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Review

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

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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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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].

Although MSC binding to endothelium depends on P-selectins, their rolling, adhesion as well as transmigration engages VCAM-1 and VLA-4 [54–56]. MSCs express all of the pointed factors in turn; very late antigen-4 (VLA-4), VCAM-1 and MMP-2 [54]. Other adhesion molecules, for instance β2 integrin molecules are expressed on the surface of MSCs after myocardial infarction by cytokines up-regulation [53–55]. Thus, MSCs express combinations of integrin subunits such as α6β1, α8β1 and α9β1. A distinct molecular mechanism, clustering of β1 integrins is then needed for downstream events such as accumulation of the cytoskeleton to emerge vascular transmigration as well as intramyocardial migration [55, 57, 58].

Besides, cytokines in particular bFGF, and also IL-6 and VEGF play key roles in evoking the expression of adhesion molecules in endothelial cells and enhancing the migratory thereby homing activity of MSCs [59]. In addition, transmigration capacity is marginally improved by bFGF, EPO and VEGF at the early points in time [21,60]. Suggestively, migration and transmigration are processes with unique characteristics which are diversely influenced by cytokines [59].

In inflamed region, MSCs quickly exit the blood circulation by integrating into the endothelium and transmigrate throughout the endothelial barrier [21]. MSCs then penetrate the basement membrane and invade the surrounding tissue. The time course transmigration of MSCs, depends not only on the endothelial phenotype but also on cytokines to trigger downstream events of morphological changes along with plasmic podia.

2.2. Molecular interplays involved in migration and homing of MSCs

Chemokines serve as regulators of blood cell maturation, trafficking and homing. The family of monocyte chemoattractant proteins (MCPs) is involved in development of inflammatory responses and crucial for the infiltration of immune cells [61]. MCPs transiently up-regulated in the heart injury, play a pivotal role in migration of MSCs. The MCP receptor CCR2 has been revealed as a key player for heart-specific homing of MSCs. CCR2 is a major receptor for MCP-1/CCL2 that interacts also with MCP-2/CCL8 and MCP-3/CCL7 [62,63].

The intracellular adaptor molecule FROUNT interacts with CCR2 [64], a G protein-coupled receptor that activates intracellular effectors; adenylate cyclases, PLCßs, PI3Ks, MAPKs and Rho-GEFs [65]. Before stimulation, CCR2 and FROUNT are evenly distributed within the cytoplasm or at a peri-nuclear localization. Binding of MCP-1 to CCR2 activates the receptor and recruits FROUNT, resulting in the formation of clusters of CCR2 and FROUNT at the plasma membrane. The formation of CCR2 and FROUNT clusters goes along with the polarization of the cells as indicated by the asymmetric distribution of CCR2/FROUNT clusters at either side of the nucleus [65,66]. The association of FROUNT with CCR2 leads to activation of PI3K which results in localized formation of actin filaments and lamellipodia protrusions.

Clustering of transducer CCR2 activates PI3K pathway and evokes events to recruit additional cells. The strong polarization of MSCs, is enhanced by strong "positive feedback loop" that selectively amplifies the signal at specific sites of the cell [64–66]. On the other hand, the chemoattractant SDF-1 released in the microenvironment, mediates additional regulatory circuit signals to enhance the homing process [56,65]. VEGF summons more MSCs by inducing SDF1/CXCL12 expression [67]. The summoned MSCs in turn express more SDF1/CXCL12 which traps additional bone marrow-derived circulating stem cells and contributes to complex process of homing and retention. The homing is mediated by the SDF1/CXCL12 receptor CXCR4 [68]. Settler MSCs exclusively interfere with further endothelial activation and inflammatory reactions, by down-regulation of ICAM-1 and E-selectin. However, FROUNT inhibition may be used to fight various chronic inflammatory immune diseases [66,69]

2.3. Hypoxic microvasculature enhances MSC implantation

MSCs have become the recent focus of intense research in the treatment of ischemic disease due to their ability to repair or rebuild injured hypoxic vessels. Under hypoxic conditions, MSCs activate proliferation and migration of microvascular endothelial cells (MEC), while simultaneously increasing the permeability of the MEC monolayer to induce more MSC infiltration for rapid tube formation [70].

Direct interactions with the endothelial targets, MSCs undergo milieu-dependent differentiation to express phenotypes that are similar to the cells in the local microenvironment. MSCs express Flk-1, a tyrosine kinase receptor for VEGF and one of the earliest endothelial differentiation markers. Flk-1 plays an important role in endothelial development which is followed in sequence of Tie-2, VE-cadherin, Tie-1 and CD34 expression [71,72].

