Circulating smooth muscle progenitor cells: novel players in plaque stability

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This editorial refers to ‘Role of human smooth muscle cell progenitors in atherosclerotic plaque development and composition’ by Zoll et al., pp. 471–480.

Our understanding of the role of stem cells in the pathogenesis of vascular disease has been rapidly evolving. It is generally accepted that bone marrow (BM)-derived endothelial progenitor cells (EPCs) participate in arterial repair and angiogenesis after injury by homing to the injured vessel and differentiating into endothelial cells.1 BM-derived cells with smooth muscle cell (SMC)-like phenotype also participate in the pathogenesis of vascular disease.2 Recently, Simper et al.3 reported the existence of smooth muscle progenitor cells (SPCs) in human blood. Hashimoto et al.4 demonstrated the existence of BM-derived progenitors for collagen-producing fibroblasts. Inflammatory cells are clearly mobilized to sites of vascular injury.5 Intriguingly, a recent paper revealed an important role for T cells in hypertension and vascular dysfunction.6 The cytokines that recruit, activate, and promote differentiation of BM-derived vascular cells have been extensively studied and include GM-CSF,7 SDF-1,8 and erythropoietin.9,10 These accumulating data establish a close relationship between BM-derived cells and vascular pathogenesis. However, the role of BM-derived vascular progenitor cells in atherosclerosis remains poorly defined (Figure 1).

In the current issue of Cardiovascular Research, Zoll et al.11 asked whether SPCs reduced atherosclerosis development by modifying plaque composition towards a more stable phenotype. In this study, ApoE−/− RAG2−/− mice were injected with human-derived EPCs or SPCs every other week. Injection of SPCs but not EPCs reduced lesion size by ~42%. SPC injection also increased collagen and SMC content and reduced macrophage content, consistent with a more stable plaque. Finally, in a small number of patients, peripheral blood SPCs were significantly reduced in patients with acute coronary syndromes compared with stable angina.

Zoll’s studies are among the first to show an important role for SPCs in atherosclerosis. SPCs appear to have a direct role as the injected SPCs incorporated into the atherosclerotic lesion (Figure 1). The finding that the number of circulating SPCs was reduced in peripheral blood of patients with acute coronary syndromes suggests a role for altered SPC function in plaque destabilization. These data are concordant with a previous study by Caplice et al.,12 showing that BM-derived α-smooth muscle actin-positive cells were localized to the surface of atherosclerotic plaques in patients with sex-mismatched BM transplantation. Noteworthy, the investigators observed no beneficial effects when EPCs were injected compared with SPCs. These findings suggest a new paradigm that BM-derived SPCs could be more beneficial than EPCs to stabilize atherosclerotic plaques. The difference between SPCs and EPCs could be explained by differing functional contributions at different stages of atherosclerosis progression.13 Other mechanisms for the beneficial effects of SPCs should be considered. SPCs may secrete cytokines and growth factors both locally and systemically that enhance plaque stability. In addition to the circulating vascular progenitors, abundant tissue-resident progenitors in the adventitia can differentiate into SMCs in atherosclerotic lesions.14

A recent paper reported findings that contradict the present study: healing SMCs were entirely derived from the local artery with no contribution from circulating progenitors in ApoE−/− mice.15 This supports the longstanding theory that plaque healing is mediated by local proliferating SMCs. A plausible explanation is that SPCs localize to the fibrous cap whereas resident SMCs localize to areas of neovascularization. This concept is supported by studies of hypoxia-induced mobilization and proliferation of BM-derived cells.16 Incidentally, tissue-resident vascular progenitors could also have originated from BM-derived progenitors.17,18 An important issue for the future will be to develop markers that clearly define both the origin of plaque SMCs and their function. Finally, the factors that regulate plaque SMC (and circulating SPC) homing, differentiation, proliferation, apoptosis, synthesis of matrix, and matrix-degrading enzymes remain to be defined.

What are the clinical implications of this study? Zoll et al.11 suggest that decreased SPC number may be a causal factor in acute coronary syndromes. In contrast, a recent paper revealed that an angiotensin II receptor blocker reduced the number of SPCs and decreased neointimal hyperplasia.
after mechanical arterial injury, suggesting a pathological role for SPCs. These two papers suggest that SPCs may be pathogenic in settings such as restenosis, whereas beneficial in the late stages of atherosclerosis. A key aspect of the present study that deserves comment is the accumulation of SPCs in the lung. It has been reported that BM-derived α-smooth muscle actin-positive cells promote pulmonary vascular remodelling and contribute to the development of pulmonary arterial hypertension. Additionally, it was reported that intravenously injected EPCs migrate to the pulmonary circulation, which had beneficial effects to ameliorate pulmonary vascular remodelling in a mouse model of pulmonary arterial hypertension. These complex effects of injected progenitor cells indicate that future animal studies are necessary to confirm the safety profile before using progenitor cells in patients with acute coronary syndromes and cardiovascular diseases.

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References


