1016/j.cmet.2015.09.007.
11. Giralt M, Villarroya F. White, brown, beige/brite: different adipose cells for different functions? Endocrinology 2013;154:2992–3000. doi: 10.1210/en.2013-1403.
12. Yang X, Sui W, Zhang M, Dong M, Lim S, Seki T, *et al*. Switching harmful visceral fat to beneficial energy combustion improves metabolic dysfunctions. JCI Insight 2017;2:e89044. doi: 10.1172/jci.insight.89044.
13. Trujillo ME, Scherer PE. Adipose tissue-derived factors: impact on health and disease. Endocr Rev 2006;27:762–778. doi: 10.1210/er.2006-0033.
14. Scheja L, Heeren J. The endocrine function of adipose tissues in health and cardiometabolic disease. Nat Rev Endocrinol 2019;15:507–524. doi: 10.1038/s41574-019-0230-6.
15. Cao Y. VEGF-targeted cancer therapeutics-paradoxical effects in endocrine organs. Nat Rev Endocrinol 2014;10:530–539. doi: 10.1038/nrendo.2014.114.
16. Cao Y. Adipose tissue angiogenesis as a therapeutic target for obesity and metabolic diseases. Nat Rev Drug Discov 2010;9:107–115. doi: 10.1038/nrd3055.
17. Cao Y. Angiogenesis modulates adipogenesis and obesity. J Clin Invest 2007;117:2362–2368. doi: 10.1172/JCI32239.
18. Cao Y. Angiogenesis and vascular functions in modulation of obesity, adipose metabolism, and insulin sensitivity. Cell Metab 2013;18:478–489. doi: 10.1016/j.cmet.2013.08.008.
19. Cao Y, Arbiser J, D'Amato RJ, D'Amore PA, Ingber DE, Kerbel R, *et al*. Forty-year journey of angiogenesis translational research. Sci Transl Med 2011;3:114rv3. doi: 10.1126/scitranslmed.3003149.
20. Ferrara N, Adamis AP. Ten years of anti-vascular endothelial growth factor therapy. Nat Rev Drug Discov 2016;15:385–403. doi: 10.1038/nrd.2015.17.
21. Cabral T, Mello LGM, Lima LH, Polido J, Regatieri CV, Belfort R Jr, *et al*. Retinal and choroidal angiogenesis: a review of new targets. Int J Retin Vitr 2017;3:31. doi: 10.1186/s40942-017-0084-9.
22. Berry DC, Stenesen D, Zeve D, Graff JM. The developmental origins of adipose tissue. Development 2013;140:3939–3949. doi: 10.1242/dev.080549.
23. Hausman GJ, Richardson RL. Adipose tissue angiogenesis. J Anim Sci 2004;82:925–934. doi: 10.2527/2004.823925x.
24. Ouchi N, Parker JL, Lugus JJ, Walsh K. Adipokines in inflammation and metabolic disease. Nat Rev Immunol 2011;11:85–97. doi: 10.1038/nri2921.
25. Mei R, Qin W, Zheng Y, Wan Z, Liu L. Role of adipose tissue derived exosomes in metabolic disease. Front Endocrinol 2022;13:873865. doi: 10.3389/fendo.2022.873865.
26. Czech MP. Mechanisms of insulin resistance related to white, beige, and brown adipocytes. Mol Metab 2020;34:27–42. doi: 10.1016/j.molmet.2019.12.014.
27. Cao R, Brakenhielm E, Wahlestedt C, Thyberg J, Cao Y. Leptin induces vascular permeability and synergistically stimulates angiogenesis with FGF-2 and VEGF. Proc Natl Acad Sci U S A 2001;98:6390–6395. doi: 10.1073/pnas.101564798.
28. Kamba T, Tam BY, Hashizume H, Haskell A, Sennino B, Mancuso MR, *et al*. VEGF-dependent plasticity of fenestrated capillaries in the normal adult microvasculature. Am J Physiol Heart Circ Physiol 2006;290:H560–H576. doi: 10.1152/ajpheart.00133.2005.
