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Review

Inflammatory Microenvironment of Acute Myocardial Infarction Prevents Regeneration of Heart with Stem Cells Therapy

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Key Words
Acute myocardial infarction • Inflammatory microenvironment • Stem cell therapy

Abstract
Over the past years, the benefits of stem cell therapy approach for treatment of the cardiovascular diseases have been shown through the rebuilding of new cardiomyocytes and blood vessels. while a successful regeneration of the myocardium has been proven on the animal models of acute myocardial injuries resulted from the stem cells transplantation, no significant long-term regenerative with autologous stem cell therapy in patients with acute myocardial infarction have been reported based on recent meta-analyses. It seems that the inflammatory microenvironment of acute myocardial infarction has an inhibitory effect on the stem cells potential for regenerating the injured myocardium. Secretion of critical cytokines with pro-inflammatory properties including tumor necrosis factor-α, interleukin-1β, and interleukin-6 as well as induction of hypoxic condition and finally formation of cytotoxic elements cause the cellular death and hinder the stem cells proliferation and differentiation. Based on the evidence, application of some approaches like co-delivery of mesenchymal stem cells with the other useful cells, using the stem cells derived productions, administration of preconditioned and modified cells, and also using the anti-inflammatory agents besides the cell therapy are hypothesized as the primary developed safe and practical approaches for

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decreasing destructive effects of the inflammation on the implanted stem/progenitor cells. In this review, we critically discuss the quiddity of the inflammatory microenvironment and its promoted mechanisms as the main elements to hinder the efficacy of stem cell therapy in the cases of acute myocardial infarction. Also, we finally propose some applied solutions to the problem of cardiac regeneration with stem cells therapy.

Introduction

Recent epidemiological reports have demonstrated acute myocardial infarction (AMI) includes wide varieties of cardiovascular diseases (CVDs), which are the main causes of death among human populations [1]. Over the past decade, stem cells (SCs) have shown great promise for the regeneration of the injured heart tissue. In several clinical trials, cardioprotective and regenerative potentials of the SCs were studied among the AMI patients [2-5]. More specifically, different types of pluripotent stem cells (PSCs) and adult stem/progenitor cells (ASPCs) have been proven to have heart regeneration potential and the ability for generating the myocardium cells lineages such as cardiomyocytes (CMCs), vascular smooth muscle cells (VSMC), and vascular endothelial cells (VECs). Moreover, the paracrine/autocrine release from the implanted SCs into the injured cardiac microenvironment is believed to be another cardioprotective function of the implanted SCs [6, 7].

According to previous published systematic review and meta-analysis, SCs-based therapy in patients with AMI did not contribute to long-term efficiency for improving the heart's injury [8]. The results of this meta-analysis highlight the complex microenvironment of the AMI and the interaction of its components with implanted SCs. During the early phases of the MI, secretion of pro-inflammatory cytokines and recruitment of immune cells in response to hypoxic cells and injured myocardium generate the inflammatory microenvironment of the AMI [9, 10]. Production of the main pro-inflammatory cytokines like tumor necrotic factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) into an infarcted tissue can induce CMCs degeneration *via* stimulation of apoptotic, necroptosis, and autophagy cascades [11-13]. On the other hand, hindering cardiac lineage differentiation of the transplanted SCs in response to these pro-inflammatory cytokines has been reported as another disruptive function of AMI's inflammatory microenvironment [14].

We believe that regulating the complex cytokine network of AMI as well as optimizing the SCs against such a stressful condition might be a safe and efficient approach for increasing the efficiency of the SCs-based therapy in AMI cases. The present review aims to introduce the inflammatory microenvironment in AMI as the critical barrier to heart SCs-based therapy and to offer some important safe and viable methods for overcoming these challenges.

Stem cells in the acute myocardial infarction cell therapy

Generally, SCs have been introduced as undifferentiated cell populations existing in all stages of mammalian development and show self-renewal capacity. These cells are capable of producing same cellular states through symmetrical and asymmetrical division. SCs could also potentially generate all cell lineages belong to developing and somatic tissues [15, 16]. Several types of human pluripotent and adult SCs with cardiogenic potential have been isolated so far and were utilized during various pre-clinical and clinical trials (Fig. 1). We focus on the most studied human SCs and their biology.

Pluripotent Stem Cells

Embryonic stem cells (ESCs), which are directly isolated from the mammalian blastocyst inner cell mass (ICM), represent the first well-known PSCs [16]. The pluripotent state of the ESCs is primarily controlled by expression of several core transcription factors such as octamer-binding transcription factor 4 (Oct4), sex determining region Y-box 2 (Sox2),

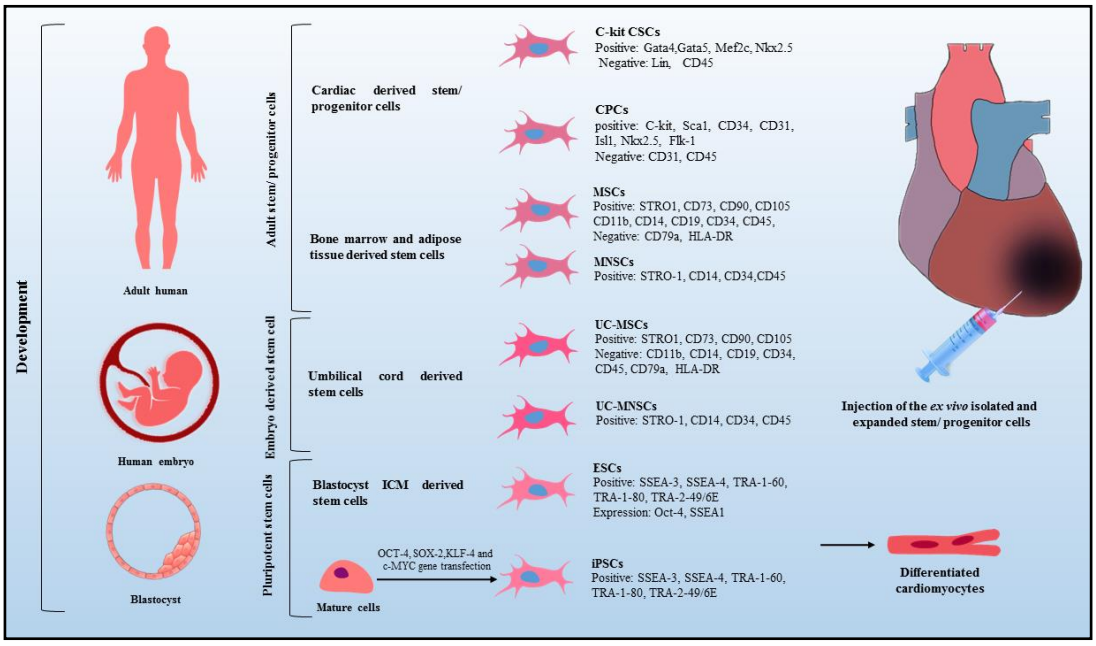

Fig. 1. Different sources and characteristics of the human pluripotent and adult stem cells for AMI cell therapy. Ex vivo differentiated cardiomyocytes from human PSCs for regenerating infarcted myocardium have shown. ESCs and iPSCs are the two main types of PSCs. Human ESCs directly isolate from blastocyst ICM, and human iPSCs may be directly generated from matured somatic cells through transfection of ESCs specific transcription factors. Human embryo umbilical cord is the primary source for obtaining UC-MSCs and UC-MNSCs. In adults, MSCs and MNSCs can be isolated from bone marrow and adipose tissue as enrichment niches. Also, C-kit$^+$ CSCs and CPCs can be directly harvested from human myocardium. The cells can be characterized by the positive or negative expression of several markers and transcription factors. Abbreviations: CPCs: cardiosphere-derived stem cells, CSCs: cardiac stem cells, ICM: inner cell mass, ESCs: embryonic stem cells, iPSCs: induced pluripotent stem cells, MNSCs: mononuclear stem cells, MSCs: mesenchymal stem cells, UC-MNSCs: umbilical cord-derived mononuclear stem cells, and UC-MSCs: umbilical cord-derived mesenchymal stem cells.

and homeobox protein Nanog [17]. Human ESCs are further characterized by the positive expression of stage-specific embryonic antigens 3/4 (SSEA3/4), tumor resistance antigen 1-60 (TRA1-60), and tumor resistance antigen 1-80 (TRA1-80) markers [18] (Fig. 1). The ESCs potential for generating functional CMCs in an *in vitro* condition has been reported by Boheler, et al. (2002) for the first time [19]. This ESCs cardiomyogenic potential can be controlled by several growth factors, including vascular endothelial growth factor (VEGF), bone morphogenetic protein (BMP), and fibroblast growth factor-2 (FGF-2) [19]. It seems that these growth factors induce cardiomyogenic differentiation of the ESCs through activating several well-known downstream pathways such as phosphoinositide 3-kinase (PI3K) class IA, protein kinase C (PKC), and Wnt/β-catenin signaling [20].

