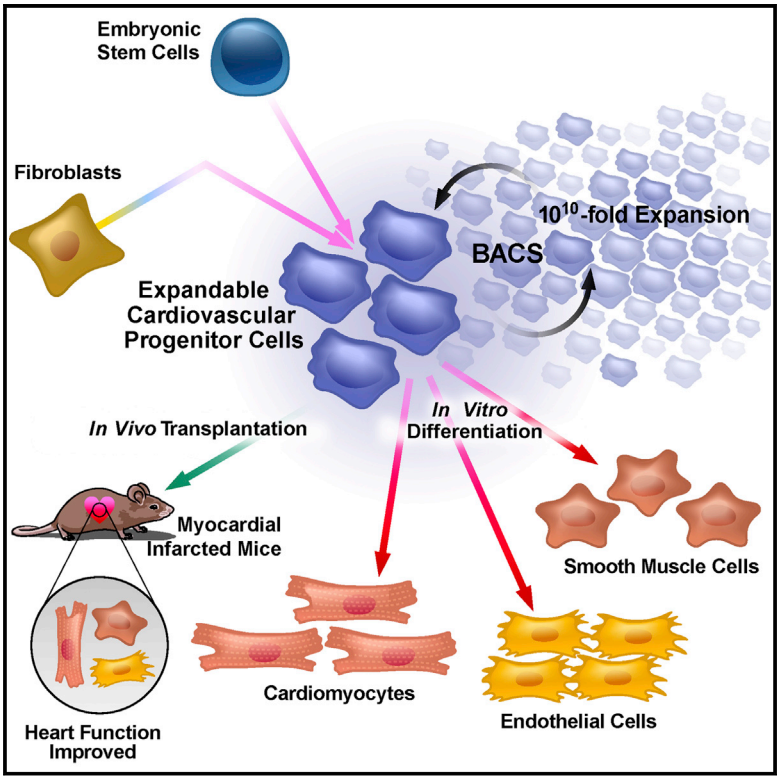
Article

Cell Stem Cell

Expandable Cardiovascular Progenitor Cells Reprogrammed from Fibroblasts

Graphical Abstract



Highlights

- Fibroblasts can be reprogrammed into cardiac progenitor cells (CPCs)
- CPCs expanded long term under defined conditions generate cardiovascular cells
- Transplanting expanded CPCs improves heart function after myocardial infarction
- CPCs can be captured during PSC differentiation and expanded in the same conditions

Authors

Yu Zhang, Nan Cao, Yu Huang, ..., Benoit G. Bruneau, Deepak Srivastava, Sheng Ding

Correspondence

sheng.ding@gladstone.ucsf.edu

In Brief

Zhang et al. report the capture and expansion of cardiovascular progenitor cells derived from mouse fibroblasts and pluripotent stem cells under chemically defined conditions. Expanded CPCs robustly differentiate only into the three main types of cardiovascular cells and can improve cardiac function following transplantation into hearts after myocardial infarction.

Accession Numbers

GSE77375

Zhang et al., 2016, Cell Stem Cell *18*, 368–381
March 3, 2016 ©2016 Elsevier Inc.
http://dx.doi.org/10.1016/j.stem.2016.02.001

CellPress

Cell Stem Cell
Article

Expandable Cardiovascular Progenitor Cells Reprogrammed from Fibroblasts

Yu Zhang,[1,2,8] Nan Cao,[1,2,8] Yu Huang,[1] C. Ian Spencer,[1] Ji-dong Fu,[1,7] Chen Yu,[1,2] Kai Liu,[1,2] Baoming Nie,[1,2] Tao Xu,[1,2] Ke Li,[1,2] Shaohua Xu,[1,2] Benoit G. Bruneau,[1,3,4,5] Deepak Srivastava,[1,3,4,6] and Sheng Ding[1,2,*]

