Young Hearts Run Free

Therapeutic Potential of Neonatal Human Cardiac Progenitor Cells Secretome

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An unbridled imagination is the fountain of youth; it's what keeps us young at heart.

—Richelle E. Goodrich

The burden of cardiovascular disease is one of the greatest health issues facing the United States, with >1 in 3 American adults experiencing at least 1 form of cardiovascular disease. There is an estimated economic cost of $320.1 billion each year, including the 15% of total medical expenditure in the United States attributable to cardiovascular disease.[1] Existing therapies for cardiovascular disease prolong the life of the patients but do not actually regenerate the lost cardiac muscle tissue. Accordingly, stem cells have shown a great promise in cardiac repair and regeneration. Among resident cardiac progenitors, c-kit$^+$ cardiac progenitor cells (CPCs) sparkled remarkable interest and recent controversy related to their contribution in cardiomyocyte turnover.[2] Regardless, several independent laboratories demonstrated transplantation of c-kit$^+$ CPCs improved cardiac function in preclinical models of myocardial injury.[3,4] Furthermore, a phase 1 clinical trial using autologous c-kit$^+$ CPC intracoronary infusion in patients with heart failure showed improvement in left ventricular systolic function and reduction in infarct size,[5] suggesting that despite negligible cardiomyogenesis potential, c-kit CPCs do exert therapeutic potential. However, as is the case with other adult progenitors, the regenerative potential of CPCs declines with the advancement of age and thus may not result in consistent and long-lasting therapeutic effect.[6] On these lines, the current report in *Circulation Research* by Sharma et al[7] has shown that human neonatal CPCs (nCPCs) outperform human adult CPCs (aCPCs) in functional recovery post-myocardial infarction (MI), effects which are mediated at least in part by heat shock factor-1 (HSF-1).

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Stem cell hypothesis of aging postulates that youthful stem cells have better intrinsic ability to repair/regenerate after an injury.[8] Consistent with this hypothesis, current report by Sharma et al[7] observed nCPCs transplantation post-MI was associated with greater cell retention and functional benefit compared with aCPCs. Furthermore, a recent report using c-kit^{BAC}-EGFP (bacterial artificial chromosome-enhanced green fluorescent protein) mouse has shown substantial cardiac regeneration in the cryo-injured neonatal hearts, in part via contribution of c-kit$^+$ CPC to cardiomyogenesis and angiogenesis.[9] Thus, nCPCs mediated cardiac functional benefits in this study confirm a greater regenerative power of neonatal c-kit CPCs. To circumvent aging-related stem cell dysfunction issues, this study also suggests transplantation of allogenic nCPCs, which may be a potential off-the-shelf cell-based agent for cardiac regeneration.

A general consensus has emerged in recent years that adult stem/progenitor cells largely exert their therapeutic benefits that are attributed to their secretion of paracrine factors. Several stem cell–derived paracrine factors have been studied as a therapeutic module for cardiac repair, including conditioned medium, cytokines, growth factors, and extracellular vesicles, including exosomes and microvesicles.[10–13] Of note, the current paradigm in cardiac regenerative medicine is to understand potential stem cell–derived factors that may enhance cardiac repair process and is of immense biological and therapeutic importance.

To further understand the role of paracrine factors in cardiac repair, Sharma et al[7] designed in vitro experiments to investigate whether total conditioned medium (TCM) or exosomes secreted by nCPCs or aCPC modulate angiogenesis and wound healing. Intriguingly, nTCM significantly enhanced angiogenesis and wound healing compared with nCPC exosomes or aTCM. Mirroring the results seen in in vitro, the authors found that nTCM treatment post-MI resulted in improved cardiac function compared with nCPC exosomes or aTCM with enhanced angiogenesis. Remarkably, nTCM treatment post-MI was associated with significantly higher functional benefit compared with nCPC exosomes indicating the potential significance of nTCM as a therapeutic candidate for enhancing cardiac repair post-MI. Because TCM is known to harbor multiple biological factors (proteins, RNA, extracellular vesicles, exosomes, etc)[10] that can be transferred to target cells leading to phenotypic modulation, current study sought to investigate CPC proteome as potential modulators of cardiac repair mechanisms. Systematic evaluation of expressed proteins and pathway analyses using all available data sets identified heat shock proteins upregulation in the nTCM compared with aTCM, which affects ≈20% of the canonical signaling pathways. Analysis of upstream regulators of heat shock proteins revealed HSF-1 as

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(*Circ Res*. 2017;120:751-752.
DOI: 10.1161/CIRCRESAHA.117.310574.)

***Circulation Research* is available at http://circres.ahajournals.org**
DOI: 10.1161/CIRCRESAHA.117.310574

one of the master regulators. Interestingly, HSF-1 has been shown to be involved in strengthening elderly hearts against stress.[14] Furthermore, Sharma et al[7] asked whether HSF-1, one of the predicted master regulators of heat shock proteins, whose function in the context of CPCs has not been analyzed to date, can regulate the CPC function and its secretome? Interestingly, knockdown of heat shock protein-1 in nCPCs impaired their function and secretome. Of clinical relevance, overexpression of HSF-1 in aCPCs exhibited enhanced metabolic activity and resistance to oxidative stress. Intriguingly, HSF-1 overexpression in aCPC augmented their paracrine factors secretion leading to enhanced angiogenesis in vitro. It would be of interest to see whether overexpression of HSF-1 in aCPCs decreases their senescence markers (telomere length, p16INK4a expression, and β-galactosidase activity)? Together these results confirm that HSF-1 is not only essential for the functional activity of CPCs but also for control the quality of their secretome. Moreover, such regulatory mechanisms that govern nCPC function and its secretome will contribute to unravel the hurdles in reactivating the regenerative capability of aCPCs derived from elderly patients.

Of note, a recent study suggested that hypoxia-preconditioned nCPCs restore cardiac function via exosomal miRNA.[15] Results from this study by Sharma et al[7] strongly support the synergistic role of both TCM and exosomes in augmenting cardiac repair post-MI. However, future studies are warranted to comprehend the role of extracellular or exosomal RNA-mediated functional benefits observed in this study.

The current report by Sharma et al[7] has provided an important information to the active field of cardiovascular research in outlining secretome as an important component of human CPCs function. Although clear-cut molecular mechanisms of the HSF-1 controlling CPC function and its secretome are not fully understood, however, nCPC or its secretome as a potential source for allogeneic therapy is extremely encouraging. Further work related to HSF-1–mediated rejuvenation of aCPCs might be a novel therapeutic target for adult cardiac regeneration. Comparison and integration of the growing number of proteome data sets from different stem cell secretome will also help to obtain an entire picture of the critical regulators of cardiac regeneration.

Sources of Funding

Work described in this article was in part supported by National Institute of Health grants HL091983, HL126186, and HL053354 (R. Kishore) and American Heart Postdoctoral grant 15POST22720022 (V.N. Srikanth Garikipati).

Disclosures

None.

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KEY WORDS: Editorials ■ cytokines ■ exosomes ■ heart failure ■ myocardial infarction ■ oxidative stress