c-kit–Positive Cardiac Progenitor Cells
The Heart of Stemness

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One decade ago, the discovery of resident stem cells in the adult rat heart1 abolished the paradigmatic view of the heart as a terminally differentiated postmitotic organ, incapable of self-renewing, and opened a new era on resident cardiac stem cell therapeutic role to induce heart regeneration. Other studies had shown that bone marrow (BM)–derived cells injected into the injured heart could improve its function, at least in animal models,2 but the cardiac stem cell was still unclear whether these cells are present in the adult heart.3 In addition, at least in animal models,2 but the cardiac stem cell was expected to be more likely to differentiate into cardiomyocytes than cells derived from organs other than the heart, such as the BM or the adipose tissue. In keeping, a recent study confirmed a higher regenerative potential of cardiac progenitor cells (CPCs) compared with BM-derived stem cells in a mouse model of myocardial infarction.4

Since the initial discovery of the c-kit+ cardiac stem cell, other cardiac stem cell and CPC populations have been identified. In rodents, different CPCs have been isolated on the basis of the expression of stem cell antigen 1 (Sca1)4,5 and their ability to actively extrude dyes and toxic compounds through the ATP-binding cassette surface transporter,6 identifying in this way a cardiac resident side population (SP). Islet 1–positive cardiac aggregates named cardiospheres7 have been obtained from the heart of different species. Cardiospheres and cardiospherederived cells (CDCs) have been extensively characterized and shown to contain a mixed cell population, including c-kit+ cells and cells expressing the stromal cell marker CD105.8

This complicated scenario is reproduced in humans, where both c-kit+ cells11 and SP cells12 have been identified. Furthermore, cardiospheres and CDCs8 have been obtained from human cardiac specimens, and recently cardiac stromal cells13 and cardiac atrial appendage stem cells,14 having a high-regenerative potential, have also been isolated. It is noteworthy that CDCs, cardiac stromal cells, and cardiac atrial appendage stem cells share important similarities, such as the expression of some surface markers.

In the article by Dey et al,15 published in this issue of Circulation Research, the authors performed a transcriptional profiling of 3 different cardiac stem cells, that is, c-kit+, Sca1+, and SP as well as 2 BM progenitors, c-kit+ and mesenchymal stem cells of age- and sex-matched mice. Cardiomyocytes were used as reference population for complete cardiac commitment.15

The detailed analysis of differentially expressed genes and molecular pathways activated in cardiac stem cell populations revealed different levels of cardiac commitment in CPCs. The authors showed that c-kit+ cells are the most primitive undifferentiated population, SP cells have an intermediated phenotype, and Sca1+ cells display the transcriptional profile closest to cardiomyocytes. Because SP and Sca1+ cells share Sca1 antigen, but not c-kit surface marker, they may represent a different state of the same progenitor cell; this remains an open question that could be answered by in vivo lineage tracing studies. On the contrary, c-kit+ CPCs are a cardiac population with unique stem characteristics, showing a downregulation of genes encoding for cell to cell and extracellular matrix adhesion proteins, and an upregulation of developmental genes (Figure A).

A comparison between CPCs and BM-derived progenitor cells has also been performed. This analysis demonstrated that the expression of genes of extracellular matrix, cytoskeletal elements, gap junction, and of cardiac-specific genes was enriched in CPCs and downregulated in BM-derived progenitors. In contrast, genes involved in DNA replication, repair, and cell cycle regulation were downregulated in the cardiac-derived cells and highly upregulated in BM-derived cells (Figure B).

The study by Dey et al15 represents the first attempt to hierarchically distinguish the plethora of stem cell populations useful for cardiac regeneration on the basis of their gene expression profile. Moreover, the results address an important concern regarding the origin of cardiac stem cells and the differences among them. Specifically, the authors show that cardiac-derived and BM-derived c-kit+ cells are clearly distinct in terms of their molecular signature, contrasting the idea of a possible extracardiac origin of CPC c-kit+ cells.

Finally, despite the CDC isolation protocol being incompatible with the experimental design adopted in this study, where all cells were freshly isolated and were not cultured or expanded in vitro, Dey et al15 compared their data with publicly available microarray database for cardiospheres. Interestingly, cluster analysis revealed that primary CDCs are similar to BM-derived mesenchymal stem cells, whereas secondary CDCs, generated by passaging primary cardiospheres, are closer to Sca1+ progenitors and distinct from the c-kit+ population.

Nowadays, the available reports on rodent and human CPCs are mainly focused on phenotypic and functional studies; therefore,
this is the first original work in which a detailed molecular analysis of mouse CPCs has been reported. Previous molecular screenings have focused on a single CPC population6,16 or on microRNA expression and modulation,13,17,18 leaving a gap in our understanding of CPC genetic signature.

The approach taken by Dey et al15 opens the way to new studies in cardiac regenerative medicine. Recent reports suggest that cardiac fibroblasts are highly plastic and can be reprogrammed in vitro and in vivo to form new cardiomyocytes that contribute to cardiac regeneration after injury.19–21 Thus, an important issue that should be addressed in future studies is a direct comparison of the gene expression profile of cardiac stem cells with cardiac fibroblasts and, eventually, other cell types reprogrammed to differentiate into myocardial cells. Furthermore, 2 phase I clinical studies have been recently performed, Cardiac Stem Cell Infusion in Patients with Ischemic Cardiomyopathy (SCIPIO) (NCT00474461)22 and Cardiomyocyte-Derived Autologous Stem Cells to Reverse Ventricular Dysfunction (CADUCEUS) (NCT00893360)23; these trials have exploited the therapeutic potential of autologous cardiac-derived progenitors, c-kit+ and CDCs, respectively, to ameliorate chronic or subacute ischemic heart failure. Preliminary results seem attractive in terms of scar size reduction and increase in viable myocardium. Therefore, it would be of interest to establish how close the molecular signature of human c-kit+ CPCs and CDCs, undergoing clinical evaluation to their murine counterpart, is.

In summary, the study by Dey et al15 identifies molecular pathways specific for different cardiogenic stem and progenitor cells, underlining the importance of gene expression profiling, in addition to functional studies, to develop new strategies aimed at improving CPC cardiac regenerative potential.

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None.

**References**


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