Review

Cell Therapy for Heart Disease: Great Expectations, As Yet Unmet

Christof Stamm, MD [a,c,*], Boris Nasseri, MD [a], Yeong-Hoon Choi, MD [b] and Roland Hetzer, MD [a,c]

[a] *Deutsches Herzzentrum Berlin, Cardiothoracic Surgery, Berlin, Germany*
[b] *University of Cologne, Cardiothoracic Surgery, Cologne, Germany*
[c] *Berlin-Brandenburg Center for Regenerative Therapies – BCRT, Berlin, Germany*

Regenerative medicine is often touted as an achievement of the new millennium, but many approaches to improve health by stimulating the organism's own capacity for healing have existed for a long time. Some components of today's regenerative medicine, however, are indeed fundamentally new developments, and one of those is the concept of increasing the number of contractile cells in the heart to cure heart failure, either by stimulating intrinsic regeneration processes or by transplanting exogenous cells. The aim of this paper is to review the current status of some key aspects of cell therapy and obstacles to clinical translation.

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It has long been assumed that the heart has no intrinsic muscular regeneration capacity, because cardiomyocytes permanently and irreversibly rest in the G_1/G_0 phase of the cell cycle (Fig. 1). Although this view has recently been challenged by experimental and clinical data that indicate a substantial cellular turnover in the myocardium as well as the existence of specific cardiac stem cells, the heart's overall capacity for self-regeneration is clearly insufficient in most patients [1–13]. Until the 1990s, strategies to stimulate myocardial regeneration have mainly focussed on blood vessel growth by pro-angiogenic growth factors, either by directly delivered proteins or by transfection with respective genes. So far, both have had very limited clinical success. Since the early 1990s, the concept of using transplanted cells for regeneration of diseased myocardium has found tremendous echo, but its clinical efficacy is still controversial. Our group has been involved in the clinical translation of myocardial cell therapy since 2001. Faced with an increasing number of patients with end-stage heart failure and limited therapeutic options, we attempt to incorporate clinical studies with different cell products in our cardiac surgical practice. By doing so, we have had encouraging experiences, but have also encountered numerous obstacles that slow the progress of cardiac regenerative medicine. In the following, we briefly discuss the different experimental and clinical strategies to cell-based cardiac regeneration from the clinician's point of view.

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* Corresponding author at: Deutsches Herzzentrum Berlin, Cardiothoracic Surgery, Berlin, Germany. Tel.: +49 30 4593 2109.
E-mail address: stamm@dhzb.de (C. Stamm).

Experimental Cell Therapy

Transplanting Contractile Cells

The primary goal of cardiac cell therapy is to increase the number of contractile cells in the ventricular myocardium to improve systolic heart function. Additional possible actions of cell therapy in the heart include paracrine effects supporting angiogenesis, modulation of extracellular matrix components, supportive effects on cardiomyocytes suffering from ischaemic stress, and stimulating interactions with resident cardiac progenitor cells (Fig. 2). Originally, immortalised myocyte lines and neonatal cardiomyocytes were used for transplantation experiments [14–16], and the notion that exogenous contractile cells may be able to incorporate in postnatal myocardium was revolutionary. At the same time, it became clear that transplanted cardiomyocytes will not survive in terminally ischaemic tissue. A solution to this problem seemed to be the use of skeletal muscle progenitor cells [14,17], which have a high tolerance to ischaemia and maintain contractile work even through prolonged periods of anaerobic metabolism. Clinical myoblast transplantation as part of a surgical procedure was introduced in 2001 [18]. Initial feasibility studies were promising and laid the foundation for an avalanche of cell therapy studies, but it soon became clear that skeletal myoblasts cannot couple electrically with surrounding cardiomyocytes because they do

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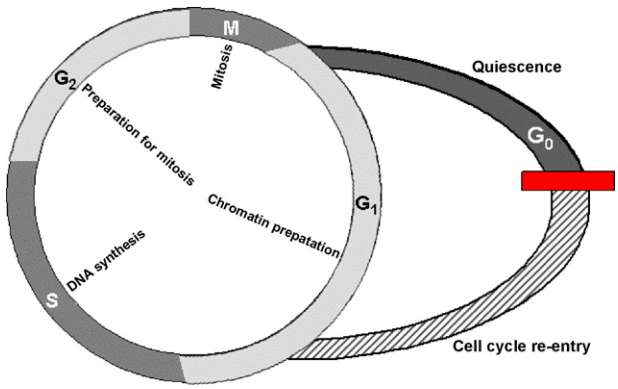

