Response to Letter Regarding Article, “A Detailed Analysis of Bone Marrow From Patients with Ischemic Heart Disease and Left Ventricular Dysfunction: BM CD34, CD11b and Clonogenic Capacity as Biomarkers for Clinical Outcomes”

We thank Drs Gremmels, Papazova, Flederus, and Verhaar for providing their perspective of our study.1

The primary question raised by these investigators whose research focus is on multipotent mesenchymal stromal cells (MSCs) is whether endothelial colony-forming cells (ECFCs) derived from bone marrow (BM) can originate from rare MSCs.

The answer is yes.

To answer more fully, it should be noted that there are no ECFCs in the human body. ECFCs are a synthetic representation of vasculogenic capacity, which varies depending on input cell source. We chose to use this laboratory assay in parallel with a cardiovascular cell therapy trial because the target organ for repair—the heart—suffered from ischemia and infarction. Until our report, all previous cardiovascular cell therapy trials used Methocult media (an assay measuring hematopoietic differentiation) as a biomarker for cell function. We chose to add the ECFC assay in addition to several other ancillary studies as a means to quantify the proangiogenic activity of BM mononuclear cells administered to patients.2

In our experience with hundreds of BM specimens, not just 6 as reported by Tura et al,3 when BM mononuclear cells are cultured in endothelial growth media 2 (EGM-2), endothelial-like colonies grow. BM-derived ECFC colonies (BM-ECFC) expressed endothelial surface proteins like CD31 (PECAM-1) and CD105 (Endoglin) and lacked hematopoietic expression (ie, CD45, CD14) and MSC expression (ie, CD146). Some endothelial adhesion molecules, such as VE-cadherin (CD144), were not present on ECFC colonies. However, BM-ECFCs functionally formed capillaries in Matrigel. The most that can be said about BM-ECFCs is that they are similar, not equivalent, to endothelial cells.

In a recent study, when we cultured BM from patients with acute myeloid leukemia—a stem cell malignancy—in EGM-2, endothelial-like colonies grow. BM-derived ECFC colonies (BM-ECFC) expressed endothelial surface proteins like CD31 (PECAM-1) and CD105 (Endoglin) and lacked hematopoietic expression (ie, CD45, CD14) and MSC expression (ie, CD146). Some endothelial adhesion molecules, such as VE-cadherin (CD144), were not present on ECFC colonies. However, BM-ECFCs functionally formed capillaries in Matrigel. The most that can be said about BM-ECFCs is that they are similar, not equivalent, to endothelial cells.

In a recent study, when we cultured BM from patients with acute myeloid leukemia—a stem cell malignancy—in EGM-2, endothelial-like colonies grow. BM-derived ECFC colonies (BM-ECFC) expressed endothelial surface proteins like CD31 (PECAM-1) and CD105 (Endoglin) and lacked hematopoietic expression (ie, CD45, CD14) and MSC expression (ie, CD146). Some endothelial adhesion molecules, such as VE-cadherin (CD144), were not present on ECFC colonies. However, BM-ECFCs functionally formed capillaries in Matrigel. The most that can be said about BM-ECFCs is that they are similar, not equivalent, to endothelial cells.

To address the question of BM MSC activity and cardiovascular cell therapy clinical outcomes, we cultured BM specimens in CFU-F assay (Mesencult media), and these results are forthcoming in future publications.

Disclosures

Christopher R. Cogle
Division of Hematology and Oncology
Department of Medicine
University of Florida
Gainesville, FL

References


Response to Letter Regarding Article, "A Detailed Analysis of Bone Marrow From Patients with Ischemic Heart Disease and Left Ventricular Dysfunction: BM CD34, CD11b and Clonogenic Capacity as Biomarkers for Clinical Outcomes"
Christopher R. Cogle

Circ Res. 2014;115:e36-e37
doi: 10.1161/CIRCRESAHA.114.305422
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 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/115/12/e36

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/