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Review

The Evolution of the Stem Cell Theory for Heart Failure

Jean-Sébastien Silvestre [a,*], Philippe Menasché [a,b,**]

[a] INSERM UMRS 970, Paris Cardiovascular Research Center, Université Paris Descartes, Sorbonne Paris Cité, Paris, France
[b] Assistance Publique-Hôpitaux de Paris, Hôpital Européen Georges Pompidou, Department of Cardiovascular Surgery, Paris, France

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ABSTRACT

Various stem cell-based approaches for cardiac repair have achieved encouraging results in animal experiments, often leading to their rapid proceeding to clinical testing. However, freewheeling evolutionary developments of the stem cell theory might lead to dystopian scenarios where heterogeneous sources of therapeutic cells could promote mixed clinical outcomes in un-stratified patient populations. This review focuses on the lessons that should be learnt from the first generation of stem cell-based strategies and emphasizes the absolute requirement to better understand the basic mechanisms of stem cell biology and cardiogenesis. We will also discuss about the unexpected "big bang" in the stem cell theory, "blasting" the therapeutic cells to their unchallenged ability to release paracrine factors such as extracellular membrane vesicles. Paradoxically, the natural evolution of the stem cell theory for cardiac regeneration may end with the development of cell-free strategies with multiple cellular targets including cardiomyocytes but also other infiltrating or resident cardiac cells.

Contents

Heart failure (HF) is a leading cause of mortality worldwide and a major problem of global health causing around 5% of the acute hospital admissions and accounting for around 10% of hospitalized patients in Europe and the United States. Importantly, the number of patients with HF is steadily increasing, as a consequence of an aging population and/or enlarging prevalence of cardiovascular risk factors such as diabetes (Gilbert and Krum, 2015) and improved survival rates after acute myocardial infarction (MI) putting a greater number of patients at risk of developing a late left ventricular dysfunction. Nevertheless, long-term survival has improved with recent medical therapies aiming at reducing cardiac overload and neurohumoral activation, as well as mineralocorticoid deregulation. Significant advances have also been achieved through surgical revascularization strategies including percutaneous coronary angioplasty and coronary artery bypass grafting. Current strategies for treating end-stage HF are based on replacing or supporting the failing heart by cardiac transplantation or left ventricular assist devices.

* Correspondence to: J.-S. Silvestre, INSERM UMRS 970, Paris Cardiovascular research Center, Université Paris Descartes, Sorbonne Paris Cité, Paris, France.
** Corresponding author.
E-mail addresses: jean-sebastien.silvestre@inserm.fr (J.-S. Silvestre), philippe.menasche@aphp.fr (P. Menasché).

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However, more than 50% of HF patients die in 4 years after diagnosis and 40% of them perish or are readmitted to hospital within the first year. The poor prognosis of symptomatic HF is likely associated with the limited long-term efficacy of conventional therapeutic strategies on the underlying ongoing loss of cardiomyocytes, which is followed by the deleterious formation of a fibrotic scar in the failing heart.

Over the last decade, the classical paradigm that the human heart is a post-mitotic and terminally developed organ with no cell renewal capability has been undermined with the demonstration that cardiomyocyte turnover can occur in adult mammals, including humans (Sahara et al., 2015; Bergmann et al., 2009; Bergmann et al., 2015). However, such inherent capability of humans to regenerate myocardium with aging or after injury in adulthood is entirely insufficient to fully compensate for the loss of function associated with these conditions. Such statement confronts the scientific community with a unique and exciting challenge: can we enhance the regenerative capacity of cardiac tissue to abrogate adverse ventricular remodeling? Consistent with this, multiple different approaches have been developed to promote cardiomyocyte regeneration/proliferation in human injured hearts, including transplantation of autologous non-cardiac/cardiac somatic stem cells, injection of in vitro-derived cardiomyocytes, direct reprogramming of cardiac fibroblasts into cardiomyocytes in vivo, stimulation of dedifferentiation/proliferation of resident cardiomyocytes, and activation of endogenous cardiac progenitor cell populations. These therapeutic strategies, classified as either cell-based or cell-free, are currently being investigated for their cardiac repair potential and clinical application.

In particular, various cell-based approaches for cardiac repair have achieved encouraging results in animal experiments, often leading to their rapid proceeding to clinical testing. Although a multitude of clinical trials have been performed to date, their results remain ambiguous and no single-cell-based therapy for heart disease has been conclusively proven effective so far (Behfar et al., 2014). As a prototypic example of such controversy, two recent meta-analysis of cell-based therapy one in chronic HF (Fisher et al., 2015) and one in patients with acute MI (Gyongyosi et al., 2015) result in entirely different conclusions. In the meta-analysis of 31 randomized cell therapy trials in HF which included 1521 patients, exercise capacity, left ventricular ejection fraction and quality of life are improved in the treated patients (Fisher et al., 2015). In contrast, a second meta-analysis based on individual patient data reveals that cell therapy does not impact cardiac function and remodeling as well as the clinical outcome in patients with acute MI (Gyongyosi et al., 2015).

