Divide to survive: myocardial regeneration and functional recovery after cell cycle activation in injured hearts

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This editorial refers to 'Cardiomyocyte cell cycle activation improves cardiac function after myocardial infarction' by Hassink et al.,10 pp. 18–25, this issue.

Necrotic and apoptotic cell deaths are the two main causes of the heart’s loss of cardiac tissue and haemodynamic function after myocardial infarction (MI). The loss of functional cardiac myocytes through necrotic/apoptotic processes during ischaemia in the absence of de novo cell proliferation has been postulated to be a fundamental cause of ventricular remodelling, increased tissue fibrosis, and diminished ventricular pump function.

In the past decade, several approaches have been tested hoping to increase the number of myocytes after MI, including transplantation of progenitor or adult cells,1 mobilization of endogenous stem cells,2 and cell cycle activation.3 Each of these approaches demonstrated some degree of myocardial functional improvement, with cell cycle activation being the most promising one.4

Although there is evidence for adult cardiomyocyte proliferation,4 it is clear that this process is not capable of fully recovering the damaged heart, partially because cell division after DNA synthesis must progress through restriction check points. Cell division check points are highly regulated, with appropriate requisites, such as genome and organelle duplication, chromosome segregation, and DNA integrity.

Restriction check point transit is controlled by the activity of cyclin-dependent kinases (CDKs) and their co-factors, the cyclin proteins (cyc). Thus, recent experiments have aimed to modulate CDKs/cyc activity in order to promote sustained cell division. Adenoviral expression of cyclin A1 has been shown to increase myofilament density and myocardial function.5 Targeted expression of cyclin A2 appears to augment endogenous regenerative mechanisms via induction of a side population cells with enhanced proliferative capacity.6 Cardiac-restricted expression of cyclins D1, D2, or D3 resulted in increased DNA synthesis, although only D2-expressing mice retained this feature after MI.7,8 Accordingly, low levels of expression of cyclins resulting from downregulated transcription factors (such as lower cyclin D1 expression due to downregulation of the KLF transcription factor family) have been suggested to underlie proliferation defects in embryos and might be related to impaired cell proliferation after MI.9

Extending the group’s previous studies with the expression of cyclin D proteins,7,8 Hassink et al.10 present an article that contributes towards the development of a clinical strategy to promote cardiac tissue regeneration and functional recovery after MI. The data show that transgenic mice expressing cyclin D2 (cycD2) under the transcriptional regulation of the cardiac myosin heavy chain (MHC) promoter display a progressive reduction in infarct size when compared with non-transgenic animals. Most prominently, hearts analysed 180 days post-MI showed a significant reduction of left ventricle infarcted area (~56% vs. 35% for non-transgenic vs. transgenic animals). Interestingly, MHC-driven expression of cycD2 was not acutely cardioprotective, as measured by the presence of similar infarct size in MHC-cycD2 and non-transgenic hearts 7 days post-MI.

Hassink et al.10 also show that cardiomyocytes with well-structured sarcomeres were found to replace large portions of scar tissue in the apical regions of the heart. More importantly, these newly formed cardiomyocytes expressed connexin43 (a major component of gap junctions) and were coupled to the remote myocardium in a functional syncytium. This feature was demonstrated by intracellular calcium transient imaging in vivo using two-photon molecular excitation laser scanning microscopy. The imaging results show that cells in the newly formed myocardium exhibited the characteristic spontaneous increase in intracellular calcium concentrations evoked by regular action potential

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stimuli. The authors also demonstrate a progressive improvement in several haemodynamic parameters in MHC-cycD2 mice compared with sham-operated animals, particularly 180 days post-MI. Namely, substitution of new and physiologically healthy myocardium for scar tissue in transgenic animals showed a direct correlation with the reduction in infarct size and improvement in the heart’s functions. It should also be noted that disorganized tumour-like growth was not observed, although increased cell cycle activity persisted in aged MHC-cycD2 mice.

Undoubtedly, the use of constitutively active promoters targeting cell proliferation-related genes is not the most appropriate therapeutic strategy. However, it clearly serves the purpose of experimentally proving the concept that enhanced cell proliferation can be a tool for myocardial regeneration and functional recovery in injured hearts.

Conflict of interest: none declared.

References