Stem Cells Therapy for Ischemic Heart Disease

Nicola Pradegan and Gino Gerosa

1 Introduction

With more than 17 million deaths worldwide each year, IHD caused by coronary artery disease is the most common cause of death and a major cause of hospital admission in developed countries. In Europe, IHD is the main cause of death among women >50 years of age and men [1, 2].

Conventional therapies have significantly reduced mortality of acute IHD, leaving an increasing number of patients with chronic IHD and/or HF without further treatment options. An increasing morbidity rate of this nature in an aging population is a huge burden for current society. HF is an expensive disease, both in terms of financial burden ($30 billion/year in medical expenditures in the US) and reduced quality of life and workdays lost [3]. Although HF survival has improved since 1979, the death rate remains very high, with more people dying of cardiac disease than cancer and chronic lower respiratory disease combined. Therapies aimed at restoring the billions of cardiomyocytes lost during myocardial infarction or damaged by nonischemic cardiomyopathies are sorely needed.

Among different medical strategies developed in the last decades to relieve symptoms, prevent disease progression, and improve survival and quality of life, stem cells therapy has emerged as a promising therapeutic approach to promote myocardial repair and regeneration. Cardiovascular disease is perhaps the field with the most clinical research on cell-based therapeutics, with over 200 clinical trials since 2001 examining multiple stem cell products for a diverse array of cardiac syndromes. Despite this extensive body of

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research, stem cell therapy has yet to transition from research to practice, as there is no definitive evidence of an efficacious cell product.

With this chapter, we aim to overview the biology of stem cell types used in cardiovascular research, and current preclinical and clinical applications regarding stem cells use in acute and chronic IHD.

2 Stem Cells Source

Stem cells are undifferentiated cells defined by their capacity for both self-renewal and ability to differentiate into other mature cell types. While embryonic stem cells are the prototypical pluripotent stem cells, capable of becoming any other cell type in an embryo, there are numerous stem cells populations found in adult tissues. These adult stem cells have a more limited differentiation potential and generally exist to maintain tissue homeostasis and replenish lost cells from that particular tissue. Some of these adult stem cells can naturally (albeit rarely) transdifferentiate to form cells outside of their original tissue of origin.

Several studies have shown that various cell types exerted beneficial effects on cardiac repair. Overall stem cells effect is summarized in Fig. 1.

- **Skeletal myoblast** was the first cell type to be clinically tested, but the efficacy was unsatisfactory mainly due to the high incidence of arrhythmias [4].
- **Bone marrow-derived mononuclear cell** contains the undifferentiated HSC and MSC as well as other committed cells in various stages of maturation. Its abundance and easy