[1]Gladstone Institute of Cardiovascular Disease, San Francisco, CA 94158, USA
[2]Department of Pharmaceutical Chemistry, University of California, San Francisco, San Francisco, CA 94158, USA
[3]Roddenberry Center for Stem Cell Biology and Medicine, Gladstone Institutes, San Francisco, CA 94158, USA
[4]Department of Pediatrics, University of California, San Francisco, San Francisco, CA 94143, USA
[5]Cardiovascular Research Institute, University of California, San Francisco, San Francisco, CA 94158, USA
[6]Department of Biochemistry and Biophysics, University of California, San Francisco, San Francisco, CA 94143, USA
[7]Department of Medicine, Heart and Vascular Research Center, MetroHealth Campus, Case Western Reserve University, Cleveland, OH 44106, USA
[8]Co-first author
*Correspondence: sheng.ding@gladstone.ucsf.edu
http://dx.doi.org/10.1016/j.stem.2016.02.001

SUMMARY

Stem cell-based approaches to cardiac regeneration are increasingly viable strategies for treating heart failure. Generating abundant and functional autologous cells for transplantation in such a setting, however, remains a significant challenge. Here, we isolated a cell population with extensive proliferation capacity and restricted cardiovascular differentiation potentials during cardiac transdifferentiation of mouse fibroblasts. These induced expandable cardiovascular progenitor cells (ieCPCs) proliferated extensively for more than 18 passages in chemically defined conditions, with 10^5 starting fibroblasts robustly producing 10^{16} ieCPCs. ieCPCs expressed cardiac signature genes and readily differentiated into functional cardiomyocytes (CMs), endothelial cells (ECs), and smooth muscle cells (SMCs) in vitro, even after long-term expansion. When transplanted into mouse hearts following myocardial infarction, ieCPCs spontaneously differentiated into CMs, ECs, and SMCs and improved cardiac function for up to 12 weeks after transplantation. Thus, ieCPCs are a powerful system to study cardiovascular specification and provide strategies for regenerative medicine in the heart.

INTRODUCTION

Heart failure (HF) is a devastating disease and a major cause of morbidity and mortality worldwide. HF often follows myocardial infarction (MI) that is usually accompanied by a massive loss of cardiomyocytes (CMs). These CMs cannot be regenerated by the adult mammalian heart and cannot yet be replaced and/or regenerated via cell-based therapies. Unfortunately, transplanting CMs into an infarcted heart yields only transient and marginal benefits (Burridge et al., 2012). Shortly after transplantation, most CMs are soon lost. These effects are likely caused by the limited proliferative capacity of fully differentiated CMs and a lack of blood-vessel formation to supply oxygen and nutrients (Lam et al., 2009). Thus, to create more effective regenerative therapies, we need to find a cell type that can be extensively expanded in vitro and robustly differentiated into cardiovascular cells in a diseased heart.

Cardiovascular progenitor cells (CPCs) may offer a promising avenue for cardiac-regenerative therapy. These cells evolve from the mesoderm during cardiogenesis, a well-orchestrated process in developing embryos that is recapitulated in differentiating pluripotent stem cells (PSCs). Patterned mesoderm gives rise to a hierarchy of downstream cellular intermediates that represent lineage-restricted CPCs for fully differentiated heart cells, including CMs, endothelial cells (ECs), and smooth muscle cells (SMCs) (Burridge et al., 2012). Each step in this hierarchy is tightly controlled by multiple stage-specific signals (e.g., Wnt, Activin/Nodal, bone morphogenetic protein [BMP], fibroblast growth factor [FGF], and Notch) (Burridge et al., 2012; Bruneau, 2013). Additionally, the gradual loss of multipotency, or commitment of cell fate, is usually accompanied by a decreased capacity of cellular proliferation. Thus, by isolating CPCs that can extensively self-renew and possess multiple, but restricted, potentials to directly differentiate into these three cardiovascular cell types, we may encourage the development of more effective and potentially safer therapies for cardiac regeneration.

A previous study identified one type of primitive CPCs that express two key marker genes, MESP1 and SSEA1 (Cao et al., 2013); however, these cells more closely represent a mesodermal precursor and are not fully committed to a cardiac fate. To differentiate into CMs in vitro, these primitive CPCs require multiple and sequential developmental signals. This notion is supported by studies in which $Mesp1^+$ cells not only contributed to heart development but also gave rise to non-cardiovascular mesodermal lineages, such as hematopoietic and skeletal muscle cells (Chan et al., 2013; Devine et al., 2014). Consequently, such properties of primitive CPCs may comprise their own ability to efficiently differentiate and restore lost CMs within the damaged heart, which lacks the complex paracrine environment and tight temporal and spatial control seen in developing