Stem Cells Transplantation in Myocardial Tissue Induces Pro-Arrhythmic Effects and Promotes 4 Reperfusion. Comparison between Intramyocardial and Intravenous Approach

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Abstract

Ischemic heart disease is a life threatening condition whose prognosis remains poor as current treatments are palliative and the loss of cardiac tissue is not restored. Stem cell therapy appears to be a promising option for myocardial repair after myocardial infarction (MI). Recent experimental and clinical work has suggested that stem cell therapy contributes to cardiac regeneration and improve myocardial function. Unfortunately, there is still a lack about important issues such as mechanism of action of stem cells, dose, long-term engraftment, route of delivery and frequency of cell administration. Also, there is a concern about proarrhythmic effect of stem cell therapy. Some studies have provided basis that stem cells can show intrinsic pacemaker function and provide areas of slowed conduction that can set the stage for arrhythmias.

Keywords: Stem cells; Bone marrow; Arrhythmia; Myocardial repair

Introduction

Ischemic heart disease is a leading cause of human deaths worldwide. Both acute and chronic ischemic injury leads to a permanent loss of cardiac tissue and heart failure. Although there are some procedures (surgical and interventional methods) to restore vascularization and improve function of ischemic myocardium, viability of necrotic tissue is difficult to restore and to date no therapy has demonstrated to promote the regeneration of myocardial damage [1,2].

Cell-based therapy has emerged as a novel potential approach for regenerating heart tissue. Several cell types (cardiomyocytes, skeletal myoblasts, smooth-muscle cells and bone marrow-derived mononuclear cells) have shown to improve heart functional recovery after ischemic injury as shown in animal models [3,4].

At this time, the best cell type for the treatment of MI remains uncertain, and the mechanisms underlying cellular therapy are not fully understood. Mesenchymal stem cells (MSCs) are present in many tissues and have been shown to differentiate into many cell types, including muscular tissues as smooth muscle cells and cardiomyocytes [5,6].

An advantage of these cells is that they are immune privileged. Thus, these cells do not cause the activation of immune response, which enables them to be used in an allogeneic setting. The only study to compare clinical effects of autologous and allogeneic MSCs in patients with ischemic heart failure was conducted by Hare et al. comparing 3 doses of autologous or allogeneic MSCs (20, 100, and 200×106 cells) in patients with ischemic cardiomyopathy and demonstrated that all doses favorably affected patient functional capacity, quality of life, and ventricular remodeling [7].

There are still some unsolved issues, such as optimal dose, cell type, delivery method and frequency treatment. Also, an important issue to consider is the occurrence of arrhythmias, which have been described associated to several factors, such as type of cells and delivery method, among others.

Although stem cells have an intrinsic potential for arrhythmogenicity it is important to recognize that patient’s conditions increase the risk due to heart tissue conditions. Hidalgo et al., described some risk factors associated to supraventricular tachyarrhythmias following high dose therapy and hematopoietic stem cell transplantation in patients with different types of cancer [8]. Here, we briefly described factors associated to proarrhythmicogenic risk.

Cell types evaluated for cardiac repair

Cell therapy is a promising modality for myocardial repair after MI and other forms of structural cardiac disease (congestive heart failure). Different types of cells have been used in clinical trials with encouraging results. Strategies used for this purpose include skeletal myoblasts, mesenchymal stem cells, cardiac progenitor stem cells, embryonic stem cells and combination of cell types. Clinical trials are focused not only in the improvement of heart function, but also in the regeneration of cardiac tissue, and potentially to achieve the electromechanical integration of cells into the heart.

Skeletal myoblasts

Skeletal myoblasts (SM) were the first type of cell used for cardiac repair therapy [9]. Some advantages of using this type of cells are the feasibility for expansion in culture and the ability to use as an autologous source. Preclinical data were encouraging after SM transplantation, since myocardial performance increased and improved left ventricular function [10].

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function [10-13]. However, MAGIC and MARVEL clinical trials did not show significant clinical improvement with this type of cell. Furthermore, the risk of generating tachyarrhythmias and the lack of regeneration of cardiac tissue have discarded these cells as candidates for use in cardiac regeneration therapy [14-16].