Induced pluripotent stem cells (iPSCs) are another type of the PSCs that can be derived from the mature somatic cells through transfection of the ESC-specific transcription factors, including OCT-4, SOX-2, kruppel-like factor-4 (KLF-4), and c-MYC [21]. Human iPSCs are characterized by the expression of the same markers specific to human ESCs, including stage-specific embryonic antigen-3 (SSEA-3), stage-specific embryonic antigen-4 (SSEA-4), TRA-1-60, TRA-1-80, and tumor resistance antigen-2-49/6E (TRA-2-49/6E) (Fig. 1). Several *in vitro* and *in vivo* studies have shown that the iPSCs are able to differentiate onto the functional CMCs and VECs. Besides, human iPSC-derived CMCs were observed to create a functional 3D cardiac micro-tissue [22]. Although direct implantation of the undifferentiated ESCs and iPSCs can effectively regenerate the injured tissues, teratogenicity is still one of the main

limitations against the clinical application of these cells [16, 23]. The administration of the *ex vivo* PSC-derived CMCs appears to be a safe strategy to face such challenges.

Adult stem/progenitor cells

The adult SPCs are known as populations of animal cells with self-renewal and multipotent differentiation abilities. Presence of SPCs in the adult animal tissues implies to the regenerative potential of their organs throughout the lifespan. Mesenchymal stem cells (MSCs), bone marrow-derived mononuclear cells (BM-MNCs), and cardiac stem/progenitor cells (CSPCs) have been already studied for improving the heart injuries in patients with AMI [16] (Fig. 1).

MSCs and BM-MNCs are the most exploited SCs during clinical trials on heart regeneration. Human MSCs are isolated from different ontogenic sources including the bone marrow, the blood, the adipose tissue, and the umbilical cord. Additionally, MSCs and BM-MNCs constitute a large number of $CD34^+$, $CD146^+$, and $CD133^-$ population of the human bone marrow cells [16] (Fig. 1).

Despite that the MSCs can be derived from different niches and are positively characterized by the expression of same markers such as CD70, CD90, and CD105 as well as negative expression of CD34 [24]. The MSCs show different gene expression patterns and regenerative potentials in the experimental studies [25]. The fate of MSCs are controlled directly through interaction with several growth factors, cytokines, and chemokines into the microenvironment of injured tissues. In this regard, VEGF, stromal cell-derived factor-1 (SDF-1), basic fibroblast growth factor (b-FGF), and C-X-C chemokine receptor type 4 (CXCR4), as well as their downstream signaling pathways, have been demonstrated to actively stimulate the survival, proliferation, and differentiation of human MSCs [26]. The paracrine/autocrine activity of MSCs and BM-MNCs is an important mechanism for promoting cell survival, growth, and finally regeneration of an injured myocardium [27].

The CSPCs are populations of the cardiac-derived cells [28] that have potentials in generating the myocardium lineages like functional CMCs, VSMCs, and VECs under both *in vitro* and *in vivo* conditions [29]. The heart resident CSPCs have shown limited proliferative and paracrine/autocrine secretory responses around the infarcted myocardium zone following the heart injuries [30]. Expression of tyrosine-protein kinase Kit surface antigen (C-kit or CD117) is a major characteristic for the most types of the human and the mice CSPCs [30]. Furthermore, CSPCs are classified by expression of the cardiac-specific transcription factors such as GATA Binding Protein-4 (GATA-4), NK2 Homeobox 5 (Nkx-2.5), and myocyte enhancer factor-2 (MEF-2) [31] (Fig. 1). In terms of the heart regeneration, $C\text{-}kit^+$ cardiac stem cells (CSCs), $Sca\text{-}1^+$ CSCs, cardiosphere-derived stem cells, and side population CSCs are the well-known SC populations within the mammalians heart [28, 29, 32]. The CSPCs cardiomyogenic differentiation can be regulated by several critical signaling pathways such as β-catenin and lipid raft/JNK/STAT3 [33].

Acute myocardial infarction stem cell therapy

During the myocardial infarction (MI), reduction of the ventricular wall thickness and induction of the heart failure resulting from the cardiomyocyte degeneration are inevitable processes. Heart SCs-based therapy introduces the most hopeful approach to protect and regenerate the missed myocardium areas [16]. Scientists believe that implanted SCs can regenerate the injured heart tissue through three main mechanisms including I. Secreting various kinds of the paracrine/autocrine factors into the injured microenvironment, II. Inducing endogenic CSPCs proliferation and differentiation, and III. Generating new CMCs and VECs into the failed areas. Thus far, several types of human cells including PSCs-derived CMCs [34, 35], CSPCs [2], MSCs, and BM-MNCs [36] have been examined in non-human primates and human patients with AMI during several phases of trials (Table 1).

Table 1. Summary of some pre-clinical and clinical AMI stem cell therapy trials on non-human primate and human from 2010-2017 according to the cell type. Keys. AMI: acute myocardial infarction, CMCs: cardiomyocytes, ECs: endothelial cells, FHF: first heart field, H: human, IC: intracoronary, IM: intramyocardial, LV: left ventricular function, Ref: references, LVEF: left ventricular ejection fraction, NHP: non-human primate, SHF: second heart field, VSMCs: vascular smooth muscle cells, and WJMSC: Wharton's jelly-derived mesenchymal stem cells

Stem Cell Type	Niches/ source	Differentiation into cardiac lineages			Species/ Sample size	Injection protocol	Detected outcome		Follow-up (months)	Ref
		CMC	VSMC	EC						
ESCs	Inner Cell Mass (ICM) of the developing blastocyst	yes	yes	yes	NHP N= 35	IM, 15× 10^6 human ESC-derived C-kit+ CSCs	LV	49.25% improvement	2	[35]
					NHP	IM, 10^9 human ESC- derived CMCs	LVEF Re-masculinization Infarction size	Unchanged Significantly improved Unchanged	2 months and 24 days	[127]
iPSCs	Generate from adult stem or matured cells	yes	yes	yes	NHP N= 10	IM, 4×10^8 allogeneic iPSC-derived CMCs	LVEF Scar/ remodeling	64.6± 1.5% improved 16.3± 5.0% reduced	3	[128]
CSPCs	For CSCs: Ventricular and atrial myocardium For CPCs: Right ventricle, atrial wall, and conus muscle	yes	yes	yes	H N= 17	IC, 12.5- 25 × 106 Autologous cardiosphere-derived cells	LVEF Cardiac contraction Viable heart mass Scar/ remodeling	Unchanged Systolic thickening increased to 35.9 ± 31.8% Increased to 14.3 g -7.2% decreased	12	[2]
					H N= 31	IC, Autologous cardiosphere-derived cells	LVEF LV Viable heart mass Scar/ remodeling	Unchanged Unchanged 60% increased Decreased to -7·7%	6	[129]
					H N= 23	IC, 1 × 10^6 CSCs were infused into anterior wall infarcts and 0.5 × 10^6 cells into infarcts arias	LVEF Infarction size	Increased to 16·7 unit Decreased from 32·6 g to 7·8 g	4	[130]
BM-MNCs	Bone marrow, circulative blood, cord blood				H N= 205	IC, 1 × 10^6 BM-MNCs	LVEF Scar/ remodeling	Unchanged Improved from 1208; 644/2366 to 371; 176/620	4	[131]
					H N= 152	IC, BM-MNCs	LVEF Infarction size MI core	Unchanged Unchanged Increased from 6.9% to 7.7%	4	[36]
					H N= 200	IC, 153 -119 ×10^6 BM-MNCs	LVEF LV Infarction size Scar/ remodeling	Unchanged Unchanged Unchanged 33.9 decreased	4	[132]
					H N= 23	IC, 220±42×10^6 BM-MNCs	LVEF Scar/ remodeling	+7.9±1.5% improved Unchanged	6	[133]
					H N= 27	IC, 1.3 ×10^6 BM-MNCs	LVEF Infarction size	15.4% improved 26.3% reduced	4	[134]
					H N= 116	IC, 6 × 10^6 WJMSC	LVEF Myocardial viability	Improved to 7.8 ± 0.9 6.9 ± 0.6 % improved	18	[42]
					H N= 20	IV, 4 × 10^6 BMSCs	LVEF LV Infarction size	Improved from 43.06% to 47.80% Unchanged Unchanged	6	[135]
MSCs	Bone marrow, circulative blood, cord blood, adipose tissue, muscle tissue	yes	no	yes	H N= 58	IC, 7.2±0.90×10^7 BMSCs	LVEF LV Cardiac contraction	5.9% ± 8.5% improved Unchanged Unchanged	6	[136]
					H N= 9	IC, 31 ± 2 × 10^6 BMSCs	LVEF LV	Unchanged Unchanged	60	[137]
					H N= 43	IC, 3.08 ± 0.52 × 10^6 BMSCs	LVEF Infarction size Scar/ remodeling	Unchanged Unchanged Unchanged	12	[138]

