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Review

Recent advances in cardiac regeneration: Stem cell, biomaterial and growth factors

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ABSTRACT

Myocardial infarction has been repo[illegible] be responsi[illegible] about 7.3 million deaths each year globally. Present treatments for myocard[illegible]farction have been [illegible]re palliative rather than curative. Over the past few years, stem cells ha[illegible] demonstrated its potency in regenerating damaged cardiac tissue, especially after myocardial infa[illegible]on. Howeve[illegible]mited short half-life of the protein and cell therapy and low transplanted cell survival ra[illegible]s demonstr[illegible]d via several clinical trials have lead to development of more potent and novel delivery [illegible]ns like [illegible]material delivery system and the use of various growth factors. In this revie[illegible]e will be en[illegible]nd discussing the recent advances in cardiac regeneration with focus on ste[illegible]aterial and growth factors.

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1. Stem cells and gro[illegible]tors ap[illegible]ation in cardiology

Various [illegible]tem/p[illegible]r cells have been commonly used to [illegible]genera[illegible] cardiac [illegible]sues damaged by myocardial infarcti[illegible]able [illegible] stem cell-derived cardiomyocytes (hSC-DCMs[illegible] been [illegible]orted to be effective in regenerating cardiac tissue[illegible]r myocardial infarction. There are four potential mechanisms ha[illegible]een proposed to be involved in stimulating myocardiac repair and functional recovery: Firstly, cardiac regeneration: mesenchymal cells may have the tendency to differentiate into cells that looks like cardiomyocytes; Secondly, the cardiac repair might be through paracrine effect; Thirdly niche contribution: mesenchymal stem cell help to maintain the cardiac niche for cardiac stem cell; and lastly, because of its immunomodulatory tendencies, mesenchymal stem cells helps in the management of immune rejection and its also responsible for inflammatory regulation on cardiac repair and regeneration. It should be noted that all these proposed mechanisms work dependently to regulate stem cell function (Fig. 1) [1–4].

However, stem cell therapy has produced low cell survival and there are still major limitations encountered with consistent derivation of hSC-DCMs populations [6]. Several studies have reported the expression of cell inhibitors like p16 (INK), p21 and p19 (ARF) and cellular stress when mesenchymal stem cell (MSC) are cultured for a very long time, however co-culturing the MSC

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Table 1
Major stem cell used for Cardiac repair.

Type	Source	Advantages	Disadvantages
Embryonic stem cells	Inner cell mass of pre-implantation blastocyst	Pluripotent, self-renewal capacity	Graft versus host disease, ethical debate, and tumorgenesis
Mesenchymal stem cells	Bone marrow/adipose tissue	Multipotent, easy to isolate and expand, lack of immunogenicity,	Heterogenicity
Endothelial progenitor cells	Bone marrow, peripheral blood	Movement from bone marrow or peripheral blood, important in neovascularization	Need for expansion, Heterogenicity,
Skeletal Myoblasts	Skeletal muscle	High scalability, resistance to ischemia, multipotent, no teratoma formation	Electrophysiologically incompatible, lack of gap junction
Cardiac stem cells	Heart	Resident cells, robust cardiovascular differentiation potential, reduced tumor formation	short survival, and limited supply