Hypoxia per se induces high level expression of VEGF and MMPs in both MSCs and MECs. MMPs degrade collagen fibers (a key component of basement membranes) and VEGF provokes stem cells proliferation and migration [73]. Overexpression of hypoxia-inducible factor-1 (HIF-1) is induced in MSCs which thereafter promote VEGF expression [70,74].

MSC response to hypoxia is emerged by stimulating HIF-1 pathway. Hypoxia results in HIF-1 stabilization, nuclear translocation and transcription of genes containing hypoxia response elements (HRE). HIF-1 interacts with the coactivator protein p300 that results in transactivating of hypoxia responsive genes [75,76] including VEGF gene, central to be activated under hypoxia condition. On the other hand, the inflammatory signals antagonize HIF-1 function, for example, NF-κB interferes with VEGF expression. Since, NF-κB and HIF-1 act at the same target genes [35,77]. However, functional studies have presumed collaboration between p300, HIF1 and NF-κB since both transcription factors are essential for wound healing [75–77]. Thereby depending on condition, inflammation and hypoxia behave in synergism or counterpart to influence the outcome [77].

The overexpression of HIF-1 under hypoxic/ischemic stress causes MSCs to survive more successfully by mediating cellular adaptive response [75,77]. Elevated HIF-1 level also up-regulates MMPs to promote the migratory activity in the collagen-rich microenvironment [78]. For ischemic diseases, MSCs recruiting to the site of injury are essential to inaugurate the reconstruction process.

2.4. Signaling switches participating in MSC proliferation

Highlighting growth factors and signaling pathways involved in MSC proliferation is crucial for achieving better MSC expansion. The JAK-STAT and ERK1/2 signaling pathways are involvers in MSC proliferation. Platelet-derived growth factor-BB (PDGF-BB) and basic fibroblast growth factor (b-FGF), but not epidermal growth factor (EGF) have been shown to induce MSC proliferation, importantly, without affecting differentiation potential [79]. The JAK-STAT pathway is proved to be activated by PDGF-BB and bFGF, while PDGF-BB, bFGF and EGF all activate the extracellular signal-regulated kinase1/2 (ERK1/2) through MAPK pathway [80,81]. Following phosphorylation, ERK1/2 is translocated into the nucleus where they activate various transcription factors [82]. Similarly, STAT proteins, a group of latent cytoplasmic transcription factors are activated by the JAK tyrosine kinase family. STAT tyrosine phosphorylation promotes formation of STAT dimers followed by nuclear translocation of the activated dimers. In the nucleus, STAT dimers promote transcription of several target genes, often associated with cell proliferation [83,84].

Likewise, serine phosphorylation of STAT mediated by MAPK family represents an important aspect of STAT-mediated transcriptional regulation [85]. All of the growth factors activate STAT serine phosphorylation through the ERK1/2 pathway, while only a few factors such as PDGF-BB, bFGF and SDF1/CXCL12 was reported to induce STAT

tyrosine phosphorylation. Such dual phosphorylation is proposed crucial for complete activation of STAT. Tyrosine phosphorylation is essential for dimerization and serine phosphorylation is required for maximal transcriptional activity of the activated dimer [79, 83–86].

Accordingly, PDGF-BB as well as bFGF induces MSC proliferation via complete activation of STAT3, however, bFGF switches on STAT pathway first by the ERK1/2 signaling. While, EGF switches on the ERK1/2 pathway for other MSC physiological processes [79,81,82]. Besides, both pathways are essential for the progression of MSCs from G1 phase to S phase. Assumedly, the genes activated by complete-phosphorylated STAT3, are involved in the G1/S transition. It should be noted that ERK1/2 is mainly linked to the cell differentiation as has been shown with TGF-β and IGF-induced proliferation and osteogenic differentiation of MSCs [83,87].

3. Some features of MSCs for improving in vivo therapeutic capacity

3.1. Preconditioning hypoxia strategy improves in vivo survival capacity of MSCs

After transplantation, a significant number of transplanted cells undergo cell death, which could hamper the potential benefits. Under in vivo hypoxic conditions, MSCs may undergo significant stress which leads to cell death [88]. A number of studies have been published regarding the effects of hypoxia on MSC expansion and differentiation [88–90]. Short-term (48 h) severe hypoxia (≤1% O2) has displayed down-regulation of osteogenic differentiation markers; cbfa-1/Runx2 (osteoblastic transcription factor), osteocalcin (osteogenic marker) and type I collagen (the main component of bone matrix), while having no effect on MSC survival. MSCs' permanent exposure to hypoxia (120 h) has been reported to result in increased cell death rates, while 48 or 72 h exposure does not [33].