Differentiation of the human PSCs for generation of new heart lineage cells into the cardiac microenvironment has been clearly understood [16, 37]. In the AMI animal models, implantation of the human undifferentiated PSCs into the injured myocardium has resulted in the improvement of heart functions through promoting a cardiomyogenic and angiogenic response [37]. Authors of an experimental study on the porcine model of ischemic myocardium have also demonstrated that direct injection of the human iPSCs could improve the animal's myocardial perfusion. They observed an increased response of myocytes generation, which was resulted from the differentiation of implanted iPSCs [38]. Conversely, a pre-clinical trial on non-human primate models of AMI indicated that the intramyocardial transplantation of human ESCs-derived CMCs did not significantly improve the animal's heart function [39]. Hence, it suggests that the application of undifferentiated PSCs have more efficiency to regenerate the injured myocardium in comparison with *ex vivo* generated and differentiated CMCs. Unfortunately, the high tendency of undifferentiated PSCs to teratogenic tumor formation [23, 40] and immunogenicity potential of these cells [41] are the main limitations for developing the undifferentiated ESCs- and iPSCs-based AMI regeneration in the clinical phases.

Safety and efficacy of the adult SPCs in AMI patients were studied in several clinical trials (Table 1). MSCs and BM-MNCs are the most trialed cells in these patients. Both of

these SCs could protect CMCs from death through secreting several types of paracrine/autocrine factors into the AMI microenvironment [16, 27]. These cells not only induce the revascularization of injured heart but also promote the formation of new cardiac muscle by promoting the endogenic CSPCs proliferation and differentiation [7]. The gelatinous mass within the umbilical cord, Wharton's jelly connective tissue, is known as a rich source of viable and fresh MSCs. LR Gao, et al. (2015) have tested the efficacy of Wharton's jelly-derived MSCs through intracoronary infusion among AMI subjects. During the first four months, significant improvements were noticed in the patient's heart function indexes after treatment with MSCs. However, after an eighteen-month follow-up, a meaningful reduction was observed in the myocardial viability (PET) and perfusion within the infarcted territory (SPECT) following treatment with Wharton's jelly-derived MSCs [42]. Similar results were obtained by Huang, et al. (2015) through the intracoronary administration of BM-MNCs in a first ST-elevation myocardial infarction. They discerned a positive response in some patient's heart functions like LVEF [43]. In addition, using the hypoxia-preconditioned BM-MNCs in the AMI patients was noticed to significantly improve the efficacy of BM-MNCs-based heart regeneration [44] (Table 1).

Intramyocardial cell injection is another effective stem cell therapy method for the IHD cases [45]. Although different clinical observations have confirmed the efficacy and feasibility of this approach in non-AMI patients [46, 47], high invasiveness, limited numbers of useful stem cells, and low-cost efficiency can be considered as main limitations compared to the systemic delivery method [47, 48]. Up to now, a few clinical trials have examined the benefits of intramyocardial stem cell transplantation for the AMI subjects. As the "first-in-man study", Krause, et al. (2009) used intramyocardial delivery of MSCs in the AMI patients. Their results have clearly shown that this cell transplantation method could not provide a long term and stable improvement in the heart function. Nevertheless, their study confirmed the feasibility and safety of such a method of cell delivery in the AMI cases [49].

CSPCs have been highlighted as powerful cells with the capability of regenerating heart injuries in both pre-clinical and clinical trials (Table 1). In addition to creating several types of heart cells, transplanted CSPCs may promote survival and induce proliferation of the endogenic CSPCs through the expression of the numerous paracrine/autocrine factors into the AMI microenvironment, including tyrosine-protein kinase Met (c-Met), insulin-like growth factor-1 (IGF-1), and hepatocyte growth factor (HGF) [50]. Cardiosphere-derived progenitor cells (CPCs), as the most studied CSPCs, are colony-form heterogeneous cellular populations which can be directly harvested and then cultured from the myocardium tissue biopsies. In a clinical trial, after intracoronary injection of the autologous CPCs, regional function of infarcted segments was significantly improved, which was associated with reduced cardiac fibrosis, subsequently leading to the regeneration of a viable myocardium in patients with AMI. Moreover, Makkar, et al. (2012) have reported an unprecedented increase in the viable myocardium through the intracoronary infusion of the CPCs [2] (Table 1).

While many pre-clinical and some clinical trials prove positive effects of the heart SCs-based therapy, results from Lee SH, et al. (2016) meta-analysis (up to 2014) have revealed that utilizing SCs for the treatment of AMI may not be effective, except for short-term impact on recovery of the heart function [8]. In our opinion, inflammatory microenvironment in the acute phase of MI may exert an inhibitory role in the cell therapy. Therefore, we review the inflammatory microenvironment of AMI and the interaction of implanted SCs with this inflammatory condition.

Inflammatory microenvironment of AMI

Inflammation is known as an immunologic response, which plays a fundamental role in controlling of the tissue repair and degeneration. The AMI inflammatory microenvironment consists of various elements capable of inducing different responses on the infarcted area cells. The processes that promote such an inflammatory microenvironment include

