International Journal of Cardiology 163 (2013) 125–131

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Molecular characteristics of bone marrow mesenchymal stem cells, source of regenerative medicine

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ARTICLE INFO

Article history:
Received 27 August 2011
Received in revised form 3 November 2011
Accepted 4 November 2011
Available online 2 December 2011

Keywords:
Heart disease
Bone marrow-mesenchymal stem cells
Molecular mechanism

ABSTRACT

Bone marrow-mesenchymal stem cells (MSCs) are multipotent stem cells capable to differentiate into a variety of lineages. MSCs have emerged as reservoirs for tissue regeneration and wound healing. Through stress signals, MSCs show great tropism for the injured site to manage regenerative process via direct or indirect interactions. MSCs avoid the immune rejection, a high quality factor for treatment of degenerative diseases. Understanding the molecular mechanisms underlying dynamic regulation of various signals, plays an important role for future treatment of heart disorders.

1. Introduction

1.1. Role of MSCs during cardiac regeneration

Heart disease such as acute myocardial infarction (AMI), chronic ischemic disease, and other damaging stimuli such as sepsis and inflammation can lead to a massive and irreversible loss of cardiomyocytes. These disorders can be associated with progressive heart failure, arrhythmias and sudden death [1,2]. Several investigations have demonstrated that transfusion of autogenic or allogeneic MSCs in the acute phase significantly improves the heart failure [3,4]. Accordingly, MSCs attenuate myocardial injury through differentiation into a variety of lineages including vascular smooth muscle cells, endothelial cells and cardiomyocytes, depending on the milieu [5,6]. There is also evidence that the trophic mediators secreted by MSCs can improve cardiac function via a combination of multiple mechanisms such as reducing inflammation, activating host tissue stem cells, inducing angiogenesis and inhibiting fibrosis remodeling [7,8]. Thus, MSCs are able to ameliorate heart injury and compensate stress by both cardiac cell replacement and also supplying large amounts of anti-apoptotic and mitogenic factors [9,10].

1.2. MSCs penetration and management of cardiac milieu

Within the field of cardiac therapy, MSCs have emerged as an appealing model [11–13]. MSCs mediate their therapeutic action not only by stemness multipotency but also primarily by secretion of multiple growth factors and cytokines (trophic action) [14,15]. Upon injury, cardiac cells secrete proteases and express the monocyte chemoattractant protein-1, MCP-1. The secreted proteases interact with the collagen matrix and digest it into fragments. The digestion fragments appear to be chemotactic for MSCs. Besides, arresting in the proper vascular position involves adhesion integration and transmigration endothelial layer [16, 17].

MSCs express CCR2, the receptor for MCP-1 which in turn promotes transmigration and homing of MSCs [17,18]. Upon transmigration, MSCs manage to secrete matrix metalloproteinases (MMPs) which display crucial roles for matrix remodeling and stem cell homing at the site of injury. MMPs are capable to break down the endothelial basement membrane and facilate MSCs journeying toward chemotactic agents [19–21]. The putative proteases released into collagen I or collagen IV matrices, produce proteolytic fragments for attracting more MSCs toward the site of injury where the medium is a result of stress [22].

Chemokines with chemoattractant activity result in monocyte/macrophage infiltration, stress oxidative, myocardial destruction and interstitial fibrosis which lead into more ventricular chamber dilation [23,24]. In the acute myocarditis, MCP-1 expression is considerably increased in the heart and serum MCP-1 level is elevated [25]. Cardiomyocytes are to be in stress in response to MCP-1, whereas MSCs have shown to attenuate the increase in MCP-1 as well as the

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doi:10.1016/j.ijcard.2011.11.017

infiltration of inflammatory cells [24,26]. In response to the chemoattractant factors, MSCs exhibit cardioprotective effects by secretion of anti-inflammatory factors [24].

MSCs produce large amounts of angiogenic and anti-apoptotic factors such as VEGF, HGF, insulin-like growth factor-1 and adrenomedullin to rescue myocardium from dying and from failing. [27]. Secretion of various cytokines including IL-1β, IL-6, IL-8, MCP-1, VEGF, G-CSF, SCF and IL-11, by MSCs plays major roles in modulating cardiac microenvironment and preventing morphological changes [21,28]. For example, IL-6 plays roles in the differentiation and development of various stem cells. IL-6 inhibits osteoblast differentiation, while promoting cell survival and proliferation. The cytokine IL-1β is a major intermediary of immunological reactions, which regulate the expression of IL-6 [29]. TSG-6 is another anti-inflammatory factor which mediate cardiac repair after myocardial infarction [30]. The vascular endothelial growth factor (VEGF) is one of the most important cytokines participating in the recovery of microvascular injury. It has been demonstrated that VEGF directly stimulates to mobilize bone marrow progenitor cells, to induce MSCs and to activate endothelial progenitor cells [31]. VEGF can per se be secreted by MSCs and boost the activity for cardiovascular reconstitution [31]. High levels of VEGF can stimulate PDGFR, thereby regulating cell migration and proliferation [32]. Transactivation of VEGF is stimulated by hypoxic condition which provoking revascularization [33].

With regard to MSC-derived factors, MSC-mediated stabilization of contractile frequency and reduction in arrhythmias has been observed following infusion of MSCs in clinical trials [34]. MSCs are powerful benefactors to maintain normal Ca^{2+} signaling for restoring normal function to damaged cardiomyocytes in the presence of harmful stimuli. MSCs induce gap junction formation which plays a key role in Ca^{2+} signaling [13,36]. Early clinical trials with skeletal muscle myoblasts report an increased incidence of ventricular arrhythmias, which is now appreciated to represent a serious clinical risk factor [37]. The differences in outcomes may be related to the ability of MSCs, and not skeletal myoblasts, to form connexin-based gap junctions with cardiac myocytes [36]. Taken together, MSCs are a better candidate to manage the stressful condition in a paracrine manner [38].