Under normoxic condition (20% pO2), MSCs cease to proliferate after 15–25 population doublings, while MSCs cultured under hypoxic condition (1% pO2), retain their ability to proliferate with an additional 8–20 population doublings. In hypoxia 2% pO2 and 3% pO2, MSCs display a 30-fold increase in cell number and 10-fold increase in population doubling rate, respectively. The hypoxia >1% pO2, for example, 3% pO2 emerges more favorable for MSC expansion [89]. In a short time, hypoxia increases MSC proliferation by promoting progression of the cell cycle [90]. The discrepancies may be due to differences in species, oxygen concentration, or length of culture periods.

3.2. Hypoxia and underlying molecular mechanism in MSCs to escape from senescence

As indicated, MSCs when transplanted in vivo, undergo temporary hypoxia exposure. Importantly, in vitro hypoxia-preconditioning (HPC) can preserve in vivo cell survival by preparing MSCs to confront fallowing hypoxic challenge and prevent deleterious effects [91].

Supposedly, preconditioning of MSCs with short periods of hypoxia/re-oxygenation, prior to the in vivo hypoxic challenge, leads to a decrease in pro-oxidant enzymes, as well as an increase in anti-oxidant enzymes, what allows the cell to metabolize ROS (such as H_2O_2) into H_2O and O_2 [89]. In general, hypoxia does extend MSC lifespan more than growth rate, due to escape from cellular senescence [90]. HPC is associated with better MSC survival due to increases expression of pro-survival genes such as Akt and bcl-2 [90–92].

Hypoxia causes MSC mobility to leave the injury site, but HPC preserves the cells to persist prolonged hypoxia milieu, thereafter preventing MSC lost [89].

Depending on physiological state, an in vivo oxidative stress is characterized by either an increase in pro-oxidants or a decrease in anti-oxidants, or a combination of both acting in concert [89]. The prolonged hypoxia triggers a significant increase in the expression of p67phox and p47phox, subunits of pro-oxidant NAD(P)H oxidase, leading to an increase in ROS and reduces cell survival [93].

Under hypoxic challenge, there is a decrease in the expression of anti-oxidant enzyme catalase, a major metabolizer of ROS, while the levels of SOD and its subunits can be unaltered. Decrease in the endogenous scavenger enzyme catalase will not allow for the metabolism of H_2O_2, leading to intracellular accumulation of H_2O_2, with deleterious effects on the cells [89,93].

There are reports about the involvement of ERK signaling in MSC differentiation. Activation of ERK pathway triggers osteogenic or adipogenic differentiation [94]. Presumably, down-regulation of phospho-ERK expression may help cells to escape from cellular senescence [89,95]. Hypoxia leads to improvement of MSC survival by down-regulation of MAPK pathway. Although MAPK pathways have profound effects on MSC growth, at the same time they may induce cellular senescence [96]. Notably, different degrees and terms of hypoxia also age of MSCs (senescence) have differential effects on the activation of pathways [89]. For example, observations imply that hypoxia can activate both p38/MAPK and Akt pathways by increasing their expressions [97].

Although complete molecular mechanisms underlying MSC behaviors are not known, but reduction in oxygen can cause down-regulation of phospho-ERK expression [95]. Hypoxia down-regulates p16 gene expression (Cyclin-dependent kinase inhibitor 2A). The p16 plays an important role in regulating the cell cycle. The up-regulation of p16 gene has shown as a key player to induce human MSC senescence [95]. The late senescence of MSCs in hypoxic condition is related to down-regulation of p16 gene [95,98]. ROS induces p16 gene expression [99], and the p16 pathway in turn increases the production of ROS, which enhances cellular senescence [100]. Inhibition of phospho-ERK signal reduced the up-regulation of p16 gene expression. According to these reports, MSCs cultured under hypoxia, escape from senescence via inhibition of p38-MAPK-ERK pathway and down-regulation of p16 as well as pro-oxidant NAD(P)H oxidase [95].

