Response to Letter Regarding Article “Extracardiac Progenitor Cells Repopulate Most Major Cell Types in the Transplanted Human Heart”

We thank Drs Kaye and Esler for their comments on our recent article exploring recipient-derived cardiomyocytes, endothelial cells, smooth muscle cells, and Schwann cells in sex-mismatched heart transplant patients. Using the Y chromosome to track male cells in the female heart, we concluded that 11.2% of Schwann cells were derived from extracardiac sources, suggesting that recipient-derived circulating progenitor cells play a role in the reparative process of peripheral nerves in the transplanted heart.

The Schwann cell data came from autopsy specimens taken 9 to 50 months after transplantation (Table 1 of our original article). Schwann cells were identified by using an antibody against S100 calcium-binding protein, widely used in clinical pathology practice. Schwann cells were only found in large nerve fibers near the epicardium, not in the endocardial regions where biopsies are obtained. We are aware that S100 has various subsets and is present in other cell types, including skeletal and heart muscle (subsets S-100A1 and S-100A6) and dendritic cells. To obtain the most specific expression for Schwann cells, we used an antibody (Dako, Z0311) that has the highest affinity for the S-100B subset (found predominantly in Schwann cells, melanocytes, and adipocytes) and weakest affinity for the S-100A1 and S-100A6 subsets. Cells were only counted as positive if they were spindle-shaped and located in an obvious nerve bundle. Comparable frequencies were obtained by bright-field and confocal fluorescent microscopy (minimizing the risk of mistaking leukocytes for Schwann cells). For these reasons, we believe that our study truly identified Schwann cells derived from extracardiac sources.

The comments by Kaye and Esler raise the question of what structural criteria one would need to definitively identify reinervation in a transplanted heart. When a peripheral nerve is transected, the distal axon undergoes Wallerian degeneration, whereas the proximal stump typically forms a growth cone and invades the old axonal tract, guided by the surviving Schwann cells. Our study did not address the source of these nerve fibers because of the difficulty of studying their cell bodies, which are located some distance away (in the paravertebral ganglia for sympathetic nerves, in the epicardial ganglia for parasympathetic nerves). Hence, we do not know whether these were regenerated distal axons (presumably host-derived) or residual postsynaptic parasymathetic axons (graft-derived). Our identification of Schwann cells derived from extracardiac sources might therefore be better classified as a novel component of peripheral nerve repair, rather than as true reinervation.

We appreciate the opportunity to expand on and clarify the significance of our findings.

Disclosures

Drs Laflamme and Murry have received research grant support from Geron Corp. Dr Murry has served as a consultant to and/or on an advisory board for Guidant. The other authors report no conflicts.

Elina Minami, MD
Department of Medicine
Division of Cardiology
University of Washington School of Medicine
Seattle, Wash

Michael A. Laflamme, MD, PhD
Charles E. Murry, MD, PhD
Department of Pathology
University of Washington School of Medicine
Seattle, Wash

Jeffrey E. Saffitz, MD, PhD
Department of Pathology
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, Mass

Response to Letter Regarding Article "Extracardiac Progenitor Cells Repopulate Most Major Cell Types in the Transplanted Human Heart"
Elina Minami, Michael A. Laflamme, Charles E. Murry and Jeffrey E. Saffitz

_Circulation_. 2006;113:e845
doi: 10.1161/CIRCULATIONAHA.106.613745
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 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/113/22/e845

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/