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hear forces play an important role in the regulation of vascular function and structure. Since the initial demonstration of flow-dependent dilation, the critical role of the endothelium in sensing changes in intimal shear stress, and transducing these into changes in vascular tone, has been well recognized.\(^1\)–\(^3\) The moment-to-moment adjustments in arterial diameter involve the release of endothelial-derived vasoactive factors, in particular NO, and play a central role in optimizing the conductance of the large arterial tree and maintaining peak efficiency of the circulation even when subjected to profound changes in blood flow.\(^4\) However, the mechanisms governing the longer-term adaptations of vascular diameter and branching are equally or even more important for ensuring the appropriate development, patterning, and structure of the arterial tree, but they have not been well characterized. Here, too, the endothelium plays a pivotal role in adapting the diameter of an artery to persistent changes in vascular pressures.\(^3\) The moment-to-moment adjustments in arterial diameter involve the release of endothelial-derived vasoactive factors, in particular NO, and play a central role in optimizing the conductance of the large arterial tree and maintaining peak efficiency of the circulation even when subjected to profound changes in blood flow.\(^4\) However, the mechanisms governing the longer-term adaptations of vascular diameter and branching are equally or even more important for ensuring the appropriate development, patterning, and structure of the arterial tree, but they have not been well characterized. Here, too, the endothelium plays a pivotal role in adapting the diameter of an artery to persistent changes in vascular pressures.\(^3\)

It is perhaps not surprising that many of the same factors that mediate angiogenesis during blood vessel development may contribute to the remodeling of blood vessels in response to changing flow conditions and vice versa. For example, endothelium-derived NO, the classical mediator of shear-induced changes in vascular diameter, has recently been recognized as an important downstream mediator of the angiogenic effects of a wide range of factors, including vascular endothelial growth factor (VEGF),\(^5\) basic fibroblast growth factor (FGF),\(^5\) and recently angiopoietin-1 (Ang-1).\(^10\) The angiopoietins represent a family of angiogenic factors that bind to the endothelial-selective receptor tyrosine kinase (RTK), Tie2,\(^11\) and mediate vascular maturation by inducing the recruitment of pericytes and smooth muscle to invest the nascent arterial media, causing enlargement and increasing the complexity of the developing vascular tree. There is evidence that vascular pressures influence the recruitment/differentiation of mural cells in the microcirculation\(^12\) and the Ang/Tie2 system represents an attractive candidate system for mediating chronic adaptation of blood vessels to long-term hemodynamic changes.

In this issue of Circulation Research, Porat and colleagues\(^1\) provide new insight into an unexpected contribution of a related RTK, Tie1, to changes in vascular structure in response to luminal hemodynamic conditions. Although sharing significant homology with Tie2, Tie1 has no known ligand,\(^13\) and its function is very much a matter of debate. The present demonstration that Tie1 expression is exquisitely related to vascular regions exposed to disturbed flow in both physiological and pathological conditions is very suggestive of a role in transducing changes in shear forces and possibly participating in mediating the subsequent remodeling of the arterial wall. However, this report raises more questions than it provides answers. For example, what is the functional consequence of elevated Tie1 expression and what does this have to do with vascular remodeling and the development of atherosclerosis?

Recently, Chen-Konak et al\(^15\) found that initiating normal arterial levels of shear (10 dyne/cm\(^2\)) induced transient downregulation of Tie1 expression. Protein levels returned to those of static cultures over 2 hours; however, subsequent increases or decreases in shear at this level could again inhibit Tie1 expression. These findings are thought provoking. In the context of the work of Porat et al\(^1\) they may indicate that low levels of shear at specific arterial sites can de-repress Tie1 expression while it is persistently inhibited at other sites by higher levels of shear that routinely fluctuate with changing physiological demands for tissue perfusion. Notably, Chen-Konak et al found that downregulation was accompanied by cleavage of Tie1 and binding of the endodomain to the Tie2 receptor, so Tie1 processing may have important implications for angiopoietin signaling. This association mirrors Tie1 responses to stimulation of endothelium with VEGF or phorbol 12-myristate 13-acetate (PMA).\(^16\)–\(^19\) However, once more, it is uncertain what the functional consequences of such an interaction would be. Some additional insight into this question might have been gained by testing the expression and activation state of Tie2 in regions of high and low Tie1 expression, but it would still not have been possible in vivo to distinguish any regulatory interactions between these receptors from a direct effect of shear forces on Tie2 itself.

Nonetheless, it seems inescapable that the observations of Porat and colleagues\(^1\) must provide an important clue as to the role of Tie1 in the postnatal vasculature—but what role? Does Tie1 contribute in some way to vascular remodeling?
To address this question, it would be of interest to determine whether its expression is increased in the classical models of chronic arterial remodeling with increases or decreases in flow. What is the significance of upregulation of Tie1 in the context of atherosclerosis and aneurysms? Is it part of a protective mechanism, as has been suggested for the Ang-1/Tie2 pathway, or does it contribute to the pathogenesis of vascular disease? These are critical questions that are raised by the present report and represent important challenges for investigators in this field. However, what does seem certain is that the work of Porat and colleagues has raised the bar in the elucidation of this system by pointing to a potential contribution in the regulation of postnatal vascular structure and function.

References


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Duncan J. Stewart and B. Lowell Langille

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