Vascular Progenitors and Smooth Muscle Cells
Chicken and Egg?

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The adventitia is composed of a heterogeneous population of cells, including quiescent resident inflammatory cells, endothelial cells, pericytes, fibroblasts, and recent findings that the abundant presence of resident stem/progenitor cells have been also reported in the layer. The adventitia also contains a vasa vasorum, a complete vascular tree–like structure, including arterioles, capillaries, and veins. The vascular adventitia acts as a biological processing center for the retrieval, integration, storage, and release of key regulators for the vessel wall function. In the adventitia of apoE-deficient mice, stem/progenitor cells expressing Sca1 have been identified, which may contribute to endothelial regeneration and smooth muscle accumulation in the neointimal lesions. Several groups also demonstrated that the adventitia of human vessels contains stem/progenitor cells with mesenchymal properties because they express vimentin, collagen-I, CD29, CD44, and CD105 and show adipogenic and osteogenic differentiation potential. In addition, it was shown that CD34+/CD31 cells from the adventitia of human saphenous vein gave rise to a proliferative cell population with multilineage potential. In vivo these cells improved neovascularization after they were injected intramuscularly into murine ischemic limbs. Similarly, human aortic CD105-CD34-Flik-1+ cells displayed vasculogenic potential. Thus, adult arteries contain cells with characteristics of ancestral stem cells. Local Sca1+ myeloid progenitors with hematopoietic potential and residing in a similar adventitial niche were also identified. These results uncover the complexity of vascular stem cells, which could be closely related to vascular repair and disease development. However, little is known about the origins of these stem/progenitor cells in the adventitia.

Article, see p 296

In this issue of Circulation Research, Majesky et al provided the first direct in vivo evidence that a proportion of Sca1+ progenitors can be derived from mature smooth muscle cells (SMCs) of the media. Using in vivo cell lineage–tracing models of mice to monitor cell fate of medial SMCs, the authors found that SMCs generated in situ a subpopulation of Sca1+ progenitor cells in adventitial tissues. Two independent genetic fate-mapping systems were used: a tamoxifen-inducible Myh11CreERT2 transgenic mice crossed with floxed-stop ROSA reporter mice (Myh11-CreER-βGal/YFP) and a SMC-specific SM22α-Cre transgenic mice crossed to ROSA26-YFP animals (SM22α-Cre-YFP). SMCs were traced through YFP expression, after embryonic stages e15 to e17, a developmental time point after which the arterial media has acquired its complement of SMCs, using the 2 lineage-tracing mice, combined with the expression of a SMC-specific histone mark. After this approach, they found that ≈8% of the total Sca1+ cell population were YFP-positive SMC-derived cells within the adventitia. In contrast to blood vessels, Sca1+YFP+ cells were not detected in peripheral blood mononuclear cells. In adult mice, it was found that a large percentage (30%–60%) of total Sca1+ cells in the carotid artery plus aortic arch, descending aorta, and femoral artery originated from SMCs. The observation that a fraction of Myh11-expressing SMCs in the media can be reprogrammed into Sca1+ progenitor cells in adventitia could suggest the existence of specialized cells with higher plasticity within arterial walls. These findings could be important for the development of treatments specifically targeting the cell population that might retain the structural integrity of the artery during the progression of vascular disease.

What is the function of vascular stem/progenitor cells in the remodeling of the vessel wall? The report by Majesky et al provided evidence of their multipotency potential and ability to differentiate into other cell lineages such as SMCs, endothelial-like cells, adipocytes, and chondrocytes. These findings have several implications. First, stem/progenitor cells may contribute to the formation of vasa vasorum in the context of adventitial remodeling during the development of vascular diseases because these cells display the ability to differentiate into endothelial cells in vitro and in vivo. Vasa vasorum has been proposed to sustain the development of atherosclerotic lesions. Abundance of vasa vasorum is correlated with increasing wall thickness or lesion size in the vessels across multiple species and in humans. It would be interesting to study the direct contribution of vascular stem cells to the formation of vasa vasorum in vivo. Second, a recent report has demonstrated that >50% of neointimal SMCs are derived from adventitial stem/progenitor cells after vessel injury. Genetic fate tracing using Gli1 as a marker indicates that adventitial stem/progenitor-like cells migrate into the media and neointima during atherosclerosis and arteriosclerosis in ApoE−/− mice. Application of Sca1+ cells to the adventitial side of vessel grafts resulted in enhanced neointimal lesions in...
It seems that MYH11-expressing cells can (de)differentiate into many types of cells. The question is whether all MYH11-expressing cells are mature SMCs. There is a possibility that a small proportion of MYH11-expressing cells are in fact stem/progenitor cells localized in the vessel wall. Obviously, further investigation will be needed to address this specific issue.

In summary, both vascular progenitors and SMCs are heterogeneous populations. Understanding the phenotypic and functional diversity of SMCs and adventitial stem/progenitor cells may also reveal indirect, trophic effects on vascular repair and disease development. The findings of Majesky et al provide the evidence that the identification of factors, in addition to KLF4, regulating SMC-to-progenitor cell transitions in vivo, will broaden our understanding of the multiple roles of SMCs in vascular homeostasis and disease. Manipulating adventitial progenitors may provide functional benefits in vascular regeneration and remodeling.

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None.

**References**


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