Battle of the Bulge
The Yin and Yang of Vascular Endothelial Growth Factor in Obesity
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Material force moves and flows in all directions and in all manners. It's two elements unite and give rise to the concrete. Thus the multiplicity of things and human beings is produced. In their ceaseless successions the two elements of yin and yang constitute the great principles of the universe.

Chang Tsai, Philosopher (1020–1078)

Yin and Yang are fundamental concepts of Chinese philosophy; 2 complementary yet competing forces that together influence nature and the elements. Yin is the darker, more negative side; Yang is the brighter, more positive side. The concept of yin and yang exists throughout medicine, and certainly applies to the biology of the vascular endothelial growth factor (VEGF) family.

The VEGF family consists of 5 ligands (VEGF-A through -D and placental growth factor). The most-studied VEGF ligand, VEGF-A, is encoded on chromosome 6; at least 12 splice isoforms have been described previously. Two distinct families of VEGF-A variants are created by alternate splice-site selection, whereby proximal splice selection in exon 8 results in mRNA encoding 7 proangiogenic VEGF-A isoforms, VEGF_{xxx} (where xxx is the number of amino acids), and distal splice selection results in mRNA encoding at least 5 antiangiogenic VEGF-A isoforms, VEGF_{165b} (Figure). First described in normal kidney (and down-regulated in cancer) in 2002, the most well-characterized antiangiogenic VEGF-A isoform is VEGF-A_{165b}. VEGF_{165b} has a 6-amino-acid difference on exon 8 in comparison with VEGF-A_{165} and acts as a competitive antagonist against VEGF-A_{165} by binding to the VEGF receptor-2 but not stimulating full tyrosine phosphorylation because of a lack of binding to neuropilin-1 (a VEGF coreceptor), preventing receptor activation and its downstream effects. A complex interplay exists between VEGF-A_{165} and VEGF-A_{165b} in several disease states, where a switch between proangiogenic VEGF-A_{165} and antiangiogenic VEGF-A_{165b} may lead to disease manifestation and progression. This interrelationship between VEGF-A isoforms has been studied in cancers, including renal cell carcinoma and prostate cancer, and in proliferative retinopathy, where the downregulation of VEGF-A_{165b} shifts the balance in favor of proangiogenic VEGF-A_{165} resulting in pathological angiogenesis. Thus, in these diseases, VEGF-A_{165b} acts as the yang to the yin of VEGF-A_{165}.

So how does the concept of yin and yang apply to VEGF in obesity? White and brown adipose tissues are highly vascularized, and as adipose tissue grows and regresses during changes in weight, precise regulation of angiogenesis within adipose tissues is required to maintain adequate delivery of nutrients and oxygen. Studies have demonstrated a close interplay between vascular components (endothelial cells, pericytes, and smooth muscle cells) and fat components (adipocytes, mesenchymal stromal cells, fibroblasts, and macrophages), modulated by various growth factors, adipokines, and cytokines. Proangiogenic growth factors and cytokines that have been implicated in adipose tissue angiogenesis include the VEGF family, hepatocyte growth factor, platelet-derived growth factor, and fibroblast growth factor. Specifically, the role of VEGF-A in adipose tissue angiogenesis has been extensively studied. Obese patients have increased circulating VEGF-A in comparison with lean controls, and VEGF-A levels decreased with Roux-en-Y gastric bypass surgery. Adipose tissue–specific VEGF knockout mice have reduced vessel density, have increased inflammation and apoptosis within adipose tissue, and developed severe insulin resistance and glucose intolerance when fed a high-fat diet. In contradistinction, adipose-specific VEGF-A–overexpressing mice showed increased adipose vessel density and improved glucose tolerance under high-fat–fed obese conditions. Thus a VEGF paradox exists in obesity, where VEGF levels are elevated, yet adipose tissue angiogenesis is deficient, leading to adverse metabolic effects that can be ameliorated by VEGF-targeted therapies. Although endogenous angiogenesis inhibitors, such as adiponectin, endostatin, and thrombospondin, may provide a counterbalance in regulating vessel growth and remodeling within adipose tissues, interactions with VEGF have yet to be fully elucidated.

In this issue of Circulation, Ngo et al present the first evidence for overexpression of an antiangiogenic VEGF-A isoform, VEGF-A_{165b}, in human visceral adipose tissue. Uregulation of VEGF-A_{165b} was significantly greater in visceral in comparison with subcutaneous adipose deposits in obese patients, and higher in diabetic patients versus nondiabetic patients. Total VEGF-A was elevated, yet VEGFR2 activation was reduced in the face of unchanged VEGFR2 protein expression, helping to explain the impaired angiogenic potential and negative correlation with capillary growth. Similar to findings in tumors, VEGF-A_{165b} impaired angiogenesis...
in adipose tissue, and was found to strongly correlate with reduced capillary growth. Coimmunoprecipitation experiments showed greater coupling of VEGF-A165b to VEGFR2 and, coupled with data on the antiangiogenic actions of recombinant VEGF-A165b protein in vitro, provide strong evidence that elevated VEGF-A165b in visceral adipose tissue counteracts the elevated VEGF-A levels and contributes to the defective angiogenesis in human obesity. Finally, they showed that weight loss after bariatric surgery was associated with lower VEGF-A165b levels, demonstrating that antiangiogenic isoforms can be manipulated in the clinical setting, opening up the possibility of interventions targeted against VEGF-A165b in human obesity and other conditions.