**Bone marrow derived mononuclear cells (BMMNCs)**

Bone marrow derived mononuclear stem cells (BMMNCs) constitute a mixture of mononuclear stem cells, hematopoietic, endothelial and mesenchymal stem cells. Mechanism of action of these cells is poorly understood. However, paracrine effects, differentiation into cardiomyocytes and activity on resident cardiac stem cells have been proposed [17-19].

Orlic et al., demonstrated the capability of BMMNCs to differentiate into myocytes and vascular structures, restoring cardiac tissue in an animal model; however, other authors could not confirm those findings [20,21,22]. BMMNCs have been investigated as an alternative therapy in acute MI. Intracoronary, transendocardial and transepicardial delivery routes have been used. Both feasibility and safety of BMMNCs initially were evaluated in different studies by Perin et al., Fuchs et al., and Stamm et al. These authors did not report arrhythmia during the procedure or follow up; however, these studies were small and nonrandomized [20-23]. Wollert et al., and Schächinger et al., observed a significant increase in ventricular function with no adverse effect [24,25]. Recently, Delewi et al., have concluded that no safety concerns were seen after evaluating impact of intracoronary bone marrow cell therapy on left ventricular function [26].

**Bone marrow–mesenchymal derived stem cells (BM-MSC)**

The MSC is a cell population that can be isolated from the bone marrow, adipose tissue, umbilical cord blood and many other tissues [27]. In the last years there has been many reports that bone marrow derived stem cells can differentiate in vitro and in vivo in many cell types, including osteoblasts, chondrocytes, adipocytes and cardiomycocytes [28,29]. Implantation of bone-marrow stem cells in the heart might be a new method to restore tissue viability after MI. The aim of stem cell transplantation is to repopulate diseased myocardium with cells that could restore contractility of necrotic myocardium.

Since 2001, when the first successful use of bone marrow stem cells was reported to treat a MI in an experimental model of acute myocardial infarct (AMI), several studies have demonstrated that bone marrow stem cells have the potential to restore myocardial tissue and differentiate in both contractile and blood vessel cells in ischemic myocardium [30,31]. In the report of Jackson et al., he described that isolation of cells from murine bone marrow, when transplanted into irradiated mice, were able to home into areas of damage in ischemic hearts and differentiate into both vascular endothelial cells and cardiomyocytes [32]. Noisieux et al. demonstrated that administration of 5 x 10^5 allogeneic MSC to the border zone of a MI in mice resulted in a significant reduction in infarct size and improvement in left ventricular volume [33]. In a well-designed animal study, Williams et al. showed significant reductions in scar size and improvements in ejection fraction in animals receiving intramuscular injections of MSCs at 3 months after MI as compared to controls [34].

The effects of adult bone marrow derived progenitor cells after intracoronary, transendocardial, and transepicardial administration routes have been described and the results of preclinical and clinical studies support the potential of stem cells to improve myocardial function. Chen et al. administered 48–60 billion BM-MSCs by intracoronary injection into 34 patients and reported a 14% higher ejection fraction compared to placebo-treated controls [35].

Two meta-analysis including randomized controlled studies showed variable decreases in infarct size and an average increase in left ventricular ejection fraction as well as reductions in mortality and the incidence of recurrent MI [36,37].

However, stem cell therapy in patients with AMI has shown mixed results, and the wide diversity of technical procedures used in each study has made comparison difficult [38-41].

Although several clinical trials using both autologous and allogeneic cell sources have proven to be safe and beneficial in patients with ischemic and nonischemic hearth disease, undoubtedly, the clinical acceptance of this therapy should be based on the risk-to-benefit ratio. To date, the major safety issue raised by the use of stem cells for cardiac repair has been the occurrence of arrhythmias [42].

The role of MSCs inducing arrhythmia is controversial. Briguori et al., reported after direct intramyocardial percutaneous delivery of autologous bone marrow in patients with refractory myocardial angina, one patient experienced acute heart failure 7 days after the procedure due to acute atrial fibrillation [43].

In another study, 4 of 12 patients developed transient atrial fibrillation after transepicardial injection of bone marrow cells [44].

A few of the randomized clinical therapy studies with bone marrow derived stem cells, evaluating efficacy and security suggest a small benefit in patients with ischemic heart disease, but it is considered that the method of evaluating the arrhythmic risk is generally not exhaustive. Other clinical trials reported no evidence of arrhythmic risk associated with the procedure or during follow-up care, but were small and nonrandomized [45-47].

