Role of Vessel Wall and Bone Marrow Syndecan-4 in Neointimal Hyperplasia

The Plot Thickens

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Syndecan 4 (Syn4) is 1 of a family of 4 transmembrane heparan sulfate proteoglycans found in mammals. An evolutionary conserved cytoplasmic domain on syndecans supports a key role for cell surface ligand binding and cytoplasmic signaling. Along with integrins, syndecans serve as key structural elements in concentrating ligands on the cell surface. To date, a multiplicity of functions have been ascribed to syndecans, including growth factor tethering in the extracellular matrix (ECM) and cytoplasmic signaling, which activates focal adhesion, cytoskeletal reorganization, and metalloprotease activation.1 Syndecans have previously been noted for their ECM sensing and thrombin binding properties in the context of tissue injury and repair, and they perform a key role in regulating basic fibroblast growth factor and platelet-derived growth factor–induced smooth muscle cell (SMC) signaling events supporting activation and regulation of SMC responses to vascular injury.2,3

The study by Ikesue et al4 in this issue highlights an additional intriguing role for Syn4 that may extend beyond the local vessel wall in the context of injury to bone marrow (BM)–derived cells involved in SMC driven tissue repair. These data are important as they underscore what a number of other recent studies5,6 have hinted at, namely, a complex interplay among vessel wall cell surface molecules, ECM-bound factors, and cells resident in BM during the vascular response to injury. Moreover, although controversy still exists on the precise role of BM cells in SMC differentiation and proliferation following injury, Ikesue et al’s study4 provides supportive evidence for a functional role of BM-derived Syn4 in promoting neointimal hyperplasia and vascular progenitor cell (VPC) mobilization.

Following balloon angioplasty or stenting, a number of early events occur that may affect cell surface – and matrix-bound Syn4, including protease activation in blood and at the site of injury and subsequent cleavage of proteoglycans in the ECM, releasing growth factors such as platelet-derived growth factor and basic fibroblast growth factor, both of which may act as chemotactic and mitogenic factors for SMC within the media and intima of the injured vessel. Ikesue et al’s study4 demonstrates that Syn4 deficiency abrogates basic fibroblast growth factor–protein kinase C signaling and basic fibroblast growth factor/platelet-derived growth factor–BB–induced Erk signal activation with attenuation of SMC proliferation postinjury. It is likely that vitiation of local autocrine and paracrine growth factor pathways is a significant mechanism underlying the reduction in neointima formation. However, intriguingly, this study also shows that BM transplantation of Syn4-deficient marrow into wild-type mice similarly attenuates neointima formation compared with wild-type BM transplantation into Syn4-deficient animals, suggesting that BM Syn4 is also required for neointima formation. Although this study does not clarify precisely what cells in BM contribute to this Syn4 effect, tantalizing data are presented on BM Syn4–mediated effects on ckit-sca1+ cell mobilization in peripheral blood and the capacity of these cells to differentiate into α-smooth muscle actin–positive smooth muscle–like cells in vitro. However, it remains unclear whether these VPC participate directly in neointima formation or contribute in a paracrine manner to lesion formation.

Recent debate on the role of extravascular smooth muscle progenitor cells has centered on the putative BM origin of these cells and their contribution to neointima formation. It appears increasingly evident that the majority of SMC in the neointima derive from the local vessel wall but that a small number, representing ≈1% to 5% of plaque cells, come from outside the local vascular niche. This study and others5,6 are beginning to address the potential functional significance of such extravascular sources of SMC. The nature of these progenitors is still unclear and ranges from myeloid cells to more undifferentiated lineages. For instance, Kumar et al5 recently showed that although BM-derived CX3C chemokine receptor 1-positive smooth muscle progenitor cells represented only ≈5% of neointimal cells, deficiency in BM CX3CR1 function reduced neointimal area by 40%. This is consistent with in vitro work suggesting that smooth muscle progenitors express much higher levels of ECM7 compared with normal SMC. Indeed it is intriguing to speculate whether Syn4 might regulate VPC ECM in the neointima. Alternatively, BM derived VPC may secrete proinflammatory cytokines and mitogens, as recently illustrated by Yu et al8 in a mouse model of atherosclerosis in which BM-derived SMC contributed only ≈1% of cells to the plaque but, when ablated, reduced plaque size by approximately 30%. Together, these emerging data support a functional role for BM-derived SMC in plaque formation.
Chemokines and proteoglycans play an important role in the response to vascular injury, and ectodomain shedding of surface proteoglycans by proteases not only can alter cell surface phenotype but may act as autocrine and paracrine effectors locally and distant from the injury site. For instance, syndecans undergo C-terminal fragment cleavage, releasing (both locally and into the circulation) active molecules implicated in tissue remodeling. Syn4 has been shown to directly bind stromal cell–derived factor-1 and can be shed from monocyte-derived macrophages. This binding of stromal cell–derived factor-1 may activate a feedback cleavage loop on Syn4 through matrix metalloproteinase-9 activation. Multifaceted functions of Syn4 that may affect vascular remodeling (Figure) thus include BM cell mobilization and migration in addition to promotion of growth factor-mediated vascular SMC proliferation. Ikesue et al showed that Syn4 is upregulated on VPC at 6 hours after injury and that Syn4 is implicated in mobilization of VPC into peripheral blood at day 3 post–wire injury. However, it remains unclear whether Syn4 from vessel wall or BM is both is required for such VPC mobilization. Given the previously described role of the stromal cell–derived factor-1/CXC chemokine receptor 4 axis in progenitor mobilization in the context of vascular injury and the binding relationship between this chemokine receptor pair and Syn4, it is conceivable that Syn4 facilitates mobilization of BM progenitors while simultaneously augmenting local autocrine and paracrine growth factor and chemokine/cytokine feedback loops at the vessel wall level.

In summary, this study raises a number of new questions on the role of Syn4 spanning cell and matrix machinery (proteoglycan tethering, ligand signaling, chemokine-receptor binding, and protease activation) in regulating crosstalk between the site of vascular injury and the BM progenitor microenvironment.

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