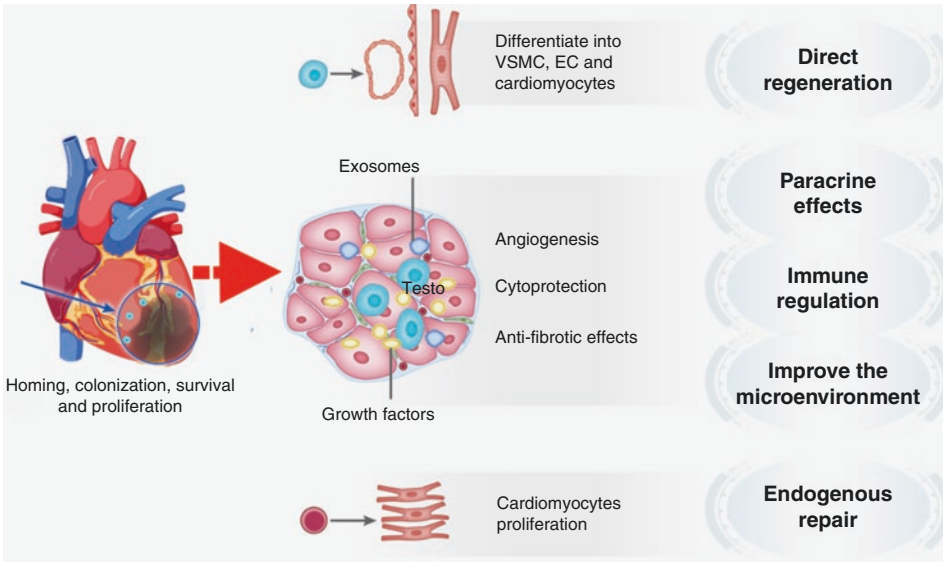

Fig. 1 Stem cells effect on cardiac remodeling and function

accessibility allow for autologous implantation without expansion in tissue culture, which avoids the decline of stem cell differentiation and migration ability, and reduces the incidence of immune rejection. Preclinical studies show discordant results in terms of angiogenesis and left ventricle function among different animal models [5–10]. Clinically, BMMNCs have been evaluated both for AMI and ischemic heart failure. In AMI, intracoronary delivery of autologous BMMNCs were evaluated in the REPAIR-AMI clinical trial: this was a large, phase III, double-blinded, placebo-controlled study designed to determine the therapeutic efficacy of BMMNCs. There were 204 patients randomized to receive either cells or placebo 3–7 days following AMI. Initial results at 4-months were encouraging, with LVEF significantly improved in the BMMNC-treated group by 5.5% on average, whereas the placebo-treated group exhibited a 3.0% in increase in LVEF. At 1-year, there were some encouraging signs. There were fewer myocardial infarctions, less need for repeat revascularization and fewer incidences of death in the BMMNC compared to the placebo group [11]. However, a longer follow-up analysis (5-year follow-up) found out that, despite a preserved benefit on mortality, improvement in LVEF was not maintained [12]. These mid-term results were also highlighted by other clinical experiences which did not find any significant improvement of myocardial function after BMMNCs administration in AMI (e.g., TIME trial [13], LateTIME trial [14], SWISS AMI trial [15], BOOST-2 trial [16], MiHeart/AMI trial [17]). In patients with post-ischemic HF, results have been more promising: in fact, a recent meta-analysis reports a mean improvement of 4.33% in LVEF as well as reductions in left ventricle volumes after MBBNCs injection in patients with post-ischemic HF [18]. This analysis suggested that overall BMMNCs for post-ischemic cardiomyopathy appear to produce positive effects on cardiac function and remodeling.

- **Hematopoietic stem cell** has multiple differentiation potentials and can be autologously transplanted, but they are limited in abundance, which leads to poor efficacy [19].
- **Endothelial progenitor cells** are isolated from peripheral blood and bone marrow and can give rise to vascular cells. Clinical application of EPC transplantation is expected to increase the capillary density and subsequently improve the microcirculation around the transplanted sites in infarcted heart. Studies have showed that EPC transplantation can also improve heart function, but its effect is restricted, which may result from its weak differentiation ability [20].
- **Embryonic stem cells** have strong proliferation and differentiation capabilities, but it has ethical controversies and high risks of teratoma formation, which create hurdles to its clinical translation [21].
- **Induced pluripotent stem cells** can differentiate into multiple cell types, are anti-inflammatory, and have therapeutic potential to repair tissues following ischemic disease. They have great proliferative capacity and might have the potential to be a major source for cardiac repair, but preclinical studies are needed to assess potential tumor formation and other safety issues [22, 23].

