Editorial

Heart Factory or Fiction?

Cardiac Progenitor Cells and Regeneration

Brian C. Jensen, MD; Cam Patterson, MD, MBA

“In the Christian tradition, the doctrine of regeneration considers the “deceitful… and wicked” heart a vessel for accepting God and thereby being born again. Indeed, many cultures have invested the heart with powers well beyond its biological role in maintaining systemic perfusion. However, the capacity of the heart for renewal was limited to metaphor until relatively recently, when science revealed a very literal interpretation of cardiac regeneration. Contrary to long-standing belief, it now appears that new cardiomyocytes are created after birth and that cardiomyocyte renewal continues in the aging human heart. Most studies estimate that the annual rate of myocyte renewal is roughly 1%,1,2 although other groups suggest that up to 40% of a heart’s cardiomyocytes might be regenerated each year.3 These new cells may arise from resident cardiac progenitor cells (CPCs), from proliferation of preexisting cardiomyocytes, or from migratory populations of epicardial cells. Regardless of their origin, their number and inherent function seem insufficient to heal the profoundly injured heart because roughly 300,000 Americans die every year of heart failure. Of course, the more sanguine among us view this striking burden as a therapeutic opportunity, and clinical trials of cardiac regeneration could indeed become a reality.

Regardless of their origin, their number and inherent function seem insufficient to heal the profoundly injured heart because roughly 300,000 Americans die every year of heart failure. Of course, the more sanguine among us view this striking burden as a therapeutic opportunity, and clinical trials of cardiac regeneration could indeed become a reality.

The present work builds on previous observations by this group and others. Aging and heart failure are thought to impair the reparative capacity of rodent CPCs,4,5 but the authors’ identification of functional defects in senescent hCPCs is novel. The present article also is the first to describe a role for ephrins in the motility of hCPCs. Ephrins are known to mediate migratory processes involving other stem cell niches, including skeletal muscle satellite cells,6 and other members of the ephrin family directly regulate migration and cell cycle reentry of intestinal progenitor cells.7 The Leri laboratory first identified the contribution of ephrin A1-EphA2 signaling to CPC motility in the setting of a mouse model of myocardial infarction,8 and here their findings are extended to cultured senescent human heart cells. The authors rightly suggest that an expanded understanding of the mechanisms underlying the regenerative capacity of hCPCs is biologically important, although they and others9 acknowledge that purifying highly functional hCPCs is required to achieve clinically meaningful myocardial regeneration. Their proposed strategy for sorting hCPCs based on the potency of ephrin A1-EphA2 interactions is novel and could be explored further with in vivo approaches.

Although the authors are to be congratulated for making further contributions to the rapidly expanding literature on myocardial regeneration, their article subtextually reinforces how much remains to be learned about stem cells in the heart. In this article, the authors used antibody-coated immunomagnetic beads to select cKit+ cells for initial culture, although further cell sorting and typing methods were not specified.10 Importantly, it is clear that the adult heart contains multiple populations of CPCs, and recent work demonstrates that these populations activate distinct transcriptional programs.11 In mice, cKit+ CPCs are 2- to 3-fold less abundant than Sca1+ CPCs, and the cKit+ substantially to the extant literature on hCPCs, including seminal observations on the number and function of CPCs in the aging and failing human heart. Here, they explore the role of ephrins in the trafficking of hCPCs, specifically focusing on the interaction between the ligand ephrin A1 and its receptor, EphA2. Using a variety of in vitro approaches, the authors demonstrate reduced motility of hCPCs with senescence induced by serial passaging. This impairment is associated with diminished responsiveness to ephrin A1, likely resulting from failure of EphA2-mediated endocytosis and subcellular transport of its ligand. These defects are rescued by lentiviral infection with exogenous EphA2, which restores the migratory capacity of experimentally aged hCPCs. The authors implicate oxidative stress as an underlying mechanism for the blunted response of EphA2 to its ligand and ultimately suggest that defects in EphA2 activity level might be useful in distinguishing “young” from “old” hCPCs for therapeutic purposes.

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

From the McAllister Heart Institute and Division of Cardiology, University of North Carolina School of Medicine, Chapel Hill.

Correspondence to Cam Patterson, MD, MBA, Chief, Division of Cardiology, University of North Carolina School of Medicine, 8200 Medical Biomolecular Research Bldg, Chapel Hill, NC 27599-7126.

E-mail cpartners@med.unc.edu

(Circulation. 2013;128:2181-2182.)

© 2013 American Heart Association, Inc.

Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.113.006262

2181
population may also contain CD45 cells, suggestive of bone marrow origin. Thus, it seems possible that the hCPCs used for these experiments may be a somewhat mixed population and nearly certain that the biology of these cells is not fully representative of all hCPC populations. Thus, the authors’ demonstration of the role of ephrin signaling is well supported in the cultured cells that they studied, but it is less clear that their findings are broadly applicable to hCPC populations in vivo.

The fidelity of the induced senescence model of cultured cKit + hCPCs to aged hCPCs in the human heart also is unclear. More specifically, the serial in vitro passage of human heart cells should not be conflated with the biological process of aging. Furthermore, it is conceivable that the pathophysiological consequences of the putative age-related loss of hCPC function might well be offset by the more rapid turnover of hCPCs in older patients’ hearts. Indeed, the authors’ previous report of rapid in vivo cardiomyogenesis in aged hearts seems somewhat at odds with the effects of experimentally induced cellular senescence reported in the present article.

Taken in the broader context, this article is the most recent contribution of a productive and influential laboratory to a deeply conflicted field. On one hand, a recent publication concludes that cKit + CPCs are necessary and sufficient for myocardial regeneration in the mouse heart. However, other leading myocardial biologists identify very little regenerative capacity from CPCs in the adult mammalian heart, finding that new cardiomyocytes are created instead by the division of preexisting cardiomyocytes. The lack of scientific consensus notwithstanding, our most prestigious academic medical centers are actively recruiting patients for participation in further clinical trials using hCPCs. Although the degree of enthusiasm for the stem cell enterprise among scientists, clinicians, and patients alike may simply be commensurate with the desparate need for new heart failure therapies, one cannot help but wonder whether its enduring metaphorical appeal also exerts some influence. Regardless of motivation, it is indisputably true that our current knowledge of cardiac stem cell biology is incomplete and that further study is required to understand its therapeutic potential. It remains to be seen whether the biology of the heart will match the very human desire for regeneration and rebirth.

Disclosures

None.

References


Heart Factory or Fiction?: Cardiac Progenitor Cells and Regeneration
Brian C. Jensen and Cam Patterson

Circulation. 2013;128:2181-2182; originally published online October 18, 2013; doi: 10.1161/CIRCULATIONAHA.113.006262
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 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/128/20/2181

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/