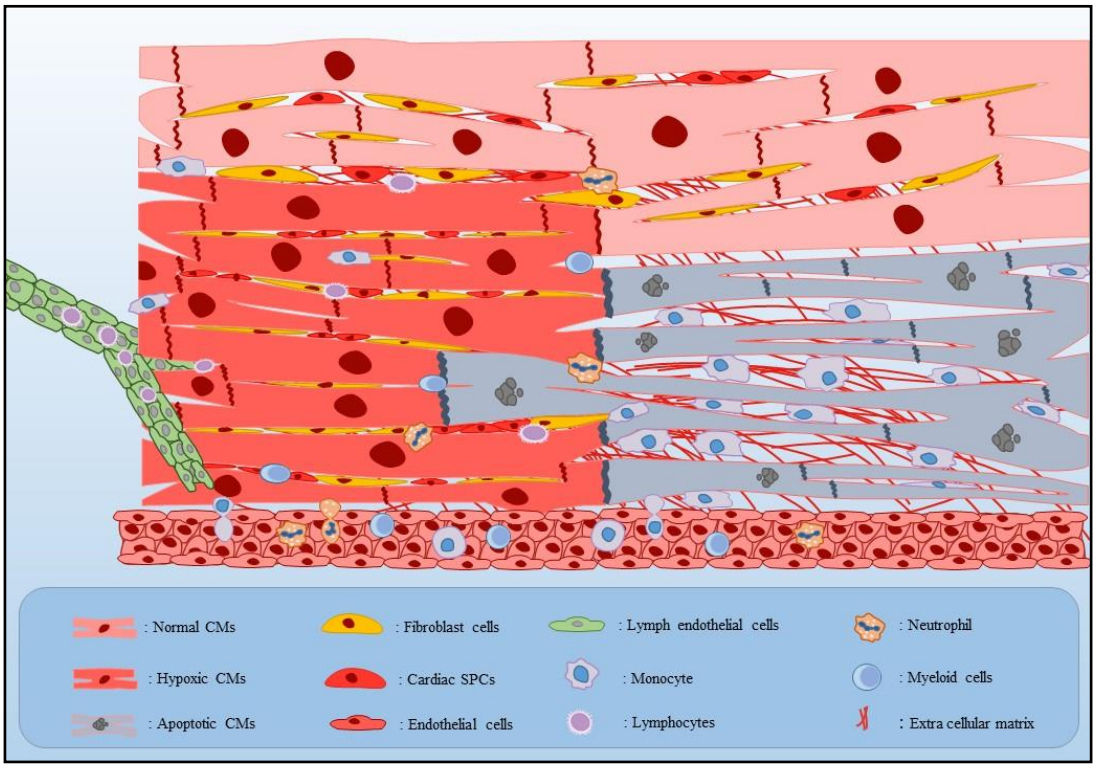

Fig. 2. Schematic representation of the AMI inflammatory microenvironment. Different populations of the fibroblasts, endogenic SPCs, and infiltrated immune cells into the separated parts of normal, hypoxic, and dead myocardium have been shown. Initially after hypoxia, injured CMs, fibroblasts, and endothelial cells actively secrete some of the major pro-inflammatory cytokines such as TNF-α, IL-1β, and also IL-6 into the hypoxic areas. In addition, endogenous SPCs proliferation would be amplified in response to the hypoxia. Next, expression of some important integral membrane proteins including CXC and CC chemokines as well as up-regulation of adhesion molecules on the endothelial cells cause infiltration of inflammatory leucocytes including monocytes, neutrophils, and myeloid cells from the vessels and lymphocytes from the lymph into the infarcted areas. Afterwards, in addition to facilitating the healing process of an injured heart through removing the debris using phagocytosis and secreting some growth factors, recruited immune cells create a stress full inflammatory condition into the infarcted heart tissue via secreting pro-inflammatory cytokines. Abbreviations: CMs: cardiomyocytes, and SPCs: stem/progenitor cells.

I. Production of free radicals following the ischemia and/ or reperfusion, II. Infiltration of leukocytes into the infarcted tissue in response to the chemokines' expression, and III. Expression of pro-inflammatory cytokines by injured cells and infiltrated leucocytes [16] (Fig. 2). An appropriate recognition of this inflammatory and stressful condition can help to develop new practical approaches to regenerate the failed myocardium.

During the early phases of MI, oxidative stress resulted from the accumulation of the free radicals can cause myocardium degeneration through induction of lipid peroxidation, protein oxidizes, and DNA strand breaks, which it ultimately promotes the cellular death process [51, 52]. In our opinion, inflammatory microenvironment in the acute phase of MI may exert an inhibitory role in the cell therapy. Therefore, we review the inflammatory microenvironment of AMI and the interaction of implanted SCs with this inflammatory condition.

It has been observed that the oxidative stress plays a primary role for generating free radicals in the cytoplasm of myocardium cells through promoting some mitochondrial pathways. In this regard, reactive oxygen species (ROS) and reactive nitrogen species (RNS) have been introduced as the main free radicals [51-53]. The production of these free radicals not only leads to apoptosis but also indorses chemotactic migration of inflammatory

cells into the injured tissue microenvironment [53]. The chemotactic response of these leucocytes toward the infarct myocardium can be started by expression of some chemokines and cytokines factors, following by the synthesis of adhesion molecule on the endothelial cells surface, and then upregulated expression of leukocytes integrin [51]. Also, ROS elevate innate immune system responses immediately after MI *via* activation of alarmins or danger-associated molecular patterns (DAMPs), as structurally diverse intracellular signals, which can increase the stress and the inflammatory responses [54, 55]. Another member of alarmins, high mobility group protein B1 (HMGB1) plays an initiative role in activating toll-like receptors (TLRs) and developing inflammation response in the infarcted regions [56, 57]. Moreover, formation of low-molecular weight hyaluronan and fibronectin into the degenerate myocardium extracellular matrix may promote the TLRs and other important pro-inflammatory signaling initiators [51, 57]. Expression of some main integral membrane proteins including CXC and CC chemokinesis is well known as the main reason underlying the recruitment of inflammatory leukocytes into the AMI microenvironment beside the adhesion molecules [16, 58]. (Fig. 2).

Ly-6C^{high} monocytes are the first stimulated immune cells in response to some CC chemokines expressions like CCL2. These monocytes can facilitate the heart healing process through phagocytosis and secreting proteolytic enzymes. Long-term activity of the Ly-6C^{high} monocytes can be a destructive element in the AMI pathogenesis [59, 60]. Furthermore, triggering the synthesis of extracellular matrix and fibrosis are the main impacts of Ly-6C^{high} monocytes activity into the infarcted microenvironment [61]. In the healing heart, switching the expression of CCL2 to the CX3CL1 as well as differentiation of the Ly-6C^{high} monocytes can contribute to recruitment and increase of Ly-6C^{low} monocytes [59, 60, 62]. The Ly-6C^{low} monocytes actively support angiogenesis and extracellular matrix synthesis by secreting VEGF and transforming growth factor- β (TGF-β) [59]. Through the AMI pathogenesis, CD-4^{+} T lymphocytes expose a positive feedback on increasing the inflammation in a post-infarcted heart. Deficiency of the CD-4^{+} T cell may disturb the transition of Ly-6C^{high} monocyte to Ly-6 C^{low} [63]. Myeloid cells, as another type of leucocytes, return into draining lymph nodes shortly after ischemic injury [61]. Myeloid cells have a particular function in the infarcted myocardium pathogenesis through secretion of several pro-apoptotic factors and cardiac collagen matrix proteolysis [10] (Fig. 2).

The complex pro- and anti-inflammatory cytokine network is an undeniable part of the stressful AMI microenvironment. Pleiotropic properties of the pro-inflammatory cytokines act as the core factors in developing the myocardium degeneration and the healing process [64]. In this respect, TNF-α, interleukin-1 (IL-1) family, and also IL-6 family are the most common inflammatory cytokines in this complex network [51, 64].

In a post-infarcted myocardium, activation of hypoxia-inducible factor-1α (HIF-1α) from the damaged cells directly stimulates secretion of the TNF-α in a post-infarcted heart [16, 65] (Fig. 3). According to the experimental models, activation of the TNF-Rs into the infarcted zone ultimately leads to the matrix metalloproteinase activity and extracellular matrix degradation [51, 65, 66]. Besides, TNF-Rs stimulation can induce activation of cellular death inducer signaling pathways in the CMCs and endothelial cells [67]. Study on the TNFR1/TNFR2-genetically knockout mice has shown that CMCs apoptosis did not appear on the TNFR1/TNFR2-knockout mice myocardium after an acute ischemic injury [51]. This study not only realized the TNF-α/ TNF-Rs as the major cell death inducer in the path of AMI pathogenesis but also suggests those as a powerful target for the future heart regeneration goals.

Irrespective of the TNF-α, secretion of IL-1 family, as another important pro-inflammatory cytokine, can mediate activation and recruitment of the inflammatory leukocyte [51, 68]. IL-1α, IL-1β, and IL-1 receptor antagonist (IL-1ra) are the main members of the IL-1 family [68]. It seems that in an AMI microenvironment, the expression pattern of chemokines, growth factors, and adhesion molecules might be controlled by the IL-1α and the IL-1β related processes [69]. Despite the recognition of the IL-1β as one of the primary death ligands and apoptotic inducer, some believe that the IL-1β might be free of any significant detrimental

outcomes on the injured CMCs [69]. As the natural inhibitor of the IL-1 family, the IL-1ra can provide a protective and anti-apoptotic role for CMCs by inhibiting the IL-1α and the IL-1 β expression in the infarcted cells [68, 70].

Notwithstanding, the fact that the level of IL-6 family members increase immediately after MI by the infiltrated leucocytes and the injured CMCs, function of the IL-6 family in an infarct heart is still to be determined [51, 71]. IL-6, IL-11, leukemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1), cardiotrophin-like cytokine (CLC), and neurotrophin-1/B-cell stimulating factor-3 (NNT-1/BSF-3) are members of the IL-6-type family cytokines which have both pro-inflammatory and anti-inflammatory implications. Increasing the cell apoptosis together with inducing the cell proliferation, differentiation, and survival are the IL-6-type cytokines contradictory attributed functions [72].

The cellular mechanisms and signaling pathways regulated by pro-inflammatory cytokine network into the AMI microenvironment are known as the most disruptive elements to the biological action of endogenous and exogenous SCs. All of these mechanisms from the beginning of hypoxia to the loss of CMCs are dynamic and aggressive processes, which can affect the implanted cells efficiency to regenerate the injured myocardium in the acute phases of AMI.

