Vascular Endothelial Growth Factor and the Angiopoietins: Working Together to Build a Better Blood Vessel

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Angiogenesis is a complex multistep process by which new blood vessels are formed from the preexisting vasculature. Angiogenesis is a crucial event in normal embryonic development, and it contributes to the development and progression of a number of diseases, including cancer, arthritis, and diabetes. Conversely, insufficient growth of collateral vessels is a major clinical problem in atherosclerotic cardiovascular disease. The involvement of angiogenesis, or the failure of angiogenesis, in these important diseases has created a tremendous effort to define the molecular mechanisms by which the process is driven.

Until recently, most of the work in the field has focused on polypeptide growth factors, such as fibroblast growth factor and vascular endothelial growth factor (VEGF), which are mitogenic for endothelial cells in vitro and produce an angiogenic response in vivo. Angiopoietins (Ang1 and Ang2) constitute a novel family of endothelial growth factors that are ligands for the endothelium-specific receptor tyrosine kinase, Tie2. Unlike other endothelial growth factors, stimulating Tie2 in cultured endothelial cells with either Ang1 or Ang2 does not produce a mitogenic response. Similar to other angiogenic factors, however, Ang1 can stimulate endothelial sprouting in vitro. Complicating matters, Ang2 appears to block the activation of Tie2 by Ang1, suggesting that it may be a naturally occurring inhibitor of Ang1/Tie2 activity. Despite the inability of angiopoietins to stimulate endothelial mitogenesis, disrupting the function of either Tie2 or Ang1 in transgenic mice resulted in early embryonic lethality secondary to defects in the developing vasculature. The defects included a decreased number of endothelial cells, simplification of the vascular branching pattern, and failure to recruit pericytes and smooth muscle cells. Consistent with its action as an Ang1/Tie2 inhibitor, overexpression of Ang2 resulted in vascular defects similar to those in the Ang1 or Tie2 knockouts.

Taken together, these studies suggested that unlike other angiogenic growth factors, such as VEGF, which function during the earliest stages of vascular development, the angiopoietins play their major role at later stages of vascular development, i.e., during vascular remodeling and maturation.

On the basis of these data, Asahara et al. in a recent issue of Circulation Research, hypothesized that angiopoietins may also be important for angiogenesis in adult tissues. In a mouse corneal micropocket assay, both Ang1 and Ang2 failed to stimulate an angiogenic response when administered alone. However, when coadministered with VEGF, both Ang1 and Ang2 augmented the formation of neovessels. Consistent with its hypothesized role in embryonic vascular development, coadministration of Ang1 resulted in an increase in total microvascular density as well as an increase in patent microvessels surrounded by smooth muscle cells. Interestingly, although Ang2 had insignificant effects on microvessel patency and smooth muscle cell recruitment, it increased both the length of microvessels and the number of migrating endothelial cells at the leading edge of the neovasculature. The authors suggest, as was previously hypothesized, that Ang2 augments angiogenesis by inhibiting Tie2, thereby “destabilizing” the vasculature and making it more responsive to angiogenesis initiators, such as VEGF. This is consistent with our recent finding that Tie2 is expressed and activated in the quiescent adult vasculature and the finding by Maisonpierre et al. that Ang2 is expressed at the leading edge of proliferating vessels. Alternatively, Ang1 and Ang2 could activate Tie2 in fundamentally different ways, stimulating different signaling pathways and resulting in differential biological responses. Just such a differential activation of an endothelial receptor has been reported for activation of EphB1 by different forms of its ligand, ephrin-B1. Although the differences in the biological effects between Ang1 and Ang2 need to be further defined at the molecular and cellular level, it is clear that the angiopoietin/Tie2 pathway importantly regulates angiogenesis in the adult cornea.

An important message from the study of Asahara et al. is that assembly of a functional vasculature likely requires the orchestration of a variety of endothelial growth factors and receptors, which play different roles at different stages of the process. Indeed, during the development of the embryonic vasculature, EphB4, a member of the Eph family of receptor tyrosine kinases, is expressed primarily in venous endothelium. Conversely, its ligand, ephrin-B2, is primarily expressed in arterial endothelial cells, suggesting a role for this system in mediating morphological and functional differences between the arterial and venous circulation. Like the Tie2 and Ang1 knockouts, disrupting the function of ephrin-B2 had no effect on the establishment of the primitive embryonic vasculature but resulted in defects in the remodeling of both the venous and arterial circulation. Neuruplin-1, a receptor for the collapsin/semaphorin family of neuronal cell guidance mediators, is expressed in the embryonic vasculature, and overexpression of neuruplin-1 resulted in hyperproliferation of the embryonic microvessels. Intriguingly, Soker et al. have recently shown that neuruplin-1 is a coreceptor for VEGF, suggesting a functional role for neuruplin-1 in VEGF-mediated signaling. Finally, targeted disruption of a chemokine receptor,
CXCR4, resulted in defects in the formation of large vessels that were localized to the gastrointestinal tract, demonstrating that organ-specific pathways may contribute to vascular remodeling. Whether or not these diverse pathways contribute to the angiogenic response in adult tissues will be an area of intense investigation.

The realization that multiple pathways are likely required for the assembly of a functional vasculature has broad implications for the therapeutic modulation of angiogenesis. For example, it has already been shown that blocking either the VEGF pathway or the Tie2 pathway can inhibit tumor angiogenesis. Since VEGF and Tie2 function at different stages of vascular development, it seems likely that inhibiting both pathways may be more effective than inhibiting each individually. By the same token, the results of the study of Asahara et al demonstrate that the combination of VEGF plus either of the angiopoietins has a salutary effect on vascular development. On the basis of their study, it is tempting to speculate that the angiopoietins will have the same effect on VEGF-induced and/or fibroblast growth factor–induced neovascularization in ischemic tissues.

References

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