29. Yang Y, Zhang Y, Cao Z, Ji H, Yang X, Iwamoto H, *et al*. Anti-VEGF- and anti-VEGF receptor-induced vascular alteration in mouse healthy tissues. Proc Natl Acad Sci U S A 2013;110:12018–12023. doi: 10.1073/pnas.1301331110.
30. Cao R, Eriksson A, Kubo H, Alitalo K, Cao Y, Thyberg J. Comparative evaluation of FGF-2-, VEGF-A-, and VEGF-C-induced angiogenesis, lymphangiogenesis, vascular fenestrations, and permeability. Circ Res 2004;94:664–670. doi: 10.1161/01.RES.0000118600.91698.BB.
31. Eriksson A, Cao R, Roy J, Tritsaris K, Wahlestedt C, Dissing S, *et al*. Small GTP-binding protein Rac is an essential mediator of vascular endothelial growth factor-induced endothelial fenestrations and vascular permeability. Circulation 2003;107:1532–1538. doi: 10.1161/01.cir.0000055324.34758.32.
32. Stenkula KG, Erlanson-Albertsson C. Adipose cell size: Importance in health and disease. Am J Physiol Regul Integr Comp Physiol 2018;315:R284–R295. doi: 10.1152/ajpregu.00257.2017.
33. Prins JB, O'Rahilly S. Regulation of adipose cell number in man. Clin Sci 1997;92:3–11. doi: 10.1042/cs0920003.
34. Bjorntorp P. Sjöström L,+SJOSTROM L: number and size of adipose tissue fat cells in relation to metabolism in human obesity. Metabolism 1971;20:703–713. doi: 10.1016/0026-0495(71)90084-9.

35. Seki T, Hosaka K, Fischer C, Lim S, Andersson P, Abe M, *et al*. Ablation of endothelial VEGFR1 improves metabolic dysfunction by inducing adipose tissue browning. J Exp Med 2018;215:611–626. doi: 10.1084/jem.20171012.
36. Seki T, Hosaka K, Lim S, Fischer C, Honek J, Yang Y, *et al*. Endothelial PDGF-CC regulates angiogenesis-dependent thermogenesis in beige fat. Nat Commun 2016;7:12152. doi: 10.1038/ncomms12152.
37. Honek J, Seki T, Iwamoto H, Fischer C, Li J, Lim S, *et al*. Modulation of age-related insulin sensitivity by VEGF-dependent vascular plasticity in adipose tissues. Proc Natl Acad Sci U S A 2014;111:14906–14911. doi: 10.1073/pnas.1415825111.
38. Xue Y, Petrovic N, Cao R, Larsson O, Lim S, Chen S, *et al*. Hypoxia-independent angiogenesis in adipose tissues during cold acclimation. Cell Metab 2009;9:99–109. doi: 10.1016/j.cmet.2008.11.009.
39. Cao Y. Positive and negative modulation of angiogenesis by VEGFR1 ligands. Sci Signal 2009;2:re1. doi: 10.1126/scisignal.259re1.
40. Iwamoto H, Zhang Y, Seki T, Yang Y, Nakamura M, Wang J, *et al*. PlGF-induced VEGFR1-dependent vascular remodeling determines opposing antitumor effects and drug resistance to Dll4-Notch inhibitors. Sci Adv 2015;1:e1400244. doi: 10.1126/sciadv.1400244.
41. Yang X, Zhang Y, Yang Y, Lim S, Cao Z, Rak J, *et al*. Vascular endothelial growth factor-dependent spatiotemporal dual roles of placental growth factor in modulation of angiogenesis and tumor growth. Proc Natl Acad Sci U S A 2013;110:13932–13937. doi: 10.1073/pnas.1309629110.
42. Cao R, Xue Y, Hedlund EM, Zhong Z, Tritsaris K, Tondelli B, *et al*. VEGFR1-mediated pericyte ablation links VEGF and PlGF to cancer-associated retinopathy. Proc Natl Acad Sci U S A 2010;107:856–861. doi: 10.1073/pnas.0911661107.
43. Hedlund EM, Hosaka K, Zhong Z, Cao R, Cao Y. Malignant cell-derived PlGF promotes normalization and remodeling of the tumor vasculature. Proc Natl Acad Sci U S A 2009;106:17505–17510. doi: 10.1073/pnas.0908026106.