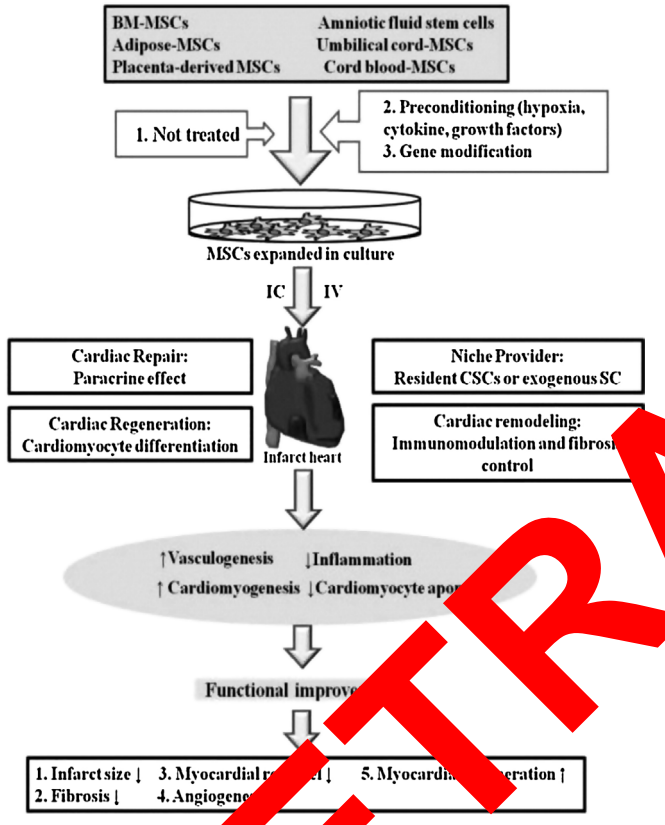

Fig. 1. Mesenchymal mecha for c ac repair. Through cardiac regeneration, paracrine mechanism, niche pro nd inflam ry control, MSCs can reduce infarct size, fibrosis yocard modeli en increase angiogenesis and myocardial regen brevia mesenchymal stem cells; CSC, cardiac stem c SC, ste lls; IV, in ous; IC, intracoronary [5].

with vascular e helial growth factor (VEGF) reduces the cellular stress and pro-sur factors like phosphorylated-Akt and Bcl-xL are increased.

Tang and other researchers reported that combined therapy of (MSCs + VEGF) to MI hearts leads to better cell engraftment and cardiac functioning compared to VEGF or MSCs therapy alone [7,8]. It should also be noted that insulin-like growth factor (IGF)-1 co-cultured with MSC is responsible for improving survival rate and also enhances the paracrine release of stromal cell-derived factor (SDF)-1α. Haider and co-worker also reported the role of insulin growth factor-1(IGF-1) in facilitating the migration and differentiation of stem cells to injured heart [9]. As reported by Higashi and colleagues that IGF-1 is responsible for processes like development, cell growth and differentiation [10]. In addition some studies have demonstrated mesenchymal s cells that rexpressed IGF-1/GF-1R used in an Intramyocardi nsplantat procedure lead to enhanced and improve diac r [11]. F hermore, it has been reported that co ent overex i of Ang-1 and Akt in mesenchymal stem s enh s the st al of these stem cells in the infarcted he t st nd also be noted that insulin growth factor and i cep e widel stributed in cells like myocytes, cardia ogenitor c CPC nd cardiac fibroblasts in the heart an activation responsible for so many biological ac ties ding telomerase activity [12].

In addition to vari ctivities coordinate by IGF-1, its also respo or the releas nd expression of some growth factor like patocyte growth factor (HGF), basic fibroblast growth factor (b- F), and imp antly, vascular endothelial growth factor which has en demon ated by so many researchers as an essential regu of the wth and development of new blood vessels in the hea ypoxic condition [8]. VEGF has been reported to indirectly secreted by MSCs and enhances regeneration of tissue after repairs [13]. At elevated levels, VEGF post-oca al infarction have been demonstrated to be related with cardiovascular protection and improvements of clinical outcomes [14]. Recent clinical trials have also confirm the potency of VEGF in augmenting perfusion of ischemic myocardium in addition to decrease in defects [15,16]. In another experimental studies, it was reported that when differentiated human umblical cord matrix stem cell combined with VEGF improved left ventricular dysfunction, induces formation of new blood vessels and reduces fibrotic tissue formation in infarcted myocardium in eight weeks post MI when compared to the effect of VEGF alone [17].

Furthermore, functional studies have demonstrated that VEGF/MSC transplantation stimulates extensive angiogenesis and myogenesis via the increased expression of cardiac troponin T, CD31, and von Willebrand factor, in an injured heart as such leading to improved functioning of the left ventricle. Hatzistergous and co-worker reported that VEGF/MSC transplantation system enhances the process of angiogenesis through the process of SDF-1α pathway activation that in turn stimulates the differentiation of cardiac stem cells into endothelial cells in infarcted myocardium [18]. As stated before, VEGF is highly expressed by stem cells and MSCs. It should also be noted that MSC-conditioned medium evidently promotes the migration of cardiac stem cell (CSC) through the stromal cell derived factor (SDF) SDF-1α/CXCR4 pathway, which is proposed to be involved by the VEGF/VEGFR-1 and VEGFR-3 (vascular endothelial growth factor receptor-3) systems (Fig. 2).

In the past few years, clinical trials have been carried out using unfractionated adult bone marrow mononuclear cells (BMMNCs) because they are easy to aspirate from bone marrows, contains cardiomyocytes and endothelial precursor cells are present within the mononuclear cell fraction of bone marrow, easily injectable into the heart and lastly, they can be used when there are variable number of cells and different administration routes.