Origin of Cells That Contribute to Neointima Growth

Hiroshi Iwata, MD, PhD; Masataka Sata, MD, PhD

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. 

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Department of Cardiovascular Medicine (H.I., M.S.), University of Tokyo Graduate School of Medicine, Tokyo, Japan; Department of Cardiovascular Medicine (M.S.), Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima, Japan; and Department of Advanced Clinical Science and Therapeutics (M.S.), The University of Tokushima Graduate School, Tokushima, Japan. Correspondence to Masataka Sata, MD, PhD, Professor and Chairman, Department of Cardiovascular Medicine, Institute of Health Biosciences, The University of Tokushima Graduate School, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan. E-mail sata@clin.med.tokushima-u.ac.jp (Circulation. 2008;117:3060-3061.).

© 2008 American Heart Association, Inc.

Circulation is available at http://circ.ahajournals.org
DOI: 10.1161/CIRCULATIONAHA.108.782961
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. In addition, it is known that macrophages can stain positive for α-SMA under some circumstances.

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.

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


Origin of Cells That Contribute to Neointima Growth
Hiroshi Iwata and Masataka Sata

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:
http://circ.ahajournals.org/content/117/24/3060

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/