Origin of Cells That Contribute to Neointima Growth

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Percutaneous coronary interventions (PCIs) have become widely adopted for treatment of coronary atherosclerosis. Although there is increasing use of new devices, restenosis still limits the long-term outcome of PCI. Histological studies revealed that uninhibited cell accumulation in the neointima plays a principal role in the pathogenesis of post-PCI restenosis. Many studies have documented that the majority of neointimal cells express some markers of smooth muscle cells (SMCs). Thus, it was generally believed that SMCs in the adjacent medial layer migrate into the subendothelial space, proliferate, and synthesize extracellular matrix, thereby contributing to neointima formation. It was hypothesized that all neointimal SMCs in post-PCI restenosis are derived from medial SMCs.

On the other hand, it has been noted that neointimal SMCs are quite distinct from medial SMCs. The SMCs of the normal adult vessel wall display characteristics of a differentiated and contractile phenotype. In contrast, neointimal cells are characterized by a large cell body that contains synthetic and secretary organelles. These “synthetic” SMCs secrete extracellular matrix components and express lower levels of the smooth muscle-specific contractile proteins. Although “contractile” SMCs are quiescent in the cell cycle, synthetic SMCs proliferate and migrate in response to various growth factors. To explain the origin of synthetic SMCs observed in restenotic lesions, it has been proposed that contractile SMCs of the media dedifferentiate into synthetic SMCs in response to various cytokines secreted by the infiltrating inflammatory cells. Therefore, much effort has been devoted to understanding the regulators of the vascular SMC phenotype that control the transition from a quiescent, differentiated cell under normal conditions to a proliferative, dedifferentiated cell in the presence of pathological stimuli.

It has been reported that some neointimal SMCs express a number of hematopoietic lineage markers along with SMC markers. Macrophage-like SMCs with phagocytotic activity have been obtained from human arteries. Although it has been assumed that medial SMCs transdifferentiate into macrophage-like cells, recent reports suggested that some synthetic SMCs with characteristics of macrophages might derive from circulating blood cells rather than from medial SMCs. Evidence in support of this hypothesis was provided in several models of vascular diseases. By taking advantage of genetically modified mice, it was directly demonstrated that bone marrow cells home in on the damaged vessels and contribute to both vascular repair and pathological remodeling.

In this issue of Circulation, Yajima et al provide compelling evidence that bone marrow–derived cells play a crucial role in neointimal formation after vascular injury. The authors found that neointimal formation was significantly attenuated in ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain)-deficient mice. The proliferation activity of ASC–/– vascular SMCs was not impaired, and ASC deficiency had no effect on reendothelialization. On the other hand, the authors demonstrated that ASC expression by bone marrow–derived cells is critical for neointimal formation by analyzing several bone marrow chimeric mice. The authors propose that ASC, particularly expressed in bone marrow but not in vascular SMCs, represents a novel therapeutic target to prevent post-PCI restenosis.

There is controversy about the method to detect differentiation of ectopic cells. In most studies, double-immunofluorescent methods are used to detect bone marrow–derived cells that express a marker of SMCs in bone marrow chimeric animals. Usually, bone marrow cells are genetically labeled with LacZ or green fluorescent protein (GFP). However, investigators have questioned the specificity of colocalizing techniques to assess the origin of cells in bone marrow chimeric animals and humans. In this regard, high-resolution confocal microscopy with z-axis analysis has been used to convincingly demonstrate that bone marrow–derived cells express α-smooth muscle actin (α-SMA) in neointima after wire-mediated vascular injury. To rigorously identify GFP-positive cells, these studies used a plastic embedding technique to preserve the GFP fluorescence signal and to avoid the use of anti-GFP antibodies that could potentially increase the risk of false signals by nonspecific antibody binding. Moreover, an ultrahigh-resolution immunoelectron microscopic observational study confirmed that α-SMA and GFP could be located within a cell. Thus, it appears certain that bone marrow–derived cells expressing α-SMA can be detected in the neointima.

Another criticism deals with the markers that are used to identify the SMC-like cells that are derived from the bone marrow. In most studies, α-SMA is used as a marker of SMCs, because anti-α-SMA antibodies with high specificity...
and sensitivity are commercially available. However, it is well established that α-SMA is not a definitive SMC lineage marker. α-SMA is reported to be expressed in a wide variety of non-SMC cell types under certain circumstances, including (1) skeletal and cardiac muscle during normal development; (2) in adult cardiomyocytes in association with various cardiomyopathies; (3) in fibroblasts or myofibroblasts in a wide range of circumstances, including wound repair; (4) in endothelial cells during vascular remodeling or in response to transforming growth factor-β stimulation; and (5) in numerous tumor cells. Therefore, more specific SMC markers, including smooth muscle myosin heavy chain, caponin, SM-22, caldesmon, and smoothelin, should be analyzed, if the goal is to assess the differentiation of bone marrow–derived cells into highly differentiated contractile SMCs. However, many studies have consistently reported that the proportion of contractile SMCs is low in neointima, which suggests that highly differentiated SMCs play a minor role in the pathogenesis of restenosis. Instead, dedifferentiated synthetic SMC-like cells that express some macrophage markers appear to play a major role in the development of neointima.

It is certain that bone marrow is not the only source of neointimal cells. Numerous reports have shown that neointimal cells are heterogeneous and that the SMCs in vascular lesions are composed of cells of diverse origins. It was also reported that the cellular constituents in neointimal lesions differ according to the type of vascular injury. The mode of injury is crucial for the recruitment of bone marrow–derived cells to vascular remodeling. The differences in the models of neointimal hyperplasia should be noted when findings from different experimental systems are compared.

In summary, bone marrow–derived α-SMA–positive cells definitively exist in the neointima after vascular injury; however, it is unlikely that bone marrow–derived cells transdifferentiate into definitive and highly differentiated contractile SMCs. Bone marrow–derived cells home in on the injured artery and play a crucial role in the pathogenesis of lesion development by either contributing to neointimal volume expansion directly or secreting various inflammatory cytokines. Thus, the α-SMA–positive bone marrow–derived cells represent a potential target for the treatment of vascular diseases, and it is clinically less important whether we define these cells as “dedifferentiated macrophage-like SMCs” or “differentiated SMC-like macrophages.” This notion is further confirmed by the study by Yajima et al.

Disclosures
None.

References
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Circulation. 2008;117:3060-3061
doi: 10.1161/CIRCULATIONAHA.108.782961
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
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