Arguero et al. in a preliminary report described results of cellular auto transplantation in 39 patients with dilated and ischemic cardiomyopathy using stem cells from peripheral blood through homophoresis and implanted via intramyocardial injection [48]. The principal event observed during the perioperative period was ventricular arrhythmia, predominantly during the surgical period. In that study, they suggest a minimum manipulation at the moment of intervention to avoid arrhythmias [48]. More recently, Macia and Boyden have reported that stem cell therapy is pro-arrhythmogenic; however, Ly and Nattel found that stem cells did not increased the risk of arrhythmia but produce anti-arrhythmic effects [49,50].

A possible explanation for pro-arrhythogenic effect is related to the heterogeneity between MSCs and cardiomycocytes (CMCs). Chang et al., in a neonatal rat model described that coupling between unexcitable MSCs and myocytes produced a decrease in conduction velocity after co-culture MSCs and rat myocytes at different concentrations [51].

In contrast, Mills et al., in their study shown that MSC therapy preserved electrical viability and impulse propagation in the border zone with MSC expressing connexin proteins and reduction in arrhythmia induction [52].

In a rat model, Wang et al., reported that MSC diminished ventricular arrythmias by electrophysiological modulation at ventricular level and action potential duration [53].

However, stem cells have an intrinsic arrhythogenic potential, because of their common lack of electromechanical integration into the recipient myocardium. In vitro experiments have shown that MSC
decreased conduction velocity compared with controls; the mechanism underlying these arrhythmias may be different from that seen with myoblasts in that MSCs express functional connexin 43–supported gap junctions, thereby leading to postulate that arrhythmias were rather caused by the coupling of cardiomyocytes with unexcitable MSCs. [54,55]

Also, in a study by Pak et al., injection of MSCs increased the risk of arrhythmias after stimulate sympathetic innervation [56]. Undoubtedly, the role of MSCs in the risk of arrhythmia is controversial and it is necessary to increase our knowledge about the electrophysiological properties of MSCs and their interaction with CMCs.

Cardiac stem cells

Several groups have described the potential of the heart to generate new cardiomyocytes [57,58]. It is well known, since the Beltrami’s report showed that cardiomyocytes in human hearts have mitotic potential, capability of self-renewal and to differentiate into the three cardiac lineages (cardiomyocytes, smooth muscle cells and endothelial cells). Senyo et al., have suggested a second mechanism of action with existing cardiomyocytes re-entering the cell cycle, generating new cardiomyocytes [57,59,60].

C-kit+ cells (cells that express the tyrosine kinase receptor in their surface) and the cardiosphere-derived cells (CDCs) are the most clinically relevant of these cells used in therapy for cardiac regeneration [60,61]. At present, there is not concluding data about efficacy and safety of CDCs. Efficacy has been tested in animal models comparing these CDCs and other extra cardiac cells like BM-MNCs and adipose derived stem cells to address myocardial repair. CDCs provided the greatest functional result and a greater myogenic, paracrine and angiogenic potential [62].

The preclinical evidence and clinical trial CADUCEUS reported that CDCs treatment was safe (i.e. no ventricular tachycardia, ventricular fibrillation, sudden unexpected death, or tumor formation occurred) and it was associated with a reduction of scar size, although ventricular volumes and left ventricular ejection fraction did not differ between groups of study [63,64].

Since CDCs are derived and located in the heart it is important to increase our knowledge of the molecular mechanisms that explain their mode of action. Further investigation in well conducted phase II studies is needed.

Not only autologous stem cell therapy may offer advantages for cardiac regenerative therapy. Due to their immunoprivileged profile and immunosuppressive properties, research has also focused in allogeneic stem cells sources for therapy. Preclinical studies demonstrated that allogeneic MSCs injected in the necrotic area provided near-normal cardiac function [29].

Hare et al., conducted a randomized, double-blinded, placebo-controlled phase I trial in patients with MI. The study showed no evidence of tumor formation or immunogenicity. It also suggested a greater benefit in cardiac function and improved outcomes regarding arrhythmias [65].

Induced pluripotent stem cells (iPSCs) represent a new source of cells that holds a great promise for reparative medicine. Although iPSCs prevent the immunogenicity issues inherent to allogeneic embryonic stem cells application, they do not avoid oncogenic risks. Their use in clinical trials is not ready for application yet.

