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A Tug of War in the Periphery

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Compromised blood supply to a limb is usually compensated by the growth of collateral blood vessels in a process called neovascularization. Impairment of this process results in peripheral artery disease (PAD), which presents with ischemic manifestations ranging from pain to gangrene, a devastating complication warranting amputation of the limb. Multiple risk factors such as smoking and metabolic syndrome, including obesity and diabetes, predispose to PAD. Vascular endothelial growth factor-A (VEGF-A), which is induced by hypoxia or ischemia, is the predominant growth factor involved in neovascularization. However, it is unclear why neovascularization remains impaired in patients with PAD despite elevated concentrations of VEGF-A in their blood. This question was addressed by Kikuchi *et al.*, whose work implicates an imbalance between different isoforms of VEGF-A as a mechanism of reduced neovascularization.

VEGF-A gene undergoes alternative splicing, giving rise to two isoforms: proangiogenic VEGF-A_{165a} and antiangiogenic VEGF-A_{165b}. The authors confirmed the elevation in total VEGF-A in the blood of patients with PAD. Closer examination showed that these patients had increased VEGF-A_{165b}, but reduced VEGF-A_{165a}. To identify the source of this VEGF-A, the authors examined peripheral blood monocytes, because inflammation is closely associated with the development of PAD. Real-time polymerase chain reaction (RT-PCR) revealed an increase in VEGF-A_{165b} and a reduction in VEGF-A_{165a} transcript in the monocytes. It is known that Wnt5a regulates splicing of the *VEGF-A* gene in monocytes, and Wnt5a transcript was increased in monocytes derived from patients with PAD. The in vivo importance of Wnt5a was examined by generating an animal model of Wnt5a knock-in (KI) specifically in monocytes and then subjecting the animals to hind-limb ischemia. The ischemic limbs of KI animals showed a striking reduction in neovascularization accompanied by increased VEGF-A_{165b} and reduced VEGF-A_{165a} in the blood. Adipocytes are known to influence monocyte signaling. Healthy adipocytes secrete Sfrp5, which suppresses Wnt5a in monocytes, whereas in metabolic syndrome, the adipocytes have suppressed Sfrp5 and likely up-regulate Wnt5a in monocytes. Indeed, in two mouse models of obesity, Sfrp5 was reduced in the adipocytes, whereas Wnt5a was increased in the macrophages infiltrating the ischemic muscles, which had reduced capillary density.

Overall, it appears that the metabolic syndrome lowers Sfrp5 in adipocytes and thus removes the inhibition of Wnt5a in monocytes, tilting the balance in favor of antiangiogenic VEGF-A_{165b}. Although the upstream regulators of Sfrp5 in adipocytes and the mechanisms by which VEGF-A isoforms regulate angiogenesis remain to be determined, this work implicates the balance between two isoforms of VEGF-A as the critical determinant of

neovascularization in PAD. The ratio of VEGF-A isoforms can be further explored as a biomarker for PAD and may open a new approach for treating this devastating disease.

R. Kikuchi *et al.*, An antiangiogenic isoform of VEGF-A contributes to impaired vascularization in peripheral artery disease. *Nat. Med.* 10.1038/nm.3703 (2014). **[Abstract]**