Interaction of the stem cells with inflammatory myocardial microenvironment

It is observed that about 90% of all types of transplanted cells die within 4 days following transplantation into a post-infarcted heart [73, 74]. Thus, the interaction of the infarcted heart microenvironment mediators with the transplanted cells is a determinative factor in the outcome of cardiac cell therapy. It seems that multiple mechanisms such as I. Injured heart tissue inflammatory response, II. Decreasing the oxygen (Hypoxia) and substrates delivery, III. Loss of the cell-cell contact, and IV. Several cytotoxic and/or proapoptotic factors contribute to induce the cellular death on the implanted cells in an AMI inflammatory condition. Improving the implanted cell survival after the administration is a crucial matter to enhance the efficacy of stem cell therap.

It has been clearly observed that the survival of bone marrow-derived MSCs (BMSCs) within the ischemic region significantly decreased early after transplantation [75]. Interaction of these SCs with the secreted TNF-α, IL-1 members, IL-2, IL-6, interferon (IFN)-γ, and their related signaling pathways plays a vital role in the implanted cells death [76]. Additionally, some of these cytokine receptors and their related ligands including TNF-R1, IL-1R (receptor of the IL-1), apoptosis antigen 1 (APO-1 also known FAS), and TNF-related apoptosis-inducing ligand (TRAIL-R), as the main members of death ligands, can induce apoptotic cell death and tissue necrosis through activating nuclear factor- kappa B (NF-κB) cascade [76, 77]. In infarcted cells, the NF-κB is the first responder to the harmful cellular stimuli such as cytokines as well as free radicals. Generally, the NF-κB protein complex controls the cytotoxic cytokine expression and also negatively affects the cell survival in the myocardium. Activation of this factor through death ligands stimulation can directly develop apoptosis mechanisms into the SCs *via* overexpression of pro-apoptotic Bcl-2-associated X protein (Bax) gene [51, 78]. Moreover, these death ligands could mediate autophagy cascade during the cardiac injury through inhibiting mammalian target of rapamycin (mTOR) and Ras pathways [51] (Fig. 3). In MSCs, TNF-α and IFN-γ networks can synergistically enhance the autophagy and apoptosis by stimulating ROS/ mitogen-activated protein kinase 1/3 (ERK) pathway, inducing Bcl-2-homology (BH)-3 domain only protein (Beclin-1) gene expression, and inhibiting anti-apoptotic B-cell lymphoma 2 (Bcl-2) expression (Fig. 3).

Within such a complex environment, hypoxia and inflammation can induce cell death and local cellular degeneration on the endogenous and the injected SCs. By promoting several mitochondrial pore formation proteins, hypoxia-mediated oxidative stress makes an essential interposition in the SCs apoptosis induction. Decreasing the expression of anti-

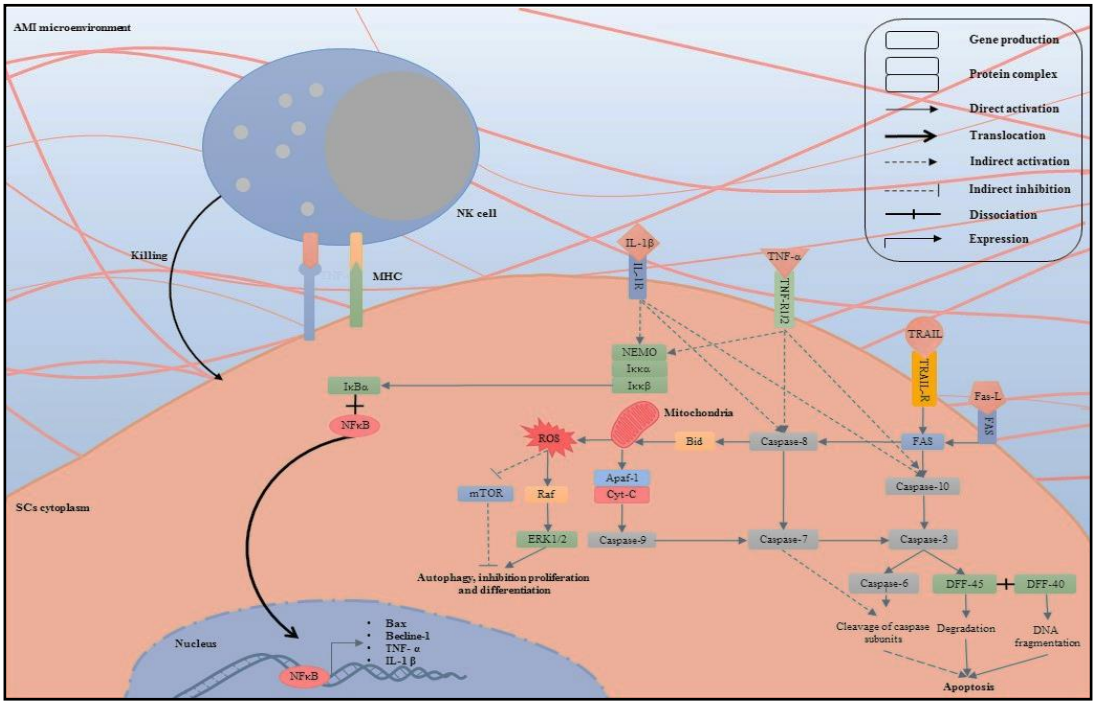

Fig. 3. The SCs interaction with AMI inflammatory microenvironment. TNF-R1/2, IL-1R, Fas, and TRAIL-R as the main death ligands have a central role in inducing SCs death into the inflammatory microenvironment of AMI. During the maintained process, activation of the Fas and the TRAIL-R ligands by their stimulators can directly promote caspase-8 and -10 related apoptosis cascades. In addition, caspase-8 and -10 related cascades indirectly can promote through TNF-α and IL-1β secretion. Following, apoptosis cell death occurs within activation of caspase-7 and then caspase-3. Moreover, activation of Caspase-3 through caspase-6 stimulation and dissociation of DFF-40 and DFF-45 leads to apoptosis in the implanted cells. On the other hand, activation of the mitochondrial related pathways can effectively enhance SCs death. Formation of apoptosome complex (Cyt-C + Apaf-1) through caspase-9 activation, ROS production via activation of MAPK (ERK 1/2) signaling pathway, and inhibiting the mTOR cause to SCs apoptosis, autophagy as well as inhibition of SCs proliferation and differentiation. Furthermore, NF-κB stimulation and translocation into the nucleus by TNF-R1/2 and IL-1R has a central roles in overexpression of pro-apoptotic and also pro-inflammatory cytokine genes. Expression of some MHCs on the implanted SCs into the AMI inflammatory microenvironment via recruitment of NK cell leads to the rejection of the SCs. Abbreviations: AMI: acute myocardial infarction, Apaf-1: apoptotic protease activating factor 1, Bax: Bcl-2-associated X protein, Becline-1: coiled-coil myosin-like BCL2-interacting protein, Bid: BH3-interacting domain death agonist, Cyt-C: cytochrome -C, DFF: DNA fragmentation factor, ERK: extracellular signal–regulated kinases, Fas: apoptosis antigen 1 (APO-1 or APT), Fas-L: Fas ligand, IL-1R: interleukin-1 receptor, IL-1β: interleukin-1 β , IκBα: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor-α, Ikκ: inhibitory Kappa Kinase α, MAPK: mitogen-activated protein kinase, MHC: major histocompatibility complex, mTOR: mechanistic target of rapamycin, NEMO: NF-kappa-B essential modulator, NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells , NK cells: natural killer cells, Raf: serine/threonine-protein kinase, ROS: reactive oxygen spices, SCs: stem cells, TNF-R: tumor necrosis factor receptor, TNF-α: tumor necrosis factor-α, TRAIL: TNF-related apoptosis-inducing ligand, and TRAIL-R: TNF-related apoptosis-inducing receptor., and Becline-1: coiled-coil myosin-like BCL2-interacting protein

apoptotic proteins like Bcl-2 and increasing the pro-apoptotic proteins expression such as Bax, Bcl-2 associated death promoter (Bad), and glycogen synthase kinase 3 β (GSK-3β) are the main targets of hypoxia-mediated oxidative stress [51, 79]. Furthermore, autophagy cell death can be induced over ROS-mediated endoplasmic reticulum (ER) specific protein misfolding, and also stimulation of Ras and ERK1/2 signaling pathways [80, 81] (Fig. 3). Likewise, the inhibitory effects of TNF-α on the secretion of stem cell factor (SCF), as one of

the important cardiogenic elements, have been already shown [82, 83]. Moreover, according to an experimental study, TNF-R inhibits of the growth factor and cytokine production of SCs. Markel, et al. (2007) observed that TNF-R1-ablated BMSCs have had higher basal levels of IL-6, VEGF, and IGF-1 compared with unstimulated wild-type SCs, although no significant alterations were observed in the secretomes of TNF-R2-ablated BMSCs [84]. Thus, taking advantage of approaches based on the AMI inflammatory microenvironment inhibition can be an effective way to decrease these detrimental effects. Relying on the above-mentioned hypotheses and through transplantation of skeletal myoblasts (SkMs) into the MI regions, a significant CMCs protection and heart regeneration was recorded *via* expression of IL-1ra (major IL-1 endogenous inhibitor) and inhibition of pro-inflammatory cytokines such as TNF-α and IL-1β into the rodent's infarcted myocardium [85]. However, the SkMs utilization, as a disparate cellular population from the heart lineage cells, seems to case some of the malintegration related problems after transplantation into the injured myocardium.

