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Review article

Cell therapy for human ischemic heart diseases: Critical review and summary of the clinical experiences

Noemi Pavo [a], Silvia Charwat [a], Noemi Nyolczas [a], András Jakab [b], Zsolt Murlasits [c], Jutta Bergler-Klein [a], Mariam Nikfardjam [a], Imre Benedek [d], Teodora Benedek [d], Imre J. Pavo [a], Bernard J. Gersh [e], Kurt Huber [f], Gerald Maurer [a], Mariann Gyöngyösi [a,*]

[a] Department of Cardiology, Medical University of Vienna, Austria
[b] Department of Biomedical Laboratory and Imaging Science, Faculty of Medicine, University of Debrecen, Debrecen, Hungary
[c] Exercise Biochemistry Laboratory, The University of Memphis, Department of Health and Sport Sciences, Memphis, TN, USA
[d] Department of Cardiology, University of Medicine and Pharmacy Tirgu Mures, Romania
[e] Internal Medicine, Mayo Graduate School of Medicine, Mayo Clinic, Rochester, MN, USA
[f] 3rd Dept. Cardiology and Emergency Medicine, Wilhelminen hospital, Vienna, Austria

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ABSTRACT

A decade ago, stem or progenitor cells held the promise of tissue regeneration in human myocardium, with the expectation that these therapies could rescue ischemic myocyte damage, enhance vascular density and rebuild injured myocardium. The accumulated evidence in 2014 indicates, however, that the therapeutic success of these cells is modest and the tissue regeneration involves much more complex processes than cell-related biologics. As the quest for the ideal cell or combination of cells continues, alternative cell types, such as resident cardiac cells, adipose-derived or phenotypic modified stem or progenitor cells have also been applied, with the objective of increasing both the number and the retention of the reparative cells in the myocardium. Two main delivery routes (intracoronary and percutaneous intramyocardial) of stem cells are currently used preferably for patients with recent acute myocardial infarction or ischemic cardiomyopathy. Other delivery modes, such as surgical or intravenous via peripheral veins or coronary sinus have also been utilized with less success. Due to the difficult recruitment of patients within conceivable timeframe into cardiac regenerative trials, meta-analyses of human cardiac cell-based studies have tried to gather sufficient number of subjects to present a statistical compelling statement, reporting modest success with a mean increase of 0.9-6.1% in left ventricular global ejection fraction. Additionally, nearly half of the long-term studies reported the disappearance of the initial benefit of this treatment. Beside further extensive efforts to increase the efficacy of currently available methods, pre-clinical experiments using new techniques such as tissue engineering or exploiting paracrine effect hold promise to regenerate injured human cardiac tissue.

Contents

* Corresponding author at: Department of Cardiology, Medical University of Vienna, Währinger Gürtel 18–20, A-1090 Vienna, Austria. Tel.: +43 1 40400 4614; fax: +43 1 40400 4216.
E-mail address: mariann.gyongyosi@meduniwien.ac.at (M. Gyöngyösi).

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1. Evolution of the cardiac tissue regeneration

Treatment of patients with cardiovascular disease in concert with improvement in outcomes has advanced considerably in recent decades. The incidence of cardiac adverse events, such as death, acute myocardial infarction (AMI), or cardiovascular-disease–related hospitalizations, have shown marked declines, in part because of better primary and secondary preventive strategies or the introduction of invasive (eg, primary percutaneous coronary intervention) or non-invasive (eg, new antithrombotic regimens) treatments, to achieve and maintain patency of the diseased coronary arteries. With these advances, the focus of innovation has partially shifted from managing acute cardiac manifestations to treatment of chronic cardiac disease and heart failure with the attempt of regeneration of the ischemic injured cardiac tissue [1].

The evidence of the trans-differentiation of multipotent cells of diverse origin into cardiomyocyte or cells with surface markers of early cardiomyocytes [2,3] stimulated an increased interest in the field of human cardiac regeneration. Furthermore, mitotic myocytes and accumulated bone marrow (BM) – and peripheral blood-originated stem and progenitor cells in the transplanted heart [4,5] or ischemic injured myocardium [6] have been found by confocal microscopy with undoubting evidence of self-regenerating capacity (even if the mitotic rate is low) of the cardiac tissue [7,8].

