Heart Factory or Fiction?
Cardiac Progenitor Cells and Regeneration

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

“Create in me a clean heart, O God.” Psalm 51:10

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 of disease 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,8,9 but the authors’ identification of functional defects in senescent hCPCs is novel. The present article also is the first to describe a role for ephrin A1-EphA2 signaling in the motility of hCPCs. Ephrins are known to mediate regenerative processes involving other stem cell niches, including skeletal muscle satellite cells,10 and other members of the 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.

In the current issue of Circulation, Goichberg and colleagues7 provide new explication of the mechanisms underlying human CPCs (hCPC) aging. The group has contributed 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 cpatters@med.unc.edu


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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 passaging 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 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 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 preexistent 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 desperate need for new heart failure therapies, one cannot help but wonder whether its enduring metaphoric 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


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