The activity of natural killer (NK) cells resulted from the cytokines network could aggressively lyse the implanted SCs [86]. NK cells, a strong cytolysis immune cells, have a critical role in the process of implanted cells/tissues rejection [87]. It has been shown that some of the major histocompatibility antigens (MHC) especially class I and II are up-regulated in the implanted SCs and/or differentiated CMCs inside an inflammatory microenvironment, which actively causes rejection of transplanted cells through NK cells cytolysis response [88].

SCs differentiation onto the heart cells lineages as well as preserving survival are other notable challenges in the way of heart SCs-based therapy. In this context, the infarcted cardiac microenvironment had a disruptive effect on the SCs cardiomyogenic potential [89]. The hindered effects of AMI microenvironment on the human ESCs cardiac lineage differentiation have been carefully determined [86]. In addition, some studies have clearly proved that the TNF-α and its mediated signaling pathways inhibit the cardiomyogenic differentiation of the CSPCs and promote a neuroaderenergic-like fate. These observations showed the probable impact of both TNF-R1 and TNF-R2 on decreasing the CSPCs differentiation potentials and proliferation through stimulation of the NF-κB and mitogen-activated protein kinase (MAPK) pathways around the infarcted zone [14].

Efficient approaches to overcome challenges

The efficacy of the cell therapy is affected by multiple biological factors. Activation of complex inflammatory network early after heart injury, diffusion of the inflammatory leucocytes into the injured tissue, and also secretion of different pro-inflammatory cytokines aggressively induce a harmful condition for all types of the implanted cells (Fig. 3). Generation of such an unstable and progressive microenvironment can dramatically inhibit the survival, function, and differentiation of implanted SCs. In this regard, the authors suggest four different experimental approaches for improving the regenerative responses after the AMI SCs-based therapy, including I. Co-delivery of MSCs with the other useful SPCs, II. Using the SPCs-derived secretomes and/or exosomes, III. Using the preconditioned and modified SPCs, and IV. Using anti-inflammatory drugs before the cell therapy (Table 2).

Due to cytokine-induced stimulation and through the paracrine/autocrine activity, MSCs can effectively improve the heart regeneration by suppressing the inflammatory response. Generally, MSCs-derived paracrine/autocrine factors are grouped into three classes including a. Immune suppressive factors such as nitric oxide (NO), interlykin-10 (IL-10) [90], transforming growth factor- β (TGF-β) [91], and chemokine ligand-2 (CCL-2) [92], b. Growth factors like epidermal growth factor (EGF), platelet-derived growth factor (PDGF), VEGF, and SDF-1 [93], and c. Surface markers such as Galectin [94], intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) [95]. It has been observed that all of these MESs-secreted factors may actively improve SCs functions in the injured myocardium.

Table 2. Main stem cell therapy studies showing more improvement in AMI due to MSCs co-injection, SCs exosomes/ secretomes synchronic administration, and preconditioned or gene modified SCs. Keys: ASCs: adipose tissue derived-stem cell, AT2R/p-ERK/eNOS/NO: angiotensin type 2 receptor / extracellular-signal-regulated kinase/ endothelial nitric oxide/ nitric oxide, Bax: Bcl-2-associated X protein, Bcl2: B-cell lymphoma 2, bEGF: human epidermal growth factor, CCL2: C-C motif chemokine ligand 2, CMs: cardiomyocytes, cTnI: although assays for cardiac troponin T, eNOS: endothelial Nitric Oxide, hEnMSCs: human endometrium mesenchymal stem cells, HIF-1α: hypoxia-inducible factor-1α, hIPSCs: human inductive pluripotent stem cell, Hs-CRP: High-sensitivity CRP, hUC-MSCs: human umbilical cord-derived mesenchymal stem cells, ICAM-1: Intercellular Adhesion Molecule 1, IL-10: interloukin-10, IM injection: Intramyocardial injection, IV injection: Intravein injection, LV: left ventricle, LVEF: left ventricular injection fraction, NO: nitric oxide, PCNA: Proliferating cell nuclear antigen, PDGF: Platelet-derived growth factor, pGSK3β: phospho Glycogen synthase kinase 3 β, PKCε: protein kinase C ε, PKG1: protein kinase G1, PTEN/ Akt: phosphatase and tensin homolog/ Protein kinase B, RhoA/ROCK/ERK: Ras homolog gene family, member A/ Rho-associated protein kinase/ extracellular signal–regulated kinases, rMSCs: rat mesenchymal stem cells, SDF/CXCR4: stem cell derived factor/ C-X-C chemokine receptor type 4, SDF-1: stem cell derived growth factor-1, SMA: smooth muscle actin, SOS-1: Son of sevenless homolog 1, TGF-β: Tumor necrosis factor- β, TNF-α: Tumor necrosis factor- α,, VCAM-1: Vascular cell adhesion protein 1, VEGF: vascular endothelial growth factor, and vWF: von willebrand factor

