Angiotensin II–Mediated Vascular Inflammation: The Balance Between Vascular Endothelial Growth Factor and Angiopoietins

To the Editor:

Vascular endothelial growth factor (VEGF) is a potent angiogenic factor and plays a key role in postnatal angiogenesis in human pathophysiology, including cardiovascular disease. The activation of the renin-angiotensin system has been similarly implicated in the cardiovascular pathophysiology. Indeed, an interaction between the renin-angiotensin system and VEGF has been established. It is against this background that we read with great interest the report by Zhao and colleagues on the central role of VEGF on angiotensin II (Ang II)–mediated vascular inflammation.

However, it is now increasingly evident that molecules traditionally regarded as angiogenic growth factors have effects that extend beyond these conventionally defined roles. In particular, angiopoietin-1 and its natural antagonist angiopoietin-2, in conjunction with VEGF, are key mediators of angiogenesis and are involved in the regulation of vascular inflammation and integrity. Angiopoietin-1 induces the recruitment of periendothelial cell support and reverses the permeability-inducing and proinflammatory effects induced by VEGF. In contrast, angiopoietin-2 destabilizes the vascular endothelium, promoting vascular growth induced by VEGF, and by competitively antagonizing angiopoietin-1 may promote the proinflammatory effects of VEGF.

Ang II has been shown to stimulate the expression of angiopoietin-2 mRNA and protein synthesis in microvascular endothelial cells in vitro, but had no effect on the expression of angiopoietin-1. In a rat corneal angiogenesis model, Ang II stimulated new vessel formation, which stained strongly for angiopoietin-2. Hence, increased Ang II with activation of the renin-angiotensin system may be associated with selective up-regulation of VEGF and angiopoietin-2. This profile of raised plasma VEGF and angiopoietin-2, but not angiopoietin-1 has already been reported in patients with heart failure. Blockade of VEGF by sFlt-1 gene transfer attenuated neointimal formation after intraluminal injury in rabbits, rats, and mice. sFlt-1 gene transfer reduced the early vascular inflammation and proliferation and later neointimal formation. sFlt-1 gene transfer also inhibited increased expression of inflammatory factors such as monocyte chemoattractant protein-1, and growth factors such as VEGF, MCP-1, interleukin-1, tumor growth factor, and platelet-derived growth factor at early stages. Hence, the dynamic balance between VEGF and other growth factors, particularly the angiopoietins, is likely to be more representative of the vascular milieu in vivo and may mediate vascular inflammation associated with Ang II. Interestingly, sFlt-1 gene transfer did not affect endothelial regeneration after endothelial injury, suggesting a minor role of endogenous VEGF in endothelial regeneration after endothelial injury. The dynamic balance between VEGF and other growth factors, particularly the angiopoietins, is likely to be more representative of the vascular milieu in vivo and may mediate vascular inflammation associated with Ang II.

Furthermore, elevated plasma levels of VEGF in hypertensive patients with high cardiovascular risk are not novel and have previously been reported by our group; these increased levels were significantly reduced after 6 months of intensified blood pressure and (where appropriate) lipid-lowering treatment. This would suggest that cardiovascular risk management might reduce VEGF-mediated vascular inflammation, as demonstrated in an animal model by Zhao and colleagues, and via this mechanism, would impede or even reverse the progression to overt atherosclerosis.

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