Almost two decades ago, the discovery of early commitment cells with the ability to form myocytes [9] triggered an intensive search for regenerative cells in the cardiovascular system. Encouraging preclinical study results led to the initiation of early clinical trials for the repair of ischemic-injured myocardium using specific cell types. The aims of the present review are to provide a critical overview of clinical cell-based therapies used in patients with ischemic heart disease, from laboratory studies to early and current clinical applications, and to discuss new directions and perspectives in cardiac regeneration.

1.1. Regenerative cell types in cardiac repair provoking clinical cell-based studies

Chiu et al. reported differentiation of satellite cells (undifferentiated *myoblasts*) into cardiac-like cardiomyocytes, leading to successful cellular cardiomyoplasty [3], which initiated clinical studies injecting autologous skeletal myoblasts administered either surgically [10] or by percutaneous intramyocardial method [11,12]. The recognition of the intrinsic arrhythmogenicity and the inability of integration of these cells into the myocardial milieau suggested another mechanisms of the reparative effect of these cells [13].

In the early 2000, Orlic et al. and the Anversa groups demonstrated several BM cell clusters (eg, Lin negative c-kit positive) capable of myogenic differentiation and expression of transcription factors, such as myocyte enhanced factor (MEF), GATA4 and Nkx2.5 [14–16]. These cells have been shown to transdifferentiate also into endothelial cells and smooth muscle cells in murine myocardial infarction [15]. Further BM-derived stem cells (endothelial progenitors, angioblasts or CD34+ cells) proved to be also angiogenic, promoting neovascularization in the ischemic myocardium [15]. Kocher et al. reported neovascularization of the infarcted mice heart by giving human *BM-derived angioblasts* intravenously and demonstrated improved cardiac function [17].

Furthermore, a population of *immature hematopoietic progenitor cells (called side population cells)* (Lin- c-kit + Sca-1+) has been found to be capable of myogenic differentiation [18]. The more committed BM-origin *hematopoietic stem cells* are multi-potent stem cells that give rise to the myeloid and lymphoid blood cell types, characterized by their small size and lack of lineage marker (Lin-), but expressing c-kit, CD34+ and CD133+. This heterogeneous cell population is thought to play a role in the regeneration of myocardium, as early-stage cardiac myogenic differentiation was demonstrated, in contrast with the BM-origin *circulating endothelial progenitor cells (EPC)* expressing CD45+ and CD34+, which regenerate only vascular smooth muscle cells and endothelial cells [2,8]. However, if human EPCs were co-cultured with rat cardiomyocytes [19,20], they were able to transdifferentiate functionally active cardiomyocytes [19,20].

When BM cells were mobilized by stem cell and granulocyte-colony stimulating factors (G-CSF) due to an ischemic and probably chemoattractive signal from the infarcted myocardium, they demonstrated homing to the border zone of infarction resulting in cardiac repair evidenced by dividing myocytes and improved left ventricular (LV) function and survival [14].

These pre-clinical findings on the cardiac regeneration capacity of the BM-origin stem cells prompted the first clinical studies using unselected *BM-origin mononuclear cells (MNCs)* for human cardiac repair in patients with recent AMI [21]. The first clinical studies reported by Strauer et al. were followed by randomized studies using unselected BM MNCs or EPCs (REPAIR-AMI, TOPCARE-AMI) in patients with AMI [22–29] or ischemic cardiomyopathy (TOPCARE-CHD) [30].

In order to achieve higher efficacy, selected BM-origin CD34+ or CD34+/CD133+ cells were injected intracoronary in patients with acute AMI, with similarly modest success, proven by the REGENT [31] and AMR-001 [32] trials. The Phase 3 RENEW trial included approximately 100 patients with chronic ischemic cardiomyopathy, and randomized patients to receive G-CSF-mediated mobilized selected CD34+ cells percutaneously intramyocardially in the active arm [33], *before premature stop of the study due to slow inclusion rate.*

Based on the uncertainty regarding the best cell type for cardiac repair, unselected BM-MNCs containing heterogeneous mononuclear cell population were chosen for cardiac repair in the majority of the early clinical studies. On the other side, the majority of the BM MNCs are lymphocytes, but BM contains also other mononuclear cell populations, such as monocytes, pericytes, pre-adipocytes or osteoblasts (which cells are undesirable in the ischemic injured myocardium), and only 1% of the extracted and infused BM stem cells are the preferred hematopoietic stem cells [34], raising doubt as to/whether BMSC will survive the test of time; the currently on-going European multicenter BAMI trial (clinical trials gov identifier: NCT01569178) will give the final answer.

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