Our growing understanding of how angiogenesis modulates adipogenesis, obesity, insulin sensitivity, and glucose tolerance has fostered great interest in therapeutic interventions that target angiogenesis within adipose tissue for the prevention and treatment of obesity and related disorders. Despite recent advances, there remain many therapeutic hurdles to targeting adipose tissue vasculature. For VEGF-targeted therapies, preclinical studies have found a benefit of VEGF overexpression in adipose tissue, yet other conflicting studies suggest that VEGF blockade is beneficial. Transgenic mice with inducible VEGF-A repression were resistant to high-fat diet–induced obesity, with induction of a brown adipose tissue–like phenotype. In this model, VEGF-A repression led to upregulation of VEGF-B and its downstream fatty acid transport proteins that control endothelial fatty acid uptake. Most recently, Wu et al demonstrated that VEGF-A–neutralizing monoclonal antibody administration in a high-fat diet–induced mouse model of obesity reversed insulin resistance, independent of changes in adiposity or insulin signaling. There are confounding issues on both sides that must be considered. Although studies using transgenic animals are important for the discovery of the fundamental aspects of disease biology and pathophysiology, limitations in the model may hinder translation to therapeutic interventions. In this case, the fatty acid–binding protein 4 (FABP4 or aP2) promoter, used in several key studies of adipose tissue–specific gene overexpression/deletion and its effects on adipose tissue angiogenesis, is not wholly specific to adipose tissue. Although FABP4 is highly expressed in adipocytes, it is also expressed on endothelial cells and is induced by VEGF; thus, observed effects in vivo may not be due solely to effects in adipose tissue. It would be informative to repeat these experiments by using alternative adipose-targeting Cre mouse models, such as the Retn-Cre mouse line. In addition, intraperitoneal VEGF-neutralizing monoclonal antibody selectively blocks extracellular VEGF effects but does not target intracellular pathways, and also has important effects on nonadipose tissue, specifically the liver. Although Wu et al nicely showed that insulin sensitivity was improved, the effects on adipose tissue angiogenesis were not examined. Therefore, whether VEGF-targeted therapies in obesity should aim for VEGF overexpression or for VEGF blockade remains unclear.

Does the explanation behind these conflicting studies lie within the report by Ngo and colleagues? Studies of VEGF in obesity to date have not considered the role of the antiangiogenic VEGF isoform, VEGF-A165b. Because the amino acid structures of VEGF-A165 and VEGF-A165b are almost identical (96% homology), previous studies examining VEGF expression may not have distinguished between the different isoforms. Ngo et al found significantly higher circulating VEGF-A165b protein levels in obese patients, but lower VEGF-A165 levels, suggesting that elevated VEGF-A levels in previous studies of obese patients may be related more to excessive VEGF-A165b. In the setting of excess antiangiogenic VEGF-A165b that blocks VEGF-A165 binding to VEGFR2, additional VEGF-A165 may help overcome this competitive blockade, leading to enhanced angiogenesis and its positive metabolic effects. Similarly, given homology, one cannot exclude a beneficial effect of VEGF-A–neutralizing
monoclonal antibody administration used by Wu et al.\(^7\) owing to the blockade of VEGF-A\(_{165}\) on the promotion of angiogenesis. As we continue to search for therapeutic interventions that target VEGF-A in obesity and related disorders, future studies must examine the effects on VEGF-A\(_{165}\). The targeted blockade or suppression of adipose tissue VEGF-A\(_{165}\) itself is worthy of future study, not only in obesity, but also in other diseases characterized by defective angiogenesis.

The complexity of VEGF isoforms continues to unfold. In cancer and retinopathy, VEGF-A\(_{165}\) acts as the yang to the yin of VEGF-A\(_{165}\) whereas, in obesity and systemic sclerosis,\(^2\) VEGF-A\(_{165}\) acts as the yin to the yang of VEGF-A\(_{165}\) (Figure). We are grateful to Ngo and colleagues\(^14\) for reminding us of the importance of considering the fundamental and unifying concepts of yin and yang in biomedical research.

Yang cannot exist by itself; it can exist only when it is supported by yin. Hence yin is the foundation of yang. Similarly, yin cannot alone manifest itself; it can manifest itself only when accompanied by yang. Hence yang is the expression of yin. Yang controls the origination and enjoys the completion while yin follows the way and completes the work of yang.

Shao Yong, Philosopher (1012–1077)\(^2\)

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None.

References

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