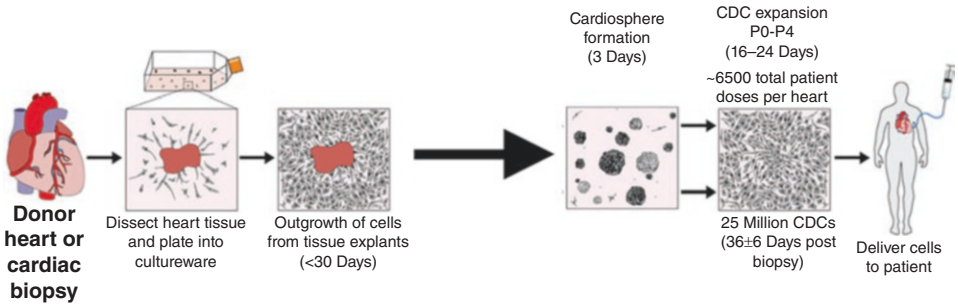

Fig. 2 Laboratory pathway to obtain cardiosphere-derived cells

- **Cardiosphere-derived cells**: The discovery of small clusters of heart cells expressing stem cell antigens (originally called "side population"—SP) capable of symmetric (self to identical self) or asymmetric (self to differentiated daughter progeny) division prompted the enthusiastic declaration that in situ, adult stem cells exist and such cells might have therapeutic potential. These in situ stem cells have been obtained by cardiac biopsies and then expanded in particular cultures to generate the CDCs (Fig. 2), which have clonogenic potential and express markers indicative of progenitor/stem cell identity [24]. To date, several trials have already tested this new population of cells. The CADUCEUS trial was the first to determine if intracoronary injection of autologous CDCs to patients soon after myocardial infarction was safe [25]. At 1 year of follow-up, CDC-treated patients had smaller scar sizes, increased viable myocardium, and improved regional function compared to control patients. A subsequent study using allogenic CDCs also confirmed the positive outcomes in terms of ventricular function improvement (even if no difference was found in terms of scar size) [26]. These results are hypothesized to be caused by the paracrine anti-inflammatory, immunomodulatory, and anti-fibrotic effect of these cells on the injured area rather than a CDC differentiation into local new myocardial cells [27].
- **Mesenchymal stem cells** are isolates by multiple tissues (e.g., bone marrow, adipose tissue, dental pulp, umbilical cord) and can be expanded in vitro. Among the different cells studied for these purposes, MSCs are the most widely studied because of their abundancy, their easy retrieval and their immune exemption [28]. This type of cell is known since early 70s, and it has been called with different names (osteogenic stromal cell, stromal stem cell, mesenchymal stem cell, mesenchymal progenitor/precursor cell, multipotent mesenchymal stromal cell). It is now called MSC because of the hypothesis that postnatal MSC might generate all mesoderm-derived tissues (including myocardium). However, the formation of similar differentiated similar cells is still a point of controversy. The main and most studied source of MSCs for cardiac regeneration is bone marrow (Fig. 3 summarizes the process to obtain bone marrow MSCs); however, further studies have demonstrated favorable results in terms of LVEF improve-

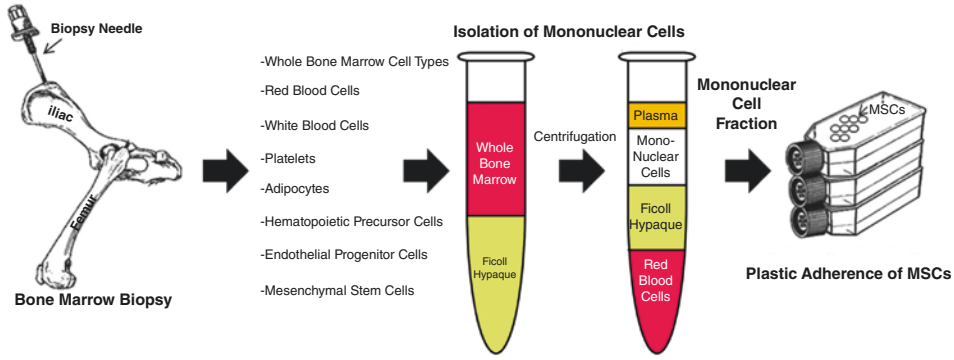

Fig. 3 Isolation of bone marrow mesenchymal stem cells

ment, perfusion, and remodeling for MSCs isolated from adipose tissue and umbilical cord in large-animal models [29, 30]. Particularly, adipose-derived MSCs can differentiate into cardiomyocytes, endothelial cells, and vascular smooth muscle cells and exhibit immunomodulatory properties that can protect other cell types (e.g., endothelial progenitor cells) from rejection.

