Adult Cardiac Cell Renewal Depends on Resident Cardiac Stem Cells

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The epidemic of heart failure has stimulated interest in understanding cardiac regeneration. Intensive research and much controversy on the adult mammalian heart's capacity for self-renewal has finally brought a consensus that new cardiomyocytes are indeed formed throughout adult mammalian life. However, the physiological significance of this renewal, the origin of the new cardiomyocytes, and the rate of adult cardiomyocyte turnover are still highly debated. Evidence has been reported supporting regeneration via transplantation of multiple cell types as well as replication of post-mitotic cardiomyocytes. Concurrently, most mammalian adult tissues harbour a subpopulation of tissue-specific stem-progenitor cells that differentiate into some -or all- the parenchymal cells of their tissue of origin. Cardiac resident stem-progenitor cells in embryonic, neonatal and adult mammalian heart have been identified by different membrane markers (*c-kit, Sca-1, Abcg-2, Flk-1, PDGFR-α*) and transcription factors (*Isl-1, Nkx2.5, GATA4, Wt-1*) In particular, the adult myocardium harbours endogenous c-kit^{pos} cardiac stem-progenitor cells (eCSCs), which participate in adaptations to myocardial stress and when transplanted intra-myocardially regenerate most cardiomyocytes and microvasculature lost in an infarct. However, the relevance of eCSCs for regeneration remains controversial. Indeed, whether the c-kit^{pos}eCSCs are necessary and/or sufficient for the adult cardiac regenerative response to damage/injury has yet to be demonstrated. Using experimental protocols of severe diffuse myocardial damage which, unlike an experimental infarct, spares the eCSCs, combined with several genetic murine models and cell transplantation approaches, here we show that eCSCs restore cardiac function by regenerating lost cardiomyocytes. Ablation of the eCSC abolishes regeneration and functional recovery. The regenerative process is completely restored by replacing the ablated eCSCs with the progeny of one eCSC. eCSCs recovered from the host and re-cloned, retain their regenerative potential in vivo and in vitro. After regeneration, selective suicide of these exogenous CSCs and their progeny abolishes regeneration, severely impairing ventricular performance. These data show that c-kit^{pos} eCSCs are necessary and sufficient for the regeneration and repair of myocardial damage.