New Perspectives on Regeneration of the Heart

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De novo cardiomyocytes from within the activated adult heart after injury
Smart et al

Nature. 2011. doi:10.1038/nature10188

Can the adult mammalian heart regenerate and replace lost or damaged tissue? Textbooks suggest it cannot but recent studies suggest we may have to revisit this issue.

Until recently, regeneration of the heart was thought to be restricted to fish and amphibians. For instance, hearts of zebrafish can regenerate completely within just 2 months of surgical amputation of up to 20% of the ventricle. This occurs by proliferation and dedifferentiation of mature cardiac myocytes. By contrast, severe injury of the adult mammalian heart leads to the formation of scar tissue, which replaces damaged and lost cardiac myocytes. Interestingly, neonatal mammalian hearts were recently shown to have some regenerative capacity, not unlike zebrafish, although this was lost beyond 7 days of age. In the last decade, several studies have described evidence for cardiac stem cell populations within the postnatal mammalian heart, which appear able to form cells with cardiac myocyte properties in culture and after transplantation back into the heart (reviewed in Rasmussen et al). This has encouraged the search for ways to stimulate these endogenous cardiac stem cells to proliferate and differentiate into cardiac myocytes and vascular cells in situ to regenerate the injured heart even though their exact identity is unknown. In a recent study for example, Loffredo et al cleverly used genetically engineered mice to demonstrate at least some degree of endogenous myocardial replacement after an experimentally induced heart attack (myocardial infarction). Cardiovascular myocytes were permanently marked by green fluorescent protein (GFP) whilst non-cardiac myocytes were marked blue by β-galactosidase. Upon myocardial infarction (MI), new cardiac myocytes formed, some of which expressed GFP indicating they were derived by division of endogenous cardiac myocytes, whilst the majority were blue, indicating they were derived from a noncardiac myocyte progenitor population. Transplantation of some types of stem cells from bone marrow enhanced this process whilst others did not. Unequivocal demonstration of slow cardiac myocyte turnover coupled with de novo differentiation of endogenous progenitors to cardiac myocytes thus indicated 2 potential mechanisms of regeneration. This study did not, however, actually identify the endogenous progenitor cell population.

A study by Smart et al, however, equally elegant in its use of lineage tracing, may now have provided some clues on the identity of at least one of these progenitor populations contributing to endogenous repair. These are the cells of the epicardium, the epithelial sheet that enwraps the heart. Epicardial cells migrating into the heart muscle during development are crucial for the formation of compact myocardium and the differentiation of other cardiac cell types, such as fibroblasts and smooth muscle cells. However, molecular markers of epicardial cells, such as Wilm’s Tumor factor 1 (Wt1) or transcription factor Tbx18, are either not restricted to the epicardial layer or are not expressed in the adult heart. However, Smart et al found that the epicardial genes Wt1 and Tbx18 were upregulated after MI in the adult mouse heart. In particular, pretreatment (priming) with the naturally occurring peptide thymosin-β4 (Tβ4) enhanced expression of these genes in the epicardial and subepicardial layers. This allowed genetic labeling of the cells that express Wt1, so that their fate and contribution to the cardiac myocyte lineage could be mapped. Firstly, the authors showed that epicardial explants of Wt1+ cells from Tβ4 primed adult hearts expressed markers of cardiac progenitor cells, such as Isl-1 and Nkx2.5. These cells were able to mature further in culture into cardiac muscle cells with characteristic sarcomeric striations. However, the crucial question was whether endogenous Wt1+ cells would show this same cardiogenic potential in vivo. Wt1+ cells were therefore traced in Tβ4-primed mice that had undergone MI. Endogenous and transplanted Wt1+ labeled cells remained in the epicardial and subepicardial layers during the first few days following MI, but at 2 weeks these cells had formed cardiac myocytes in the border zone of the infarcted area. Although this process is currently very inefficient, with only a small fraction of Wt1+ cells able to form cardiac myocytes, it does suggest that epicardial progenitor cells do have this potential in adult mammalian hearts under the extreme circumstances of an MI and that drugs like Tβ4 can enhance this process. In a final experiment, they showed that pretreatment with Tβ4 before MI did in fact improve heart function compared with mice that were not pretreated, suggesting at least (partial) regeneration of the heart. Although the authors were unable to exclude a nonepicardial cell source for the Wt1+ progenitors, the experiments they performed support the idea that activated epicardial progenitor cells may be responsible for the increased cardiogenesis in response to cardiac injury.

The finding that the response to injury of the adult heart could be enhanced by Tβ4 is perhaps more exciting in terms of potential clinical application. It is worth noting that Tβ4 has already been shown to have protective effects in myocardial infarction in vivo, and that Tβ4 primes epicardial cells for cardiogenesis, with these cells then being recruited to the heart post MI in the absence of Tβ4 treatment. Further studies will be needed to determine whether Tβ4 pretreatment also enhances recruitment of these cells.

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of potential clinical relevance. Tß4 is expressed in many different organs and has direct effects on the actin cytoskeleton and the balance between monomeric and polymerized actin, which influences a myriad of cellular processes such as differentiation, proliferation, migration and survival. In addition to activating epicardial progenitor cells, Tß4 has other beneficial effects, which include improving cardiac myocyte survival and vascular repair. Furthermore, as expected by its broad expression pattern, Tß4 noncardiac tissues. For instance, Tß4 has anti-inflammatory properties, but it also affects proliferation, migration and metastasis of tumor cells. It therefore remains important to elucidate underlying molecular mechanisms so that new specific signalling pathways mediating regeneration can be identified that can mediate cardiac repair. Nevertheless, since pretreatment with Tß4 appeared crucial for significant activation of epicardial progenitor cells in mice, future studies would need to address whether similar responses to Tß4 could be expected in humans, perhaps by examining responses of human epicardial derived cells in culture or deriving these cells from pluripotent stem cells. Suitable human cells could also be used to screen for other compounds that upregulate Wt1 in human epicardial cells. Although it is perhaps unlikely that regeneration of cardiac tissue in humans will be as effective as in amphibians and fish, combined stimulation of resident stem and progenitor cells with scar-prevention or degradation may now be realistic options in the future.

References

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doi: 10.1161/RES.0b013e3182349a8a

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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