1.3. MSCs exploit cytokine pattern to attenuate disruption

In ischemia–reperfusion injury, MSCs have benefit action on myocardium and the pattern of cytokine release. It has been shown that MSCs restore normal Ca^{2+} signaling in LPS- and IL-1β-damaged ventricular cardiomyocytes [37]. LPS and inflammatory cytokine IL-1β, as stressors can evoke inflammatory cardiac damage. These agents associate with sepsis and ischemia/reperfusion injury [39].

LPS and IL-1β act through their cognate myocardial receptors TLR4 and ILR, respectively [40]. LPS can in turn protect MSCs from oxidative stress and apoptosis via TLR4-activated PI3K/Akt pathway, and also enhance proliferation of the cells [41,42]. Presumably, stress stimulates MSCs to secrete a variety of cytokines and growth factors that enhance survival and repair of cardiomyocytes [40,43]. There are potential factors underlying this beneficial action, such as stromal derived factor-1α (SDF-1), secreted frizzled-related protein2 (sfrp-2), IL-10, TNFα-induced protein6 (TSG-6) and VEGF [26,39-44]. MSCs exploit the function of stressors LPS and IL-1β by completely blunted LPS-stimulated release of TNF-α, while the spontaneous release of a beneficial cytokine IL-10 is unaltered [37,39,40]. The expression of TNF-α in stimulated cardiac myocytes is inhibited by inactivation of NF-κB signaling cascade [37,45].

The cardiomyocyte stress begins with stimulation of NF-κB, and then is provoked by myocardial cytokines such as TNFα and IL-18. IL-18 is associated with coronary heart disease. Elevated level of IL-18 is observed in congestive heart failure and myocardial ischemia. MSCs release cardioprotective factors that prevent IL-18 production via NF-κB [37,45], thereby inducing genetic reprogramming. The cytokine change is fallowed by prevention of cardiomyocyte apoptosis [39,42]. However, in vivo instability and apoptosis of implanted MSCs, limit the efficiency of therapy. LPS protect MSCs from dying through a NF-kB-dependent pathway, thus LPS preconditioning may lead to an efficient treatment [41,42].

1.4. MSCs attenuate scar formation through CFB genetic reprogramming

MSCs have been shown to improve ventricle activity, by preventing fibrous formation [46]. In contrast, cardiac fibroblasts (CFBs) are predominantly involved in maintenance of extracellular matrix such as types I and III collagen through cell proliferation and collagen synthesis induction [47].

Collagen synthesis is regulated via fibrogenic factors secreted by CFBs, while collagen degradation is mediated via MMPs secreted by injured cells also MSCs [20,23,48]. Types I and III collagen are the major fibrillar collagen produced by CFBs. At the fibrous phase after myocardial infarction, an initial mesh of type III collagen forms the scaffold for subsequent deposition of large, highly aligned type I collagen fibers [47,49]. MSCs display downregulation and deposition of types I and III collagen scaffolds by CFBs [48–50]. Supposedly, MSC-conditioned medium may be rich in humoral factors that can activate or inactivate transcription. Although, MSCs and CFBs, both exhibit paracrine collagenase (MMP-1) and gelatinase (MMP-2 and -9) activity during the necrotic phase of infarct healing [21,48,49], but MSCs manage to prevent scar formation. MSCs excrete factors which attenuate CFB proliferation. For example, MSCs downregulate two genes A2m and Kit which are known to positively regulate cell proliferation. A2m and Kit genes also induce stem cell proliferation through cAMP-dependent and tyrosine kinase receptor pathways, respectively [49,50]. In contrast, MSC-excreted factors upregulate the other two genes Catna1 and Rarb known to be negative regulators. Catna1 encodes alpha-catenin which interacts with cadherin, a cell adhesion molecule. Targeted deletion of Catna1 leads to hyperproliferation [51]. Rarb encodes a member of retinoic acid receptors, and regulates cell growth and differentiation in a variety of cells [52].

MSC-secreted factors up-regulate negative regulators of CFB proliferation Eln, Mycd and Ddit3. These genes in order, encode Eln for tropoelastin, Mycd for a transcription factor important for smooth muscle and cardiac muscle development, and Ddit3 belongs to enhancer-binding transcription factors [47–50]. Conclusively, MSCs exert paracrine effects to regulate matrix remodeling by inhibiting CFB proliferation as well as collagen synthesis, the features beneficial for heart failure treatment.

2. Key mechanisms contributing to efficiency of MSC implantation

2.1. Endothelial phenotype, the major determinant in MSC transmigration

Apparently, various endothelial regions of the vasculature have different phenotypes and thereafter various functions. In contrast to the fastest MSC integration of coronary artery endothelium, over time transmigration of MSCs across venous endothelium is most efficient. Moreover, the aortic endothelium facilitates the slowest transmigration whereas in the myocardium, MSCs adhere and transmigrate across venous vessels most efficiently [53].

For successful systemic stem cell therapy, MSCs must transmigrate across the endothelium and invade their target tissue. Rolling and adherence of MSCs on endothelial cells have been shown to be accompanied by a rapid extension of plasmic podia [54]. The inflamed endothelial surface actively modulates leukocyte-like diapedesis of MSCs. The vascular cell adhesion molecule-1 (VCAM-1) on the endothelial surface of inflamed vessels binds to integrin α4β1 (VLA-4) on MSC surface, subsequently induces MMP-2 expression which facilitates invasion of the sub-endothelial matrix [21,55].