“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%, although other groups suggest that up to 40% of a heart’s cardiomyocytes might be regenerated each year. 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 myocardial regeneration using various cell types and preparations already have been conducted. Early trials in the field used bone marrow–derived stem cells with mixed results. More recently, 2 trials have investigated the use of CPCs, and their findings have been somewhat promising. Although treatment with stem cells appears safe, enthusiasm for their expanded use is restrained by the acknowledgment that both evidence including skeletal muscle satellite cells, and other members of the ephrin family directly regulate migration and cell cycle reentry of intestinal progenitor cells. 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, 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 others 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. Importantly, it is clear that the adult heart contains multiple populations of CPCs, and recent work demonstrates that these populations activate distinct transcriptional programs.

In the current issue of Circulation, Goichberg and colleagues 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 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, 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 regenerative processes involving other stem cell niches, including skeletal muscle satellite cells, and other members of the ephrin family directly regulate migration and cell cycle reentry of intestinal progenitor cells. 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, 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 others 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.

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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 cellular senescence reported in the present article. Regardless of motivation, it is indisputably true that our current knowledge of cardiac stem cell biology is incomplete. None.

**Disclosures**

None.

**References**


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