The accumulation of smooth muscle cells (SMCs) plays a principal role in the pathogenesis of various vascular diseases. It has been hypothesized that dedifferentiated SMCs migrate from the media to the subendothelial space, where they proliferate and contribute to atherogenesis. Similarly, it has been assumed that all of the neointimal cells in postangioplasty restenosis and graft vasculopathy are derived from adjacent medial cells. In addition to this traditional concept, recent evidence suggests that bone marrow–derived circulating precursors can also give rise to endothelial-like cells and/or smooth muscle–like cells that contribute to vascular repair, remodeling, and lesion formation in animals and in humans. However, the contribution of bone marrow–derived cells to vascular remodeling still remains controversial. It remained to be clarified how highly "bone marrow–derived circulating progenitor cells" can differentiate into mature SMCs phenotypically and functionally.

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In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Schäfer et al provide convincing evidence that bone marrow–derived cells significantly participate in neointimal formation induced by carotid arterial injury with ferric chloride (FeCl₃). Using two types of bone marrow chimeric mice, the authors found that ~21% of neointimal cells and 38% of medial cells originated from the bone marrow in this mouse model of vascular injury. A significant amount of bone marrow–derived cells in the media and neointima expressed α-smooth muscle actin and, to less extent, smooth muscle myosin heavy chain. Interestingly, the bone marrow–derived cells did not participate in reendothelialization as determined by double-immunostaining for von Willebrand factor (vWF) and LacZ.

Numerous reports have demonstrated that neointimal cells are heterogeneous and that SMCs in vascular lesions are composed of cells of diverse origin. We reported that the cellular constituents of a lesion differ depending on the type of vascular injury and that distinct mechanisms may regulate neointimal formation in different models. In our mouse model of endovascular injury which results in complete endothelial denudation and massive medial cell apoptosis, insertion of a large wire dilates femoral artery with robust contribution of bone marrow–derived cells to neointimal hyperplasia, like the lesions induced by other types of mechanical injuries. These findings are comparable with a previous report on the temporal and spatial characterization of cellular constituents during neointimal hyperplasia after wire-mediated vascular injury, in which CD45-positive hematopoietic cells accumulated on the luminal side of the artery at one week and were gradually replaced by α-smooth muscle actin positive cells. It is likely that FeCl₃ caused severe vascular injury with massive cell death and thrombus formation, which resulted in robust recruitment of circulating bone marrow–derived for the repair of the damaged artery containing only few residual cells.

Taking advantage of FeCl₃-induced vascular injury model that is characterized by thrombus formation and fibrin deposition at earlier time points, Schäfer et al investigated the role of plasminogen activator inhibitor (PAI-1) in the pathogenesis of neointimal formation. PAI-1 has been proposed to be involved in the pathogenesis of atherosclerosis. PAI-1 expression is upregulated inside the arterial wall in animal models of atherosclerosis and neointima formation after vascular injury. Schäfer et al found that FeCl₃-induced vascular injury resulted in greater neointimal formation and lumen stenosis in PAI-1−/− recipient mice which had undergone bone marrow transplantation (BMT) from PAI-1−/− donor mice (BMT[PAI-1−/−→PAI-1−/−]) than those in wild-type (WT) recipient mice which had undergone BMT from WT donor (BMT[WT→WT]). BMT from PAI-1−/− mice to WT mice (BMT[PAI-1−/−→WT]) resulted in a decrease in PAI-1 amount inside the arterial wall from 20% to 7%, thereby indicating that bone marrow–derived cells contribute to local expression of PAI-1. Deficiency of PAI-1 selectively in bone marrow affected neither neointimal area nor luminal stenosis. Notably, expression of PAI-1 by small number of bone marrow–derived neointimal cells was sufficient to suppress neointima formation in BMT[WT→PAI-1−/−] mice. It was suggested that PAI-1 expressed either by bone marrow–derived cells or by local vascular cells appeared to be sufficient to suppress neointimal growth after vascular injury, presumably in a paracrine manner (Figure). The precise molecular mechanism by which local expression of PAI-1...
Cells of diverse origin contribute to vascular repair and formation. Bone marrow–derived cells home to the site of severe vascular injury and contribute to vascular healing and lesion formation as neo-intimal and medial cells. Bone marrow–derived smooth muscle–like cells as well as media-derived SMCs secrete PAI-1 and inhibit production of plasmin that possibly regulates extracellular matrix proteolysis, cell adhesion, and migration. Heterogeneous cells appear to participate in maintenance of vascular homeostasis not only by migration and proliferation but also by producing several humoral factors.

effectively reduced neointimal formation should be defined in detail. In this regard, PAI-1 was reported to modulate extracellular matrix degradation that regulates adhesion and migration of SMCs.

Finally, the findings by Schäfer et al suggest that bone marrow–derived progenitors play a role in vascular healing and remodeling not only by differentiating into endothelial-like cells or smooth muscle–like cells but also by secreting humoral factors that potentially regulate cell migration and/or proliferation of neighboring vascular cells. Previous reports have shown that replacement of bone marrow cells with those from genetically-modified animals significantly influenced the vascular lesions induced by hyperlipidemia and mechanical arterial injury.21–25 Bone marrow–derived circulating progenitors might be an additional source of essential cellular and humoral components to maintain vascular homeostasis, particularly when artery is severely injured. Further investigation on the roles of circulating progenitor cells in vascular physiology and pathophysiology is warranted.

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