Letter to the Editor

Letters to the Editor will be published, if suitable, as space permits. They should not exceed 1000 words (typed double-spaced) in length and may be subject to editing or abridgment.

Nonbone Marrow–Derived Endothelial Progenitor Cells: What Is Their Exact Location?

In response:

In the August 3, 2007 issue of Circulation Research, Ergün and Gehling suggested in a Letter to the Editor1 that the concept of nonbone marrow–derived endothelial progenitor cells as shown by our group in the March 2, 2007 issue of Circulation Research;2 could mostly be anticipated by previous publications including their own3–5 demonstrating the existence of vessel wall–derived endothelial progenitor cells. Of course, we truly appreciate and acknowledge the important work by these authors concerning the identification and characterization of vessel wall–derived endothelial progenitor cells.3–5 but would like to emphasize that these progenitor cells represent only one of the multiple possible sources for circulating endothelial lineage fated cells that contribute to postnatal neovascularization and have been described in our recent manuscript.2 Other sources such as vessel wall–derived mature endothelial cells and, most importantly, tissue-resident progenitor cells including liver and intestinal stem cells, which are not directly related to vessels and, thus, have not yet been committed to an endothelial fate, might also play a role. Specifically, in the parabiosis model as used in our studies, we detected homing and incorporation of circulating cells in the target limb muscles by means of expression of the reporter gene β-galactosidase under the control of an endothelial tie2 promoter. This system was used to confirm the final endothelial fate of the circulating cells that had migrated into the ischemic muscles. Apparently, this model does not allow the conclusion that the cells must have had an endothelial (progenitor) cell origin before their mobilization into the circulation after the ischemic insult. Therefore, although suggested by Ergün and Gehling,1 we feel that it would have been absolutely premature and imprecise to term these cells as anything else than what they indeed are, namely nonbone marrow–derived cells. Indeed, the parabiosis model allowed us to demonstrate for the first time the relative contribution of nonbone marrow cells relative to the contribution of all mobilized cells independent of their actual source.

In our further experiments, we then focused on 2 nonexclusive potential nonbone marrow sources. We investigated liver and intestine as likely supplies for tissue-resident progenitor cells in transplantation models because of their highly regenerative nature. For the isolation of tissue-resident progenitor cells, we selected CD45 c-kit+ cells as our candidates for tissue-derived progenitor cells, which of course does not exclude the existence of other cell populations, which may have been tracked in the parabiosis model. Only a small percentage (about 10%) of the CD45 c-kit+ cells actually expressed the endothelial marker CD146 suggesting that the majority of these cells may not represent endothelial progenitor cells. With regard to these c-kit+ cells, we showed their localization in perivascular niches of the liver (see Figure 3) and their subsequent mobilization into the circulation after induction of hind limb ischemia.2 Therefore, we have demonstrated for the first time that nonbone marrow–derived cells can indeed be mobilized into the circulation and can be retrieved in ischemic tissues where they contribute to postnatal neovascularization. In the future, it would be intriguing to investigate whether these cells are related to CD34CD31 vascular progenitor cells in human vessels as described previously.3,5 It is important to note that Alessandri et al3 already showed the existence of CD34CD31 vascular wall resident progenitors in embryonic aorta in 2001, which was confirmed in adult human arteries in 2006.6 However, the mobilization of labeled CD34CD31 vascular wall resident progenitors in response to ischemia and their subsequent contribution to postnatal neovascularization in a remote tissue has not been demonstrated in any of the aforementioned manuscripts.

Therefore, we do agree with Ergün and Gehling that future studies providing smart strategies to track these cells in vivo will be crucial for the definitive proof, which cell population beside the reported CD45 c-kit+ cells is actually mobilized during remote tissue injury, and which of them may significantly contribute to vascular repair. Until this issue has been solved, however, we have to stick with the term nonbone marrow–derived tissue progenitor cells as this is what we have definitive proof for to date.

Disclosures

None.

Alexandra Aicher
Stefanie Dimmeler
Department of Internal Medicine III
J.W. Goethe University
Frankfurt, Germany

Christopher Heeschen
Department of Surgery
Ludwig-Maximilians-University
Munich, Germany

Nonbone Marrow–Derived Endothelial Progenitor Cells: What Is Their Exact Location?
Alexandra Aicher and Christopher Heeschen

Circ Res. 2007;101:e102
doi: 10.1161/CIRCRESAHA.107.162438
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/101/9/e102

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research 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 Research is online at:
http://circres.ahajournals.org//subscriptions/