44. Bjorndahl M, Cao R, Eriksson A, Cao Y. Blockage of VEGF-induced angiogenesis by preventing VEGF secretion. Circ Res 2004;94:1443–1450. doi: 10.1161/01.RES.0000129194.61747.bf.
45. Eriksson A, Cao R, Pawliuk R, Berg SM, Tsang M, Zhou D, *et al*. Placenta growth factor-1 antagonizes VEGF-induced angiogenesis and tumor growth by the formation of functionally inactive PlGF-1/VEGF heterodimers. Cancer Cell 2002;1:99–108. doi: 10.1016/s1535-6108(02)00028-4.
46. Arjunan P, Lin X, Tang Z, Du Y, Kumar A, Liu L, *et al*. VEGF-B is a potent antioxidant. Proc Natl Acad Sci U S A 2018;115:10351–10356. doi: 10.1073/pnas.1801379115.
47. Jensen LD, Nakamura M, Brautigam L, Li X, Liu Y, Samani NJ, *et al*. VEGF-B-Neuropilin-1 signaling is spatiotemporally indispensable for vascular and neuronal development in zebrafish. Proc Natl Acad Sci U S A 2015;112:E5944–E5953. doi: 10.1073/pnas.1510245112.
48. Yang X, Zhang Y, Hosaka K, Andersson P, Wang J, Tholander F, *et al*. VEGF-B promotes cancer metastasis through a VEGF-A-independent mechanism and serves as a marker of poor prognosis for cancer patients. Proc Natl Acad Sci U S A 2015;112:E2900–E2909. doi: 10.1073/pnas.1503500112.
49. Aase K, von Euler G, Li X, Ponten A, Thoren P, Cao R, *et al*. Vascular endothelial growth factor-B-deficient mice display an atrial conduction defect. Circulation 2001;104:358–364. doi: 10.1161/01.cir.104.3.358.
50. Sung HK, Doh KO, Son JE, Park JG, Bae Y, Choi S, *et al*. Adipose vascular endothelial growth factor regulates metabolic homeostasis through angiogenesis. Cell Metab 2013;17:61–72. doi: 10.1016/j.cmet.2012.12.010.
51. Tran KV, Gealekman O, Frontini A, Zingaretti MC, Morroni M, Giordano A, *et al*. The vascular endothelium of the adipose tissue gives rise to both white and brown fat cells. Cell Metab 2012;15:222–229. doi: 10.1016/j.cmet.2012.01.008.
52. Gao Z, Daquinag AC, Su F, Snyder B, Kolonin MG. PDGFRalpha/PDGFRbeta signaling balance modulates progenitor cell differentiation into white and beige adipocytes. Development 2018;145:dev.155861. doi: 10.1242/dev.155861.
53. Fischer C, Seki T, Lim S, Nakamura M, Andersson P, Yang Y, *et al*. A miR-327-FGF10-FGFR2-mediated autocrine signaling mechanism controls white fat browning. Nat Commun 2017;8:2079. doi: 10.1038/s41467-017-02158-z.
54. Yamasaki M, Emoto H, Konishi M, Mikami T, Ohuchi H, Nakao K, *et al*. FGF-10 is a growth factor for preadipocytes in white adipose tissue. Biochem Biophys Res Commun 1999;258:109–112. doi: 10.1006/bbrc.1999.0594.
55. Cuevas-Ramos D, Mehta R, Aguilar-Salinas CA. Fibroblast growth factor 21 and browning of white adipose tissue. Front Physiol 2019;10:37. doi: 10.3389/fphys.2019.00037.
56. Sean RT, Carly AG, Kayla MC, Daniel CP, Evan RM, Charles EL, *et al*. HB-EGF and ADAM 12S directed cellular reprogramming results in metabolically active brown adipose tissue-like cells. AIMS Cell Tissue Eng 2018;2:203–219. doi: 10.3934/celltissue.2018.4.203.
57. Barrientos S, Stojadinovic O, Golinko MS, Brem H, Tomic-Canic M. Growth factors and cytokines in wound healing. Wound Repair Regen 2008;16:585–601. doi: 10.1111/j.1524-475X.2008.00410.x.

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