3 MSCs Mechanisms of Action

MSCs favor cardiac repair by means of fibrosis reduction (Fig. 4), angiogenesis stimulation, and ventricular function improvement. The mechanism of action is heterogenous and includes engraftment and heterocellular coupling (stem and somatic cell intercommunication) [31] and paracrine mediated signaling [32]. Figure 5 summarizes all the mechanisms of action. The initial idea that MSCs differentiate and directly remuscularize a scarred myocardial area has been disconfirmed since multiple studies have shown that cardiomyocyte replacement by MSCs is low and does not represent a therapeutically meaningful mechanism of MSC action [33, 34]. Regarding paracrine signaling, MSCs release a variety of growth factors, with variability according to MSC tissue source. Besides, MSC secretion also includes exosomes and extracellular vesicles containing mRNA, miRNA and non-protein encoding RNA, peptides, and other bioactive compounds, which produce a wide variety of effects on target tissues (e.g., angiogenesis, reduction of infarct size, cardiac function preservation, and antiarrhythmic effect) [35]. Further studies are required to determine the extent and duration of these effects. Heterocellular coupling through gap junctions allows for the transfer of small molecules and plays a role in coordinating activities between neighboring cells during tissue function. Mitochondrial transfer is also allowed through these gap junctions, and it is involved in rescuing damaged cells, reducing the ischemia-reperfusion injury [36].

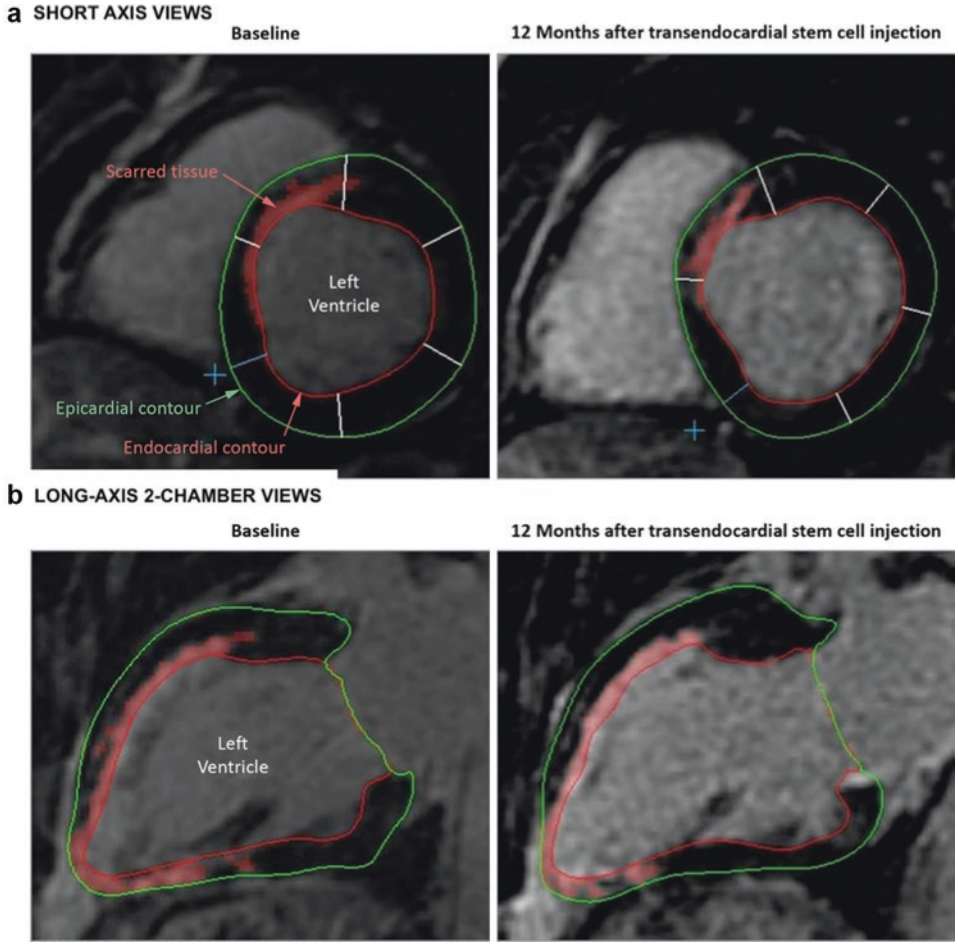

Fig. 4 Cardiac magnetic resonance showing mesenchymal stem cells effect on myocardial fibrosis on short-axis view (**a**) and long-axis 2-chamber view (**b**)

Regarding the immunomodulatory action, MSCs lack surface molecules which can activate the immune system. Furthermore, they reduce the expression of proinflammatory cytokines and lymphocytes proliferation.

