Heart Factory or Fiction? Cardiac Progenitor Cells and Regeneration

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“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 heart’s capacity for renewal was limited to metaphor until relatively recently, when science revealed a very literal interpretation of cardiac regeneration. Contrary to longstanding 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%, though 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, from proliferation of pre-existing 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, as 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, two trials have investigated the use of cardiac progenitor cells and their findings have been somewhat promising. Though treatment with stem cells appears safe, enthusiasm for their expanded use is restrained by the acknowledgement that both evidence of meaningful clinical benefit and clear mechanisms of benefit are lacking. Thus, rigorous ongoing investigation of stem cell biology in the heart will be essential in clarifying whether therapeutic cardiac regeneration could indeed become a reality.
In the current issue of *Circulation*, Leri and colleagues provide new explication of the mechanisms underlying human cardiac progenitor cell (hCPC) aging. The group has contributed substantially to the extant literature on hCPCs, including seminal observations regarding 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 current 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 manuscript 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 re-entry 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 they extend their findings 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, though they and others\textsuperscript{13} acknowledge that purifying highly functional hCPCs will be 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 using in vivo approaches.

Though the authors are to be congratulated for making further contributions to the rapidly expanding literature on myocardial regeneration, their manuscript subtextually reinforces how much remains to be learned about stem cells in the heart. In this manuscript, the authors used antibody coated immunomagnetic beads to select cKit+ cells for initial culture, though further cell sorting and typing methods were not specified.\textsuperscript{14} Importantly, it is clear that the adult heart contains multiple populations of CPCs, and recent work demonstrates that these populations activate distinct transcriptional programs.\textsuperscript{15} In mice, cKit+ CPCs are two to three-fold less abundant than Sca1+ CPCs, and the cKit+ population may also contain CD45+ cells, suggestive of bone marrow origin.\textsuperscript{15} 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. As such, 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 pathophysiologial 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 current manuscript.

Taken in the broader context, this manuscript is the most recent contribution of a productive and influential lab 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 pre-existing cardiomyocytes. Notwithstanding lack of scientific consensus, our most prestigious academic medical centers are recruiting patients actively for participation in further clinical trials using hCPCs. Though 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 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 heart’s biology will match the very human desire for regeneration and rebirth.

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