Adipose stem cells (ADSCs) have an increased proliferative potential and easily obtained by minimally invasive methods. Not only preclinical studies, but also clinical trials, have demonstrated the safety and feasibility of ADSCs. These studies showed an improved cardiac function with reduction in scar formation and improved exercise capacity [66,67].

In summary, cell-based therapy for regeneration of cardiac tissue is a promising novel approach for the treatment of ischemic heart disease. Diverse cell types have been investigated as potential candidates for this purpose. Skeletal myoblasts, with good results in animal models, have an inherent arrhythmogenic potential because they do not integrate electrically with the host myocardium. Bone marrow cells are still under clinical investigation despite inconsistent outcomes. The immunomodulatory properties of MSCs could make them excellent candidates for therapy alone or combined with another cell type. C-kit+ and cardiosphere-derived CPCs have emerged as an important option with the potential to integrate with host myocardium both electrically and mechanically, although well conducted clinical trials are needed to confirm the preliminary results.

Other risk factors for arrhythmogenic potential

Although, cardiac cell therapy appears to be effective and safe, there are still some important tasks to solve. There is a wide variation in studies in term of dosage of cells, method of delivery and characteristics of patients. Different methodologies in clinical trials show variable results in terms of efficacy and safety, leading to the difficulty to interpret, compare and conclude results. Indeed, it is clear that there are aspects pending to be solved and this question can be answered only by performing well conducted clinical studies [68-70].

Stem cell therapy has become a promising therapeutic option for cardiac repair after MI, improving cardiac function, diminishing size of infarct and promoting reperfusion possibly through a paracrine effect (secretion of growth factors). However, the type of cell, optimal dose, timing of administration and pre-conditioning of injured cardiac tissue are important factors to obtain good functional and repair results.

Despite the promising results after BMSCs based therapy for MI, validating the efficacy of delivery methods remains as a challenge, due to the engraftment and prolonged survival of the transplanted cells into the host myocardium after delivery influences the results of cell therapy for ischemic heart disease. Diverse methods of cell delivery have been used in preclinical and clinical studies.

In addition to intravenous infusion, direct surgical intramyocardial injection, catheter-based intramyocardial administration, transcendocardial Injection, trans coronary venous injection, intracoronary artery administration, retrograde coronary venous delivery system and engineered monolayer tissue transplantation, other methods have been described such as, stem cell approach of the myocardium (growth factors) prior to stem cell delivery or co-delivery of stem cells with extracellular matrix molecules, nanofibers, hydrogels, or fibrin glues [71,72]. Here, we will describe the intracoronary and intramyocardial approaches, as the other methods are not in the scope of this manuscript. There is still not a consensus with regards to the best method of delivery for cardiac cell therapy. To date, the most frequent delivery method is the intracoronary approach [71], however, intramyocardial route provides the most direct and precise cell delivery to the ischemic myocardium.

This procedure can be done during thoracotomies for open-heart surgeries and cells are injected into and around well exposed ischemic
areas with a thin needle. Initially, the clinical studies performed stem cells intramyocardial injection after coronary artery bypass graft (CABG) into the border zone [73-75].

Also, there is a transcatheter approach which avoids the risks of an open heart surgery; however, this procedure has the disadvantage that does not allow a direct visualization of the target tissue. However, the developing of mapping systems with catheters has overcome this problem [76]. Both transcatheter and intramyocardial cell delivery have shown an increase in myocardial perfusion, reduction of infarct size and improving of clinical symptoms in animal and clinical studies [77-79]. Previous clinical studies reported arrhythmia after IM injection of SM and BM cells [80,81]. Fukushima et al. in an animal model after coronary artery ligation–induced MI, more than 70% of rats in the intramyocardially injected group, showed consecutive ventricular premature complexes between 1 and 7 days after injections, and this findings were supported by Roell and coworkers in a mouse model [82,83].

A possible explanation for arrhythmogenic potential related to this route of delivery is local tissue injury and cytokines released by inflammatory cells invading the needle puncture sites [84,85]. Patients eligible for cell replacement therapy are prone to develop arrhythmias because of their underlying ischemic heart disease and heart failure dramatically increases the risk of sudden death. Despite this, Intramyocardial delivery has been associated with significantly higher myocardial cell retention rates [86,87]. Intracoronary application seems to be advantageous for heart tissue repair. This procedure is the most frequent form of cell delivery in clinical studies and especially preferred because it can be done simultaneously during a percutaneous coronary intervention (PCI) for treating acute myocardial infarction.