Figure 1. *Schematic illustration of the cell cycle. Postnatal cardiomyocytes leave the cell cycle in the G_1 phase and rest permanently in replicatory quiescence, the so-called G_0 phase. It is commonly believed that the cell cycle re-entry block (red) cannot be overcome during adulthood, so that cardiomyocyte proliferation in response to disease is impossible. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)*

not express the intercellular communication protein connexin 43. Thus, they do not form "connexon" ion channels that are typical for cardiomyocytes [19], which maintain their single-cell integrity but connect with adjacent cells via gap junction connexons to form a functional syncytium for propagation of excitation. In contrast, skeletal myoblasts and their progeny fuse to form multinucleated myofibers and connect with one specific motoneuron, prerequisite for the fine control of skeletal muscle contractile force. Therefore, skeletal myofibers remain isolated from the surrounding myocardium and may act as arrhythmogenic foci. Some investigators report that they have never encountered arrhythmia problems [20]. However, given that the observed improvement in contractility is, at best, very mild, many clinicians have abandoned skeletal myoblasts for the treatment of heart failure.

Cardiac Stem Cells

The presence of myogenic progenitors in skeletal muscle has long been known, but similar progenitor cells in the postnatal myocardium were deemed impossible. However, recent experimental data indicate that several types of cardiac muscle stem cells exist and might be involved in physiologic regeneration processes [8]. In rodents, CSC populations have been described based on expression of c-kit, Sca-1 and Isl-1 in combinations with the presence or absence of other surface markers [9,10]. As Torella et al. have pointed out [8], these are probably phenotypic variations of a unique cell type, with the exception of Isl-1+ cells in the right heart that may be remnants of the cardiac primordia. Rodent cardiac stem cells have been expanded *ex vivo* and successfully used for heart muscle regeneration in myocardial infarction models. Other groups isolated c-kit+ CSCs from human myocardium, confirmed their cardiomyogenic differentiation potential *in vitro* and successfully applied them to experimental *in vivo* models [1,11–13]. In addition to the myocardium and its resident progenitors, the pericardium, epicardium and the subepicardial adipose tissue also seem to contain precursor cells that might be useful for cardiac regeneration therapies. For example, Limana et al. identified c-kit+ and CD34+ cells in mouse and human epicardium that can acquire an endothelial phenotype *in vitro* and proliferate and migrate in response to myocardial infarction

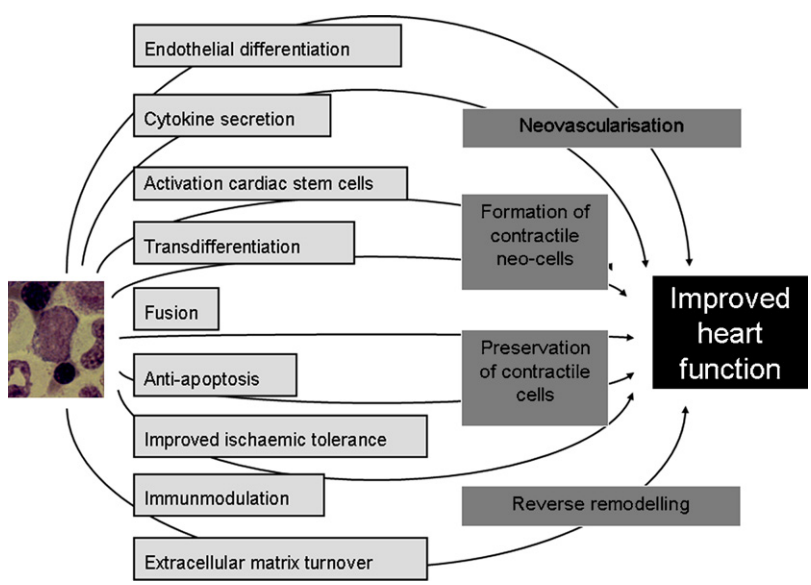

Figure 2. *Possible effects of marrow-derived stem cells on ischaemic myocardium. Not every mechanism has been directly observed with every subtype of bone marrow stem cells, especially myogenic transdifferentiation of haematopoietic stem cells is a highly controversial topic. Many proponents of cardiac cell therapy believe that, in summary, the different cell therapy-induced changes in the myocardium result in a net improvement of function. On the other hand, opponents argue that one must first identify an exact mechanism-of-action in experimental studies before clinical trials are justified.*