Stem cells and preparation	Stem cell niche	Protocol	Spices	Outcome	Discussion: mechanisms	Ref
MSCs co-injection	C-Kit+ CSCs	IV co-injection of the 1-2×10^6 EPCs with BM-MSCs	Rat	• Improved cardiac function • Increased CMs formation and capillary density • Induced expression of angiogenic genes	Regulation of AMI inflammatory microenvironment through expression different class of paracrine/ autocrine factors including: a. immune suppressive factors such as NO, IL-10, TGF-β, and CCL2, bEGF, PDGF, VEGF and SDF-1and c. surface markers such as Galectin, intercellular ICAM-1, and VCAM-1.	[92]
	h-IPSCs derived CMs	IM co-injection of the 10^6 h-IPSCs-MCs with 10^6 hMSCs	Nude hydrate	• Improved cardiac function. • Increased level expression of connexin-43, α-actinin and myosin heavy chain		[131]
	EPCs	IM co-injection of the 5×10^5 MSCs with 5×10^5 EPCs	Rat	• Improved ejection fraction • Improved arteriole density		[132]
	Autologous EPCs	IV co-injection of the 5×10^5 EPCs with 5×10^5 BMSCs	Human (n= 11)	• Increased myocardial contractibility • Decreased scar tissue		[133]
	Akt-modified hUC-MSCs- derived exosomes	IV injection, various source exosomes (400 μg of protein)	Rat	• Improved the heart functions • Increased endothelial cells level and blood vessel formation	Enhance activation of PDGF signaling pathway into the AMI microenvironment.	[134]
	Cardiosphere-derived stem cells-derived exosomes	IM injection, CDCs exosomes (or vehicle)	Porcine	• Improved LVEF • Decreased infarcted size, scar size, LV collagen content and cardiomyocyte hypertrophy • Increased vessel density in the histological observation	Enhance activation of anti-apoptotic and heart regenerative signaling factor.	[135]
	Macrophage-derived mir-155-containing exosomes	IV injection, exosomes derived from AngII-stimulated WT macrophages (100 or 200 mg)	mir-155$^{-/-}$ mice and littermate WT mice in C57BL/6	• Exhibition of fibroblast proliferation and collagen production • Reduced cardiac inflammation response into the AMI microenvironment	Inhibit cardiac fibroblast proliferation by inhibition SOS-1 expression and also inhibited cardiac inflammation by decreasing Suppressor of Cytokine Signaling 1 expression	[136]
Using of exosomes or secretomes	hEnMSCs- derived exosomes	IM injection of 1 ×10^6 exosome (mir-21-containing exosomes) secreting hEnMSCs	Rat	• Increased cardiomyocytes protection and survival • Increased neovascularization and masculinization	Enhance cell survival through activation of PTEN/Akt pathway into the AMI microenvironment	[137]
	Sca-1+ CSCs secretome	Direct interaction and culture of hypoxic cardiomyocytes with the Sca-1+ CSCs secretomes	rCMs	• Protection of CMs from hypoxic injury	Enhance activation of MCP-1-dependent mechanism into the AMI microenvironment	[97]
	Dendritic cells - derived exosomes	IV injection, exosomes derived from dendritic cells	Mice	• Improved heart functions • Increased myocardial inflammation • Reduced infarct size	Enhance activation of CD4+ T lymphocytes and its related signaling into the AMI microenvironment	[138]
	rMSCs-derived exosomes	IM injection, exosomes derived from rMSCs.	Rat	• Preserved cardiac systolic and diastolic performance • Increased neovascularization • Restrain inflammation response into the AMI microenvironment	Enhance activation of angiogenic and anti-inflammation mechanisms into the AMI microenvironment	[95]
Using of preconditioned SCs	Hypoxic preconditioning	HP protocol: 0.5% O2 for 24 h. Im injection, 1×10^7 NHP-MSCs	NHP	• Improved LVEF • Decreased infarct size • Increased myocardium thickness	Hypoxia preconditioning increase the expression of several prosurvival/proangiogenic factors into the stem cells.	[101]
	Diazoxide	IM injection. 10^6 EPCs cultured with 200 μM DZ.	Rat	• Improved cardiac function • Reduction in infarct size • Increased cell proliferation and angiogenesis	Enhance expression of prosurvival genes (VEGF, SDF-1α, PCNA, and Bcl-2), improved chemokines release (VEGF, IGF, and SDF-1α), viability, Akt phosphorylation singalongs.	[139]
	Angiotensin II	IM injection, 3×10^6 BMMNCs cultured with 100nM AngII	Rat	• Improved vessel density in peri-infarct region and attenuated infarct size	Enhance activation of AT2R/pERK/eNOS/NO, VEGF and anti-apoptotic signaling into the stem cells.	[140]
	phosphodiesterase-5 inhibition	IM injection, 5×10^5 PED-5 suppressed ASCs	Mice	• Reduced cardiac fibrosis, • Increased vascular density • Decreased resident myocyte apoptosis	Enhance activation of VEGF, b-FGF, and Angiopoietin-1 signaling pathway	[141]
	Hypoxic preconditioning	HP protocol: 0.1% O2 for 6 h. IV injection, 1×10^6 HP-CPCs	Mice	• Improved heart function • Increased infarct size	Enhance activation of SDF/CXCR4 signaling pathway.	[142]
	IL-10	IM injection, 210^6 IL-10 -MSCs modified cells	Rat	• Reduced myocardial infarct size, cardiac impairment, and cell apoptosis	Increase expression of IL-10 into the AMI microenvironment and suppress pro-inflammatory cytokines expression and signaling.	[143]
	eNOS	IM injection, 2×10^6 eNOS -BMMSCs modified cells	Rat	• Reduced myocardial infarct size, • Improved hemodynamic parameters • Increase capillary density • Reduced inflammation	eNOS, downstream factor in the VEGF signaling, through activation of Nitric Oxide (NO) can increase stem cells angiogenic differentiation and survival.	[144]
	IGF-1 and HGF	IM injection, co-injection of 25×10^6 IGF-1 -paMSCs modified cells with 25×10^6 HGF -paMSCs modified cells	Pig	• Promote angiogenic processes in ischemic tissue • Although cardiac function parameters were not significantly improved, cell retention and IGF-1 overexpression was confirmed within the myocardium	Enhanced activation of IGF-1R/PI3K/AKT signaling and secretion of VEGF.	[145]
Using of genetically modified SCs	PKCε	IM injection, 10^6 PKCε -MSCs modified cells	Rat	• Reduced infarct size and cell apoptosis • Increased angiogenesis into the infarcted	Enhance activation of SDF-1, CXCR4, PI3K and phosphorylated AKT into the MSCs and increase expression of MSC survival and VEGF, bFGF, TGFβ, cTnI, vWF, SMA and factor VIII expression.	[146]
	midkine	IM injection, 5×10^6 midkine -MSCs modified cells	Rat	• Prevented hypoxia-induced MSC apoptosis and exert MSC cytoprotection in In vitro condition. • Improvised cardiac function	Enhance activation of VEGF, IGF-1, SDF-1 and TGF-β signaling pathways.	[147]
	PKG1	IM injection, 2×10^6 PKG1 -MSCs modified cells	Rat	• Improvement heart function indices including ejection fraction and fractional shortening • Improved infarct size and also blood vessel density	Enhance activation of ant-apoptotic proteins such pAkt, pGSK3β, and Bcl-2 improves cell survival and increase angiogenesis through increasing expression of HGF, bFGF, SDF-1 and Ang-1 factors.	[148]
	VEGF plus PDGF	IV injection, 5×105 VEGF plus PDGF - human umbilical cord blood derived CD133+/CD34+ modified cells	Rat	• Improvised rat myocardial function • Upregulation of tissue connexin 43 and pro-angiogenic molecules	VEGF- PDGF through activation of pro- angiogenic factors including VEGF, pNOS3, NOS2 and GSK3 and connexin 43, a gap junctional protein, improves stem cells function.	[113]
	HGF and IGF-1 co-transplantation	IM injection of 2 μg HGF+ 2 μg IGF-1 with 1×10^7 BMSCs	Rabbit	• Improved cardiac function and LV remodeling • Reduced implanted BMSC apoptosis • Induced myocardial differentiation.	Enhance activation of IGF-1R/PI3K/AKT signaling and secretion of VEGF.	[149]
	HIF-1α co-transplantation	IM injection, HIF-1α (6×10^9 plate forming unit) with MSCs (1×10^6)	Rat	• Improved cardiac function • Increased angiogenesis	Enhance activation of angiogenic and anti-apoptotic mechanisms through increasing VEGF and SDF-1α signaling.	[150]
	SDF-1 co-transplantation	50 ng/mL SDF-1 for 60 min with IM injection of 5×10^5 MSCs	Rat	• improved myocardial function and vascular density • Suppressed implanted MSCs apoptosis, enhances their survival and engraftment.	Enhance activation of SDF/CXCR4 signaling pathway.	[151]
Using of anti-inflammatory drugs and agents	Atorvastatin	ATV was given by gastric gavage 2 h prior to MI (20 mg/kg) and continued for 4 weeks (10 mg/kg/day). with IM injection of 5×10^5 MSCs	Rat	• Improved post-infarct inflammatory microenvironment • Increase regeneration potential and efficacy of the implanted MSCs	Inhibition of RhoA/ROCK/ERK signaling pathway into the AMI micro environment.	[152]
	Atorvastatin	ATV was given 10 mg/kg/day (14 days) with IM injection of 1×10^6 ASCs	Rat	• Improved post-infarct inflammatory microenvironment • Increase regeneration potential and efficacy of the implanted ASCs.	Inhibition infiltration of inflammatory cells, myeloperoxidase activity, inflammatory cytokines (VCAM-1, TNF-a, Hs-CRP) expression, and Bax protein expression. Also increase survival and differentiation of implanted ASCs into the AMI microenvironment.	[153]

According to an experimental study in a murine model of MI, co-transplantation of endothelial progenitor cells (EPCs) with MSCs by an abdominal muscle-derived patch could significantly improve the cardiac function and increase the efficiency of myocardial infarction cell therapy. They also reported a significant increase in survival and angiogenic differentiation of implanted EPCs [96]. Recently, co-delivery of the C-Kit$^+$ CSCs with the BM-MSCs in a rat AMI model enhanced angiogenesis, improved cardiac function, and increased donor cell survival and proliferation. They proved that expression of angiogenic inducer factors like VEGF, angiopoietin-1 (Ang-1), EGF, and platelet-derived growth factor-b (PDGF-b) from the BM-MSCs and activation of AKT signaling pathway in the C-Kit$^+$ CSCs were the key mechanisms in this regenerative response [97]. Therefore, the beneficial effects of MSCs on the survival and function of co-transplanted cells are linked with MSCs paracrine/autocrine activity (Table 2).