After infusion, this approach allows for selective delivery of cells to the myocardial area of interest. Although this technique has proven to be relatively feasible and safe, there is a concern about the risk of possible embolization in the small coronary arteries; while the decreasing of distal blood flow has been showed in diverse animal studies, such findings have not been yet associated in humans. A possible explanation is the delay of delivery cells after infarction in clinical setting, while in preclinical studies injection occurs immediately [24,88,89]. However, the size and dose of cells delivered must be studied further. So far, in preclinical and clinical studies no severe arrhythmias concerns have raised after cells intracoronary infusion; however, the risk of cardiac ischemia and arrhythmia can increase after occlusion of coronary artery, mainly due to size of stem cells or after balloon inflation [90-92].

The results after intracoronary infusion, using BMCs, CDCs or C-Kit+ stem cells are still controversial regarding its actual impact on the recovery of cardiac function and larger trials are necessary with these cell types in patients with myocardial infarction. Indeed, lack of significant improvement after AMI in patients treated with BMSCs has been reported in several clinical trials and early PCI, heterogeneity of BMSCs populations infused, red blood cell contamination of stem cells and employment of heparin in the treatment of patients could affect results. No significant adverse effects were reported in those trials [93-97].

More recently, Rongchong Huang et al. showed that intracoronary infusion of BMSCs within 24 hours or at 3–7 days after PCI, increased the left ventricular contractile function and significantly improved myocardial perfusion [41]. Also, during follow-up, there were no cases of death, tumor or arrhythmias. They concluded the importance to administrate BMSCs within 24 hours to 7 days after PCI. At present, there are still some unresolved problems regarding intracoronary delivery. In patients with an AMI, is easy to deliver cells following catheter intervention and engraftment of cells may be sufficient, but the cells migrate to other organs, so the replacement of cells is a challenge. Also, the optimal dose and the timing of delivery need to be determined yet.

In summary, due to its invasive nature, the intramyocardial approach has the main drawbacks of arrhythmia and myocardial perforation after procedure; intracoronary approach has been less associated to arrhythmia; however, risk of emboli may reduce accuracy of targeting and engraftment of cells. This method is not suitable when target arteries are occluded.

It is very important to consider the role of the target tissue because arrhythmias risk after myoblast transplantation has been linked to the site of the injections, with those performed in the core of the scar being potentially less arrhythmogenic than those lining the border zone, where abnormal ventricular conduction is present [98]. Also, Bello et al., showed that measure infarct morphology and surface areas help to identify patients at risk for ventricular tachycardia [86].

Another risk factor for arrhythmia development includes the border zone. This is a fully perfused and metabolically active zone surrounding the infarct area, containing inflammatory cells and viable myocytes. This region has electrophysiological properties which have been associated with the emergence of arrhythmias [99-102].

Despite stem cells therapy is a promising option for the treatment of MI by reducing myocardial scar, infarct size and increasing vascularity, the role of BMSCs on cardiac electrophysiological properties remains unclear.

Benzhi Cai et al. evaluated the electrophysiological properties in border zone in an infarct rat model, intramyocardially transplanted with BMSCs. Their results showed that the survival of rats was improved and the electrical stimulation-induced arrhythmias were less observed compared to the control group [103]. The volume of the injection per site could also contribute to arrhythmias as suggested by the trend toward higher creatine kinase-MB values with increasing total volume injected during endoventricular myocardial cell injections [104].

Other concerning issue in clinical trials, contributing to controversial results, is related to lacking of adequate monitoring during follow up and taking β-blockers agents by the patients which may mask the proarrhythmic effect after stem cells transplantation in humans, so the occurrence of arrhythmia is unknown [105]. Table 1 depicts side effects associated to dose and route delivery.

Conclusions and Future Directions

The rising tendency in frequency of ischemic heart disease has increased the trend toward a quick developing of methods to enhance cardiac repair. Undoubtedly, continued research at this respect is required including an emphasis on safety. Preclinical and clinical work suggests that administration of stem cells is safe and effective to improve cardiac function and regenerate viable myocardium. At present, just a few researches had compared results from cell dose, method of delivery and frequency of administration [15,16,106-109]. Those studies showed different results in terms of efficacy and safety. It is noteworthy that using SM at different doses has good results; however, side effects are very frequent. The employment of BMMNCs, MSCs and bone marrow progenitor cells has shown good results and the rate of adverse effects (arrhythmia) was less frequent. Surprisingly,

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one clinical trial employing CSCs at a higher dose was associated to severe complications [110].

