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FGF10 promotes regional foetal cardiomyocyte proliferation and adult cardiomyocyte cell-cycle re-entry

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Abstract

© The Author 2014. Aims Cardiomyocyte proliferation gradually declines during embryogenesis resulting in severely limited regenerative capacities in the adult heart. Understanding the developmental processes controlling cardiomyocyte proliferation may thus identify new therapeutic targets to modulate the cell-cycle activity of cardiomyocytes in the adult heart. This study aims to determine the mechanism by which fibroblast growth factor 10 (FGF10) controls foetal cardiomyocyte proliferation and to test the hypothesis that FGF10 promotes the proliferative capacity of adult cardiomyocytes. Methods and results Analysis of $Fgf10^{-/-}$ hearts and primary cardiomyocyte cultures reveals that altered ventricular morphology is associated with impaired proliferation of right but not left-ventricular myocytes. Decreased FOXO3 phosphorylation associated with up-regulated $p27^{kip1}$ levelswas observed specifically in the right ventricle of $Fgf10^{-/-}$ hearts. In addition, cell-type-specific expression analysis revealed that Fgf10 and its receptor, Fgfr2b, are expressed in cardiomyocytes and not cardiac fibroblasts, consistent with a cell-type autonomous role of FGF10 in regulating regional specific myocyte proliferation in the foetal heart. Furthermore, we demonstrate that in vivo overexpression of Fgf10 in adult mice promotes cardiomyocyte but not cardiac fibroblast cell-cycle re-entry. Conclusion FGF10 regulates regional cardiomyocyte proliferation in the foetal heart through a FOXO3/$p27^{kip1}$ pathway. In addition, FGF10 triggers cell-cycle re-entry of adult cardiomyocytes and is thus a potential target for cardiac repair.

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Keywords

Cardiac repair, Cardiomyocyte proliferation, Fibroblast growth factor 10, Heart development