Application of the SCs-derived secretomes and exosomes can be considered as an appropriate approach for increasing the efficiency of the heart regeneration. Typically, exosomes (30-100 nm cellular vesicles) mediate cell-cell micro-communication by their essential functional molecules such as nucleotides, proteins, and bioactive lipids. These small membrane vesicles are derived from various SCs such as MSCs [98, 99]. MSCs-secreted exosomes have a critical role in the modulation of post-infarcted myocardium healing. An experimental study on the AMI rat models has demonstrated that MSCs-derived exosomes could significantly promote the myocardium function early after heart injury indication *via* reprogramming the AMI inflammatory microenvironment. These MSCs-secreted exosomes could be carefully uptaken by the VECs and also increase angiogenesis response of the human umbilical vein endothelial cell (HUVECs) as well as suppress the inflammatory leucocytes proliferation [100]. Consequently, exosomes secreted from the human CD34$^+$ cells may promote the regenerative responses in an injured myocardium through stimulation of endogenous CSPCs angiogenic differentiation [101]. Moreover, injection of ESC-derived exosomes could elevate endogenous cardiac regeneration and function in an animal AMI model. Apparently, the ESC-derived exosomes can directly enhance the survival and functions of the C-Kit$^+$ CPCs and ultimately increase generation of new CMCs in the ischemic heart (Table 2).

In addition to the exosomes, using the SCs secretomes is another compelling option to normalize AMI microenvironment. The interaction between the infarcted myocardial cells and the stem cell's secretomes *via* regulating different signaling pathways can protect damaged cells and promote the endogenous functions of CSPCs. Using Sca-1$^+$/CD31$^-$ CSCs secretomes could remarkably protect CMCs from the hypoxia-induced apoptosis under the *in vitro* condition. These protective impacts might have resulted from activation of monocyte chemotactic protein-1(MCP-1)-dependent mechanism [102]. Additionally, the analysis on the Sca-1$^+$/CD31$^-$ CSCs secretomes showed that EGF, TGF-β1, IGF-1, IGF-2, MCP-1, hepatocyte growth factor (HGF), and IL-6 are the main growth factors and cytokines released by Sca-1$^+$ CSCs into the conditioned medium [102]. Increasing the resistance of implanted SCs against the adverse AMI microenvironment is another approach for improving the cell therapy efficacy (Table 2).

Hypoxia pre-conditioned SCs could notably enhance the therapeutic potency through the expression of different cardioprotective genes together with the secretion of anti-inflammatory, anti-apoptotic, and antifibrotic factors [103-105]. Results of microarray gene expression analysis on the hypoxia pre-conditioned human BM-MSCs and BM-MNCs have revealed the overexpression of several genes including VEGF, EGF, and matrix metalloproteinase-9 (MMP-9) in the SCs after 24 hours from hypoxic pre-conditioning [106]. In an experimental study on the non-human primate models of AMI, a significant improvement was observed in the animal's heart infarct size and LVEF within 3-90 days post-intra-myocardial delivery of the allogeneic hypoxia pre-conditioned MSCs [107]. Further, using cytokines and growth factor-stimulated SCs is another viable approach for optimizing the resistance of implanted SCs to inflammation and increasing SCs survival, proliferation,

and differentiation under the AMI condition. A series of potent stimulators, including SDF-1, IGF-1, VEGF, and IL-10 can be utilized for improving the SCs potential towards the AMI regeneration [108]. Activation of SDF-1/CXCR4 (ligand/receptor) signaling in the SDF-1-stimulated SCs causes a significant increase in the SCs homing, survival, proliferation and differentiation into the infarcted regions [109]. Similarly, pre-treatment of the Sca-1$^+$ SCs with IGF-1 can efficiently induce the generation of new CMCs under AMI condition regardless of improving SCs survival [110]. Likewise, IL-10 stimulation could suppress the disruptive effects of pro-inflammatory cytokines on the implanted SCs, which subsequently improves the cell survival *via* promoting expression of the cell survival Bcl-2 gene [111]. Oxytocin (OT) pre-treated cells also showed a suitable resistant response to the oxidative stress and the inflammatory microenvironment [112, 113]. OT-mediated signaling pathways could induce PSCs and ASPCs differentiation into the CMCs and the VECs [114]. Based on the intramyocardial implantation of OT-treated UB-MSCs into MI animal models, significant reductions were observed in the rates of the infiltrated inflammatory cells into the infarct zone and level of cardiac fibrosis. Moreover, SCs function and connexin-43 activation were increased [115].

Ex vivo gene-modified cells are another useful method for improving the SCs function into the AMI microenvironment. In this approach, overexpression of growth factors, anti-apoptotic, myogenic, angiogenic, and chemoattractant genes is the primary option for increasing the regenerative potential of SCs in an infarcted environment (Table 2). Practically, implantation of the SDF-1-overexpressed MSCs into the rat's infarcted myocardium resulted in a considerable upregulation in the levels of pro-angiogenic stimulators such as the VEGF and endothelial nitric oxide (eNOS), leading to the improvement of the infarct size, the cardiac fibrosis, and the left ventricular wall thickness [116]. Moreover, protein kinase B (PKB or Akt)-overexpressed MSCs significantly inhibited the cardiac fibrosis and improved heart function in the animal AMI model [117]. Compared with non-modified SCs, CXCR4, VEGF, PDGF, and IGF-1 overexpressed SCs have been found to be associated with higher viability and differentiation potential [118-120].

Suppression some of the specific cytokine's activity or their related receptors (anti-cytokine therapies), blocking the lymphocyte migration and tropism toward the MI microenvironment, and also preventing interaction of monocyte-lymphocyte membrane receptors, have been introduced as some of the primary activities of the anti-inflammatory drugs (Table 2). These biological functions of the anti-inflammatory agents, through modulation of the stressful microenvironment, may improve the efficacy and potential of the SCs regeneration. For instance, statins as 3-hydroxy-3-methyl glutaryl-CoA (HMG CoA) reductase inhibitors are the safe agents for treating several cardiovascular diseases [121]. Atorvastatin is known to be a strong cardiovascular anti-inflammatory agent. A low dosage of atorvastatin was shown to increase the serum level of VEGF [122]. Atorvastatin is capable of supporting implanted SCs function and differentiation *via* increasing the level of some growth factors. Administration of the atorvastatin before implantation of the MSCs in a swine AMI model could diminish cardiac fibrosis and improve the implanted MSCs survival through controlling MI inflammatory microenvironment [123]. The results of a terminal meta-analysis indicated that treatment with Atorvastatin can improve the effects of implanted MSCs [124]. However, it has been already demonstrated that the cytoprotective effects of atorvastatin on the implanted SCs are completely dose-dependent. Although a considerable protective and heart-regenerative response has been observed in SCs following the administration of atorvastatin in low doses, some preclinical studies have clarified that in high doses, atorvastatin did not have a significant benefit on the regenerative potential of implanted SCs. As an attractive alternative strategy in graft rejection, application of the monoclonal antibodies by the ability to deplete specific T-cell subsets has additionally shown a brilliant output for protecting grafts following long-term tolerance to major histocompatibility complex (MHC) mismatches. In a pre-clinical study by Stuart, et al. (2000), pre-treatment of the host animals with antibodies against CD4, CD8, and CD3 was noted to significantly increase the survival of graft myoblasts *via* inhibition of the CD4$^+$/CD8$^+$ T cell and the NK

cells [125]. Also, administration of some immunosuppressive agents such as prednisone and cyclosporine could successfully protect the implanted hESC in immunocompetent mice [126]. Taken together, administration of the agents and the drugs can be a viable, safe, and efficient methods for modulation of inflammatory response into the AMI microenvironment, eventually increasing the efficacy of heart SCs-based therapy in the clinical phases.

Conclusion

While some of the publications and trials are referred the heart SCs therapy as a promised strategy for the subjects of heart regeneration, meta-analysis of previous AMI SCs therapy clinical trials, until 2014, has clearly highlighted that this approach did not has a stable and long-term efficacy for the recovery of the AMI patient's heart functions. This could be related to the primary inflammatory microenvironment responses of the AMI, which is a complex dynamical system. The delivery of SCs to such environments would result in a destructive effect on the function and proliferation of implanted SCs. This is due to the immunologic and inflammation responses of these environments on arrival of new and unwanted cells. Therefore, obtaining effective SCs-based therapy method for heart regeneration requires the proper modulation of AMI inflammatory microenvironment and optimizing implanted SCs against the inflammation. Attention to intensity, level, and phase of the inflammatory response before cell implantation in AMI patients may be the most determinative factor for prognosis of an effective MI cell-based therapy through the selection of a correct intervention time and approach.

Disclosure Statement

The authors declare they have no conflict of interest.

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