Undoubtedly, cardiac arrhythmias are a major risk factor for the mortality after an MI. The risk for arrhythmia after stem cell therapy has been related to different factors such as route of delivery, type cell and patient’s characteristics; however, several animal models have shown that the risk of ventricular arrhythmias is decreased after BMMSCs treatment [50,53]. Also, Moiz et al. in a pilot study report compared intramyocardial versus intracoronary delivery of autologous cell therapy in advanced heart failure [111]. Significant differences were not found in terms of safety and feasibility between delivery routes [111]. Some mechanism have been proposed, such as the engrafing of BMMSCs with host cardiomyocytes and by reversing connexin43 down-regulation and up-regulating transient outward potassium currents [112]. Thus, although stem cell based strategies employed to treat ischemic heart disease minimize the risk of ventricular arrhythmias, it is necessary to develop different strategies designed to prevent or eliminate risk related to factors already mentioned (use less arrhythmogenic cell types, combine cell types or improved methods of cell delivery). Currently, there is not a consensus about which type of delivery method is the safest. Arrhythmias has been reported for intramyocardial and intracoronary route and the possible mechanisms have been mentioned above, [113,114]. In our opinion the transcendacordial approach is an accurate system for delivering cells, but, the choice of delivery method depends of the clinical scenario. We recommend intracoronary route in AMI, after a PCI in a potentially well perfused peri-infarct area; but, if viable segments of myocardium are not easily accessible for intracoronary route due to occluded vessel, transcendacordial route is recommendable. However, not only the best mode of delivery is a question that remains to be solved. Which is the best and safes cell type for cardiac regeneration? This is another significant challenge. Many cell types (bone marrow mononuclear cells, bone marrow-derived mesenchymal stem cells, residual or endogenous cardiac stem cells, endothelial progenitor cells and induced pluripotent stem cells) are being evaluated and safety has been extensively proven, but there is significant heterogeneity in terms of efficacy. Age, gender, treatments, and pre-existing conditions can influence the behavior of cells, results of treatment and safety. Also, the best stem cell not only must have the potential to differentiate into cardiomyocytes, but the ability to improve cardiac health by paracrine mechanisms. Additionally, it is important a thorough characterization of the baseline risk of arrhythmias in these patients, taking into account the use of medications which can mask arrhythmias and follow-up monitoring. It is also necessary to emphasize the need for a thorough research focused in the selection of an optimal cell type, used alone or in a combination of cell populations, such as cardiac stem cells and BMMSCs, which are under investigation [115].

Although not in the scope of this manuscript, stemless approaches have been proposed as a therapeutic option for MI. Injection of growth factors and cytokines involved in the paracrine effect of stem cells, has been used to promote myocardial regeneration and improve ventricular function in animal models. These growth factors activate to the CSCs to generate new cardiomyocytes and promote revascularization [116].

Gene therapy after myocardial infarction, through the injection of transcription factors or miRNAs modulate expression of reprogramming factors in the heart and leads to the improvement of contractile function and reduction of scar formation in the heart [117]. Also, some preclinical and human phase I studies have shown beneficial effects [118]. Given that, regenerative therapies represent a novel paradigm in cardiovascular medicine, certainly, it is necessary further research to better understand the complexity of the molecular

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<td>MSCs</td>
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Table 1: Side effect after cardiac cell therapy. SM, skeletal myoblast; BMMNCs, bone marrow mononuclear cells; MSCs, mesenchymal stem cells; CSCs, cardiac stem cells HF, heart failure.
and cellular mechanisms to regenerate myocardial tissue and translate results of basic research to clinical scenarios.

Results about myocardial tissue regeneration and complete restoration of cardiac function have been contradictory; however, safety has been proved in many studies. We consider it is important to keep enthusiasm and avoid skepticism. Finally, the future of stem cell based therapies is more promising but, in addition to increase our knowledge on cellular, molecular and genetic basic research, preclinical studies and well-designed clinical trials are necessary to identify the best source of cells, optimal dose, method and time of delivery in terms of safety and efficacy.

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