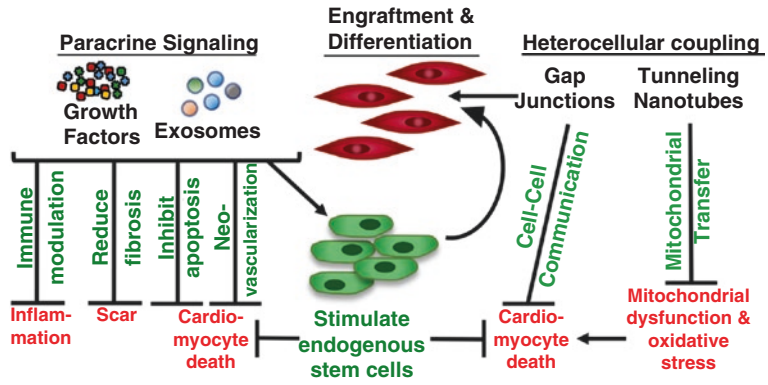

Fig. 5 Mesenchymal stem cells mechanism of action

4 MSCs Preliminary Clinical Outcomes: Acute Myocardial Infarction and Post-ischemic Heart Failure

Given the promising preclinical data on MSCs in IHD, multiple studies have investigated the clinical application of MSCs in humans. In AMI patients, autologous MSCs were first used. Two different trials demonstrated that intracoronary infusion of MSCs (before autologous bone marrow MSCs expansion and after percutaneous coronary intervention) showed better LVEF and ventricular volumes at mid-term follow-up [37, 38]. However, other studies did not find any superiority in the autologous MSCs group in terms of ventricular function improvement in patients with coronary artery disease [39]. This discrepancy might be due to different MSCs injection protocols used. Given the absence of MSCs immunogenicity and the disadvantages of using autologous cells, allogenic MSCs from healthy donors were tested. First clinical experiences show better results in terms of arrhythmias reduction [40], but trials are still ongoing.

Clinical experience with MSCs in ischemic HF has been obtained by means of several studies. Phase I [41] and Phase II studies [42, 43] using MSCs directly injected into the myocardium have demonstrated functional cardiac improvement, reverse remodeling, and improved exercise capacity and quality of life. Other studies have also analyzed MSCs effect after epicardial injection at the time of other surgical interventions (providing a unique opportunity to include cell-based therapies as an adjunct to open surgical procedures), showing an improvement in terms of scar size reduction, perfusion, and contractility [33]. When comparing autologous vs. allogenic MSCs in ischemic HF, both types showed a significant reduction in scar size at 1 year of follow-up as well as a ventricular reverse remodeling [34]. However discordant data are available regarding the dose-dependent effect.

5 Stem Cells Delivery: How and When to Do It

Delivery routes in cardiac cell therapy mainly include thoracotomy injection, system infusion, and imaging guide mini-invasive injection (Fig. 6).

1. *Thoracotomy injection*: Through this access, cells can be delivered in a trans-epicardial intramyocardial fashion directly into the targeted area. Even if this method reduces the cells loss, unfortunately it requires anesthesia and a surgical approach. For this reason, this delivery might be limited to patients undergoing cardiac surgery (e.g., coronary artery bypass grafting). Potential complications are left ventricle perforation, bleeding from the myocardium and unbalanced ventricular motion caused by the uneven distribution of cells after injection.
2. *System infusion*: It includes intracoronary and intravenous injection. Intracoronary has the advantage of increasing the number of cells homing to the ischemia area of the myocardium, while avoiding the damage caused by direct injection in the myocardium. This approach does not require chest opening and can be done at the time of PCI directly [44]. Complications can be cell loss through coronary circulation, and overdose of cell injection that can cause coronary artery occlusion. Intravenous injection is the easiest and the most economical way of infusing stem cells. Even if some researchers argued the real efficacy of this method (primarily due to pulmonary first-pass effect) [45], other studies combining intravenous and intracoronary injection demonstrated improved cardiac function, increased perfusion, and alleviated ventricular remodeling in preclinical ischemia settings [30].
3. *Imaging-guided mini-invasive injection*: This strategy includes trans-endocardial intramyocardial and trans-epicardial intramyocardial injection. These injections are

