A Neurotrophic Factor Receptor GFRA2, a Specific Surface Antigen for Cardiac Progenitor Cells, Regulates the Process of Myocardial Compaction

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Keywords

GFRA2 · Surface antigen · Cardiac progenitor cells · Non-compaction cardiomyopathy

A surface marker specific for cardiac progenitors (CPs) allows the robust isolation of CPs, effectively circumventing the necessity of genetic modification. Recently, we have reported that glial cell line–derived neurotrophic factor receptor alpha 2 (*Gfra2*), which is anchored to the plasma membrane via Glycosylphosphatidylinositol, specifically marks CPs of both the first and second heart fields within the early mouse embryo [1], identified by single-cell expression profiling on mouse embryonic CPs (Fig. 56.1) [2, 3].

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Fig. 56.1 GFRA2 is a specific marker for CPs which governs myocardial compaction. *Upper case:* A signal transduction via GFRA1/2 is upstream of NOTCH signal that is indispensable for the myocardial compaction process. *Lower case:* GFRA2 is a specific surface antigen to identify CPs from differentiating pluripotent stem cells in mice and humans. This illustration is cited from Ishida, H et al. Cell Rep. 2016 Jul 26;16(4):1026–38, and is licensed under the Creative Commons Attribution 4.0 International License. To view a copy of this license, visit <http://creativecommons.org/licenses/by/4.0/> or send a letter to Creative Commons, PO Box 1866, Mountain View, CA 94042, USA

- GFRA2 facilitates the isolation of CPs by fluorescence-activated cell sorting from differentiating mouse and human pluripotent stem cells. If utilizing pan-mesoderm marker PDGFRA and hemangioblastic marker KDR in conjunction with GFRA2, multipotent CPs giving rise to cardiomyocytes, smooth muscle cells and endothelial cells are identified as GFRA2⁺/PDGFRA⁺/KDR⁺ whereas CPs already committed only to cardiomyocytes are identified as GFRA2⁺/PDGFRA⁺/KDR^{neg}.

- In loss-of-function of *Gfra2*, the functional redundancy of GFRA1 compensated for the cardiac GFRA2 signal in the mutant mouse embryos. Compound mutant of *Gfra1/2* showed non-compaction cardiomyopathy due to the down-regulation of NOTCH signal in the developing heart. Cardiac GFRA2 signal is distinct from the canonical pathway that depends on the RET tyrosine kinase and its established ligands.

Collectively our findings establish a platform for investigating the biology of CPs as a foundation for the future development of CP transplantation therapies for treating heart failure.

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