Editorials

See related article, pages 380–387

Getting Neointimal
The Emergence of Heparanase Into the Vascular Matrix

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Blood vessels are highly active structures whose morphology rapidly adapts to maintain vascular function under altered systemic and local conditions. In some instances, this normally beneficial adaptation may be detrimental to overall function. Structural adaptations with important physiological and pathophysiological impact include angiogenesis, the remodeling of resistance arteries, and stenosis and restenosis of conduit arteries. It is highly probable that the development of these diverse phenotypes involves common pathways; therefore, the vascular research field must prioritize investigating the mechanisms relevant for determining vascular structure.

Remodeling of the vascular wall requires a highly dynamic and adaptable extracellular matrix (ECM). Heparan sulfate proteoglycans (HSPGs) are prominently expressed in the vascular ECM. HSPGs whether bound to the membranes or free in the ECM provide an extracellular storage function for a number of biologically important molecules: the heparan sulfate moieties bind ECM structural proteins and several growth factors and cytokines enabling retention of these factors in the ECM and preventing degradation of them (Figure). The HSPGs also directly transfer information from the extracellular space to intracellular kinases and cytoskeletal elements and thus modify cell adhesion and motility. In addition, HSPGs bind lipoprotein lipase to the endothelial cell surface. Thus HSPGs are important for vascular health and disease through many different pathways, and how these molecules are regulated is of considerable interest.

HSPG biosynthesis is complex involving the Golgi apparatus and a number of sequential enzymes including heparan sulfate synthase, an epimerase and several transferases. HSPG degradation is under control of the ubiquitously expressed endogluconeuridase heparanase, which cleaves the heparan sulfate chains from the core protein. Whereas there is little doubt that proliferating endothelial cells in the arterial wall synthesize and secrete heparanase, there is more uncertainty whether “normal” quiescent endothelial cells express significant levels of heparanase. At sites of vascular injury, platelets and various inflammatory cells and most likely endothelial cells release heparanase, and in this issue of Circulation Research, Baker et al6 show that the neointima displays substantial immunohistochemical staining for heparanase. The heparanase released potentially cleaves the HSPGs present on the cell surface and in the subendothelial ECM, causing growth factors and cytokines to be released with ensuing effects on the ECM structure and growth of smooth muscle and endothelial cells (Figure).

Interestingly, a heparanase-dependent proadhesive effect and beneficial effect on cell survival as well as heparanase-mediated Akt phosphorylation have been suggested by Vlodavsky et al7 to be independent of enzymatic activity. In addition, data show that endothelial heparanase promotes lipoprotein lipase release from adipocytes. These effects add an extra dimension to the evidently complex action of heparanase.

Heparanase expression and enzymatic effect on HSPGs is therefore likely to be important for the control of arterial structure (a notion supported by the suppressing effect of heparanase-inhibiting antibodies on neointima formation8), as well as for other vascular functions such as lipid metabolism and angiogenesis. This has provided new insight into the potential role of heparanase for the expression of HSPGs and for arterial compliance and neointimal proliferation following endovascular stenting. As expected, modification of the expression level of heparanase (overexpression induced by transfecting with an expression vector for heparanase; reduced expression induced by RNA interference) resulted in reciprocal changes in the HPSG levels in endothelial cells in culture. Notably, 3 lines of evidence in the present work support a role for heparanase in vascular smooth muscle growth and neointimal formation. Firstly, medium retrieved from the endothelial cell culture affected the growth of cultured vascular smooth muscle cells (ie, relative to medium from control cells); medium from cells overexpressing heparanase increased smooth muscle cell proliferation, whereas medium from cells with low heparanase expression inhibited proliferation. Secondly, transgenic overexpression of heparanase in mice led to increased wall thickness and increased compliance. Thirdly, neointimal formation after stenting correlated with the expression level of heparanase in a rat model of diabetes, and in heparanase-overexpressing mice the neointimal area was larger than in control mice and more rich in macrophages.

Baker et al6 have convincingly demonstrated the importance of heparanase for neointimal formation following stenting in rats and mice. This would suggest a new potential target for drug-eluting stents. The history of drug-eluting stents has followed the classic path for a novel scientific revelation: initial jubilation followed by substantial pessimism, which is finally replaced by a moderate enthusiasm. One of the lessons from this development is that there is likely substantial benefit to obtain from improving.

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our understanding of the mechanisms involved in controlling vascular structure and adhesiveness. Here, Baker et al. show that heparanase plays a key role in neointimal formation, and it is highly probable that inhibitors of this enzyme will be a useful tool in the future.

Little is presently known about the regulation of heparanase expression in vascular tissue. It has been demonstrated, however, that heparanase expression is upregulated in endothelial cells exposed to high glucose and to H$_2$O$_2$, with the effect of glucose being preventable by insulin exposure. There is some information on the transcription factors that may be involved. These few observations in addition to those reported by Baker et al. raise a number of interesting questions, such as which of the many effects of HSPGs are mainly responsible for the effect of heparanase. Despite the role established for HSPGs in the neointimal response to vascular injury shown previously by the authors, are (some of) the effects of heparanase independent of its effect on HSPGs? How is heparanase itself regulated, and is it possible to develop drugs that will modify vascular active heparanase in a relevant manner? Nearly a decade ago, such an interaction between metalloproteinases and heparanase was suggested to be important for smooth muscle cell phenotype.

An understanding of the interplay between the cellular and extracellular factors in the vessel wall is critically important to our comprehension of how arterial structure is regulated and how it can be compromised. Our understanding of this complex process and the clinical outcome of vascular remodeling has moved a significant step forward with the elegant emergence of heparanase into the matrix.

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None.

**References**


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