3.3. Immunosuppressive or immunogenic MSCs?

Much evidence has indicated that MSCs exert an immunosuppressive effect, particularly on T cell activity. T cells are a key component of the immune system, which play a major role in adaptive immunity. T cell responses consist of a sequence of cellular activation, proliferation and effector function. The mitogen-stimulated T cell proliferation is inhibited by MSCs [101,102]. The data strongly supporting the inhibitory effect of MSCs on T cell responses is confined to cellular proliferation rather than their effector functions. MSCs exert a non-specific immunosuppressive activity on T cells [103,104]. Despite normal expression of MHC class I, MSCs are unable to stimulate resting allogeneic T cell proliferation and IFN-γ production. Supposedly, this is due to MSCs not expressing co-stimulatory molecules (CD80 and CD86), which are essential to provide sufficient signal for T cell activation [4,105]. In spite of great promise to be an attractive therapy for graft versus host disease (GVHD) [106,107], MSCs do not always have a beneficial immunosuppressive effect [108]. Studies have emphasized the importance of cell contact dependency as well as immune factor concentrations for the immunosuppressive effect [109,110]. Addition of IFN-γ with intermediate concentrations of immunogenic factors restores the anti-proliferative effect of MSCs, whereas IFN-γ alone has no effect. Instead, on pre-activation of T cells and IFN-γ dose, MSCs may express MHC class II molecules and function as antigen-presenting cells [111,112].

The bi-functional nature of MSCs either inhibitory or stimulatory is depending on the degree of T-cell pre-activation [110,113]. When condition is rendered proinflammatory by high level of proinflammatory cytokines (interferon-γ, interleukin-2, or tumor necrosis factor-α),

MSCs inhibit proliferation. Alternatively, MSCs need to be "licensed" by IFN-γ plus either TNF-α, IL-1α, or IL-1β [109]. Administration of anti-inflammatory cytokine IL-10 abrogates the suppressive effect of MSCs, while cytokines IL-6, IL-4 have exhibited no effect [114,115]. Generally, suppression of T-cell proliferation is enhanced in a proinflammatory milieu, but attenuated by the presence of anti-inflammatory factors [111]. Some authors attribute the variable behaviors of MSCs to differences in MSC cultivation, experimental design or contamination with hematopoietic stem cells [113,114]. In summary, MSCs are able to switch from one functional cell type to other non-beneficial ones, depending on in vivo micro-milieu or the culture conditions.

3.4. Anti-proliferative effect of MSCs by Wnt signaling

Stem cells and tumor cells share similar signaling pathways such as the Wnt, Notch, Shh, and BMP pathways that regulate self-renewal and differentiation [116]. Genes regulated by Wnt signaling are involved in metabolism, proliferation, cell cycle, and apoptosis [117]. The Wnt ligands activate the pathway by binding to the frizzled receptors and co-receptors, LRP5/6. Members of the proto-oncogene Wnt family can promote cellular proliferation and lead to tumor formation. For example, Wnt3a increases expression of the anti-apoptotic protein Bcl-2 and PCNA [118]. Initiation of the Wnt signaling is modulated by soluble Wnt antagonists (sWAs), including soluble frizzled related proteins (sFRP), dickkopf proteins (Dkk) and Wnt inhibitory factor-1 (Wif1) [119]. MSCs secrete Dkk-1, a putative tumor suppressor, which its deficiency implicates in tumor progression [120]. Besides being an inhibitor of the Wnt signaling, Dkk-1 can maintain an undifferentiated phenotype of MSCs [119]. Data also demonstrate that the expression level of Dkk-1 is higher in MSCs than in the cancer cells [121,122]. The antagonist Dkk-1 competes with the Wnt for binding to the LRP5/6 and inhibits activation of the Wnt signaling pathway [123,124]. The LRPs blocker Dkk1 is required for the arrested MSCs to re-enter the cell cycle and subsequent proliferation by antagonizing the canonical Wnt signaling [119].

The canonical Wnt signaling has also been reported to inhibit MSC proliferation via a paracrine fashion [125,126]. The canonical Wnt signaling pathway includes stabilization of cytosolic b-catenin, nuclear translocation, and gene regulation. Whereby, b-catenin acts as a co-activator of transcription factors [120,127]. It has also been shown that conditioned media from MSCs down-regulates b-catenin in breast cancer cells [120]. Accordingly, MSCs can inhibit tumor progression through down-regulation of protein kinases and soluble factors [128].

One study has also revealed that the canonical Wnt signaling stimulates MSC proliferation at a low dose, while inhibiting it at a high dose [127]. This dual effect of the Wnt signaling may depend on the intensity of the Wnt signals and receptors which lead to different or even opposite biological outcomes [121].

4. Conclusion

Although stem cell therapy holds promise for treatment of heart disease such as acute myocardial infarction (AMI) and chronic ischemic disease, its current use is significantly hampered by biological and technological challenges. Human bone marrow-derived mesenchymal stem cells (MSCs) have great beneficial aspects as therapeutic agents. Increasing evidence shows that they have potential capacity for transmigrating, homing and reconstruction the injured tissue. Characterizing MSC features may help to improve expansion and transplantation outcomes of regenerative medicine. In addition, demonstration of paracrine/autocrine mechanisms improves our understanding of stem cell biology.

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