Such controversies prompt us to suggest that we need to step back in the natural evolution of the stem cell theory for therapeutic use and go "back to the trees" as claimed by the anti-progressive character from the famous novel of Roy Lewis (The Evolution Man). In other words, we need to go back to the root of stem cell biology and the concept of regenerative medicine. A clear understanding of stem cell biology and HF etiology may help researchers and clinicians in the field to provide definite evidences for stem cell efficacy in patients.

1. The Quest for the Ideal Source of Stem Cells With Regenerative or Cardiogenic Potential

There are a myriad of unresolved questions related to cell handling and preparation, repair ability of the failing heart (inflammatory status, timing of injection, endogenous cardiogenic and angiogenic potential), mode of cell delivery, clinical endpoints as well as methodologies used to assess those endpoints and this list is not exclusive.

Above all, there is no consensus on the basic question: which cell type to transplant, to improve efficacy and safety? The majority of trials used adult stem cells and mainly applied total bone marrow-derived mononuclear cells, bone marrow-derived marker selected cells or granulocyte-colony stimulating factor mobilized mononuclear cells (Silvestre et al., 2013). However, adult stem cells show a restrictive plasticity and more importantly most of the cardiovascular risk factors such as hypertension, diabetes, aging and active smoking have been shown to reduce the therapeutic potential of transplanted bone marrow-derived cells (Govaert et al., 2009; Ayala-Lugo et al., 2011; Ebrahimian et al., 2006; You et al., 2008; Roncalli et al., 2011). In addition, operating procedures to isolate these bone marrow derived cells are not standardized. Some of the trials used Ficoll-gradient, sedimentation or automated systems to isolate bone marrow cells. This may lead to profound heterogeneity in the therapeutic efficiency since cell isolation protocols have a major impact on the functional activity of medullary cells (Seeger et al., 2007). Consistent with this, bone marrow-derived cells stored in non-buffered saline supplemented with heparin, display reduction in their homing and functional activity even in animal models (Seeger et al., 2012). Other trials applied bone marrow-derived mesenchymal stem cells (Mathiasen et al., 2015;Hare et al., 2012; Heldman et al., 2014), bone marrow-derived mesenchymal stem cells exposed to a cardiogenic cocktail (Bartunek et al., 2013), skeletal myoblast-derived cells (Menasche et al., 2008) or adipose tissue-derived mesenchymal stem cells (ADSCs) (Perin et al., 2014; Houtgraaf et al., 2012). This latter source of therapeutic cells is also a good illustration of anticipated heterogeneity in future clinical trials. Adipose tissue-derived stem cells can be obtained from subcutaneous adipose tissues with the use of collagenase digestion. However, freshly isolated cells, also defined as the stroma vascular fraction (SVF), are known to be heterogeneous and contain hematopoietic cells and should be distinguished from ADSCs obtained after culture on plastic dishes. ADSCs, but not SVF, show a therapeutic effect in ischemic tissue in both mice and humans with critical limb ischemia (Planat-Benard et al., 2004; Lee et al., 2012b). In addition the source of fat has been shown to dictate human ADSCs reparative activity (Naftali-Shani et al., 2013).

Although, there are many examples of therapies that appeared promising in animal studies, but which failed in the clinics, all lessons from experimental works should at least be considered before taking any definitive conclusions on this first generation of cell therapy. Very few studies attempt to rigorously compare the therapeutic potential of different sources of stem cells. Nevertheless, the best cardiac outcomes seem to be achieved by therapeutic cells obligated to a cardiomyocyte lineage. Hence, in experimental studies which have compared different cell types, cardiac-committed cells (c-kit$^+$ or Sca-1$^+$ cardiac stem cells, cardiospheres, induced pluripotent stem cell-derived cardiomyocytes) display greater therapeutic effects compared to those of cells not committed to a cardiac lineage such as bone marrow mononuclear cells, mesenchymal stem cells or skeletal myoblasts (Rossini et al., 2011; Oskouei et al., 2012; Li et al., 2012; Zheng et al., 2013; Citro et al., 2014). Of note, the superiority of cardiac-committed cells could be evidenced on the basis of various end points such as better engraftment, reduced extent of infarction and fibrosis, increase in angiogenesis, improvement of cardiac function and even mitigation of ventricular arrhythmias. In line with these observations, cardiac-committed cell therapies are being tested in the clinics using cardiosphere-derived cells obtained from a right ventricular biopsy (Makkar et al., 2012), c-kit$^+$ cardiac progenitor cells grown from an intra-operatively harvested right appendage biopsy (Chugh et al., 2012; Bolli et al., 2013) and embryonic stem cell-derived cardiac progenitors (Menasche et al., 2015) which are currently tested in a pilot safety trial. Of interest, in a mouse model of acute MI, cardiosphere-derived cells isolated from HF patients led to the greatest therapeutic benefit with the highest left ventricular ejection fraction when compared to cells isolated from non-failing donors, suggesting that the overall efficacy of this stem cell approach is not necessarily dampened by the extent of the underlying left ventricular dysfunction (Cheng et al., 2014). Human-induced pluripotent stem cells are another potentially unlimited source for generation of cardiomyocytes (iPSC-CMs). However, current protocols for iPSC-CM derivation face several challenges, including variability in somatic cell sources and inconsistencies in cardiac differentiation efficiency. In addition, the overall therapeutic effect of the pluripotent stem cell-derived progeny may also depend on the degree of maturity of the stem/