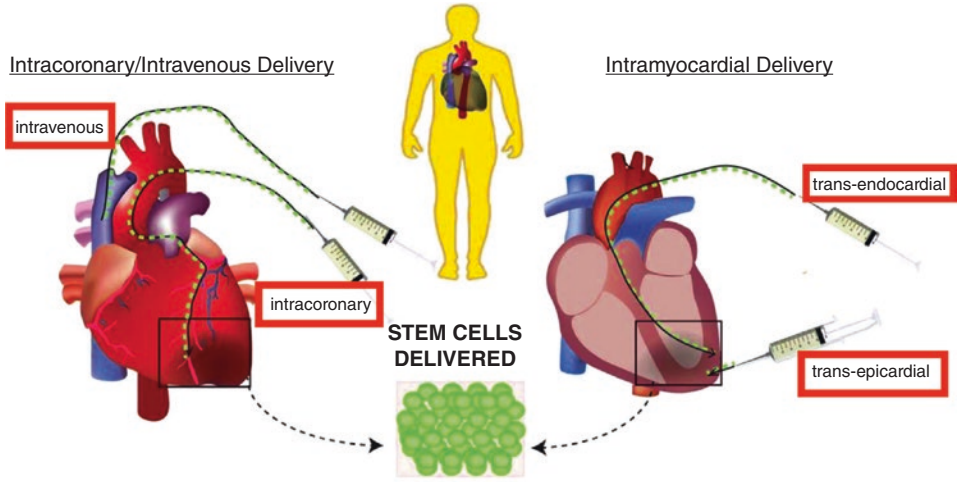

Fig. 6 Stem cells delivery

performed under echo or cardiac magnetic resonance guidance. Advantages are less trauma, fewer complications, and multiple transplantation at different time points [46].

Regarding the optimal timing of cell therapy in AMI, there is evidence that myocardial microenvironment at different time points after infarction has profound influences on stem cells survival, homing, and differentiation [47]. In acute infarct stage, the microenvironment is not conducive to the survival and growth of stem cells because of the overwhelming inflammatory response in the myocardial injury area. It was found that inflammatory reaction peaks at 1–4 days, some cytokines (such as VEGF) which were favorable to stem cells migration reached the peak of secretion at 7 days, and scars began to form at about 14 days after AMI. A recent systematic review found that cardiac function parameters (e.g., diameters, volumes, and LVEF) were significantly improved when stem cells were transplanted between 7 and 10 days after infarction [14]. For chronic IHD, there is no obvious time window problem, so we can select the time when the patients are in good condition (such as no angina attack and general physical activity without discomfort, which denotes that the heart blood supply and heart function are still good), suggesting that the patients' internal environment and myocardial microenvironment are relatively favorable for transplantation, so as to facilitate the survival, homing, and differentiation of implanted cells.

6 Future Perspectives

Current research is oriented toward different new strategies. First, a novel approach is trying to direct MSCs to a cardiopoietic phenotype (by means of a recombinant mix of growth factors, hormones and cytokines which favor the expression of pro-cardiogenic transcription factors). Preclinical and clinical studies are available and have already showed their efficacy and safety [48, 49], but still need to be evaluated in larger cohorts. Analogously, cell combination therapy with different types of stem cells might promote cardiac repair through synergistic interaction [50]. Additional strategies will include: MSC "secretome" including factors within exosomes; bioengineered cellular and acellular matrices and patches that can increase cell/factor retention; repeated injections of stem cells.

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