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REVIEW ARTICLE

Implications of mesenchymal stem cells in regenerative medicine

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ABSTRACT

Mesenchymal stem cells (MSCs) are a population of multipotent progenitors which reside in bone marrow, fat, and some other tissues and can be isolated from various adult and fetal tissues. Self-renewal potential and multipotency are MSC's hallmarks. They have the capacity of proliferation and differentiation into a variety of cell lineages like osteoblasts, chondrocytes, adipocytes, fibroblasts, cardiomyocytes. MSCs can be identified by expression of some surface molecules like CD73, CD90, CD105, and lack of hematopoietic specific markers including CD34, CD45, and HLA-DR. They are hopeful tools for regenerative medicine for repairing injured tissues. Many studies have focused on two significant features of MSC therapy: (I) systemically administered MSCs home to sites of ischemia or injury, and (II) MSCs can modulate T-cell-mediated immunological responses. MSCs express chemokine receptors and ligands involved in cells migration and homing process. MSCs induce immunomodulatory effects on the innate (dendritic cells, monocyte, natural killer cells, and neutrophils) and the adaptive immune system cells (T helper-1, cytotoxic T lymphocyte, and B lymphocyte) by secreting soluble factors like TGF- β , IL-10, IDO, PGE-2, sHLA-G5, or by cell–cell interaction. In this review, we discuss the main applications of mesenchymal stem in Regenerative Medicine and known mechanisms of homing and Immunomodulation of MSCs.

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Introduction

Mesenchymal stem cells (MSCs) are non-hematopoietic multipotent progenitor cells, which reside in bone marrow (Ben-Ami et al. 2011). The presence of non-hematopoietic stem cells in bone marrow were first recommended 130 years ago by Cohnhein, a German pathologist, (Chamberlain et al. 2007) who observed a class of the multipotent progenitors with fibroblast-like morphology which were spindle-shaped, plastic adherent, and non-phagocytic (Mohammadian and Shamsasenjan 2013). These cells which are also known as multipotent stromal or mesenchymal cells were first characterized by Friedenstein and his colleagues in 1970. *In vitro*, MSCs are able to divide up to 50 times in about 10 weeks (Lotfinegad 2014).

Self-renewal potential and multipotency are MSC's hallmarks (Mohammadian and Shamsasenjan 2013, Moriscot et al. 2005, Shi et al. 2011). *In vitro* and *in vivo*, these cells are capable of differentiating to the variety of cell lineages like adipocyte, chondrocyte, osteocyte, tenocyte, fibroblast, cardiomyocyte, skeletal myocyte, Neuronshepatocyte, and stromal cell (Gebler et al. 2012, Krampera et al. 2006b, Wang et al. 2009). In addition, MSCs supply cytokines and growth factors which support expansion of hematopoietic and embryonic stem cells (Aggarwal and Pittenger 2005); therefore, they support hematopoietic stem cells homing and self-renewal in bone marrow (Maitra et al. 2004) (Figure 1).

It is estimated that MSCs are about 0.001% of mononucleated cells in BM, despite the fact that the amount of them decline with age (Mohammadian and Shamsasenjan 2013, Mueller and Glowacki 2001, Kitoh et al. 2004). In addition to bone marrow, MSCs have been isolated from other supplies including liver, lung, brain, adipose tissue, peripheral blood, cornea, synovium, thymus, dental pulp, periosteum, tendon, spleen, fallopian tube, placenta, amniotic fluid, Whartons jelly, and umbilical cord blood (Lotfinegad 2014).

Mesenchymal stem cells (MSCs) are well-known for the expression of surface markers such as: including CD105(SH2), CD73(SH3,4), stromal antigen-1, CD90, CD44, CD166(VCAM), CD54, CD102(ICAM-2), and CD49(VLA). (Aggarwal and Pittenger 2005) Conversely, MSCs are distinguished from hematopoietic cells by lacking hematopoietic specific markers including CD11b, CD11c, CD14, CD19, CD31, CD34, CD45, CD79a, HLA-DR, lymphocyte function-associated antigen 1 (LFA1), glycophorin A, as well as platelet, and endothelial cell markers (Ghannam et al. 2010a, Shi et al. 2011, Volarevic et al. 2011). It is believed that MSCs are remains of the embryonic stem cells which exist in adult human body and express the embryonic stem cell transcription factors including: HOX, SSEA-1 (stage-specific embryonic antigen 1), Nanog, Oct-4, Rex-1, and GATA-4 (Krampera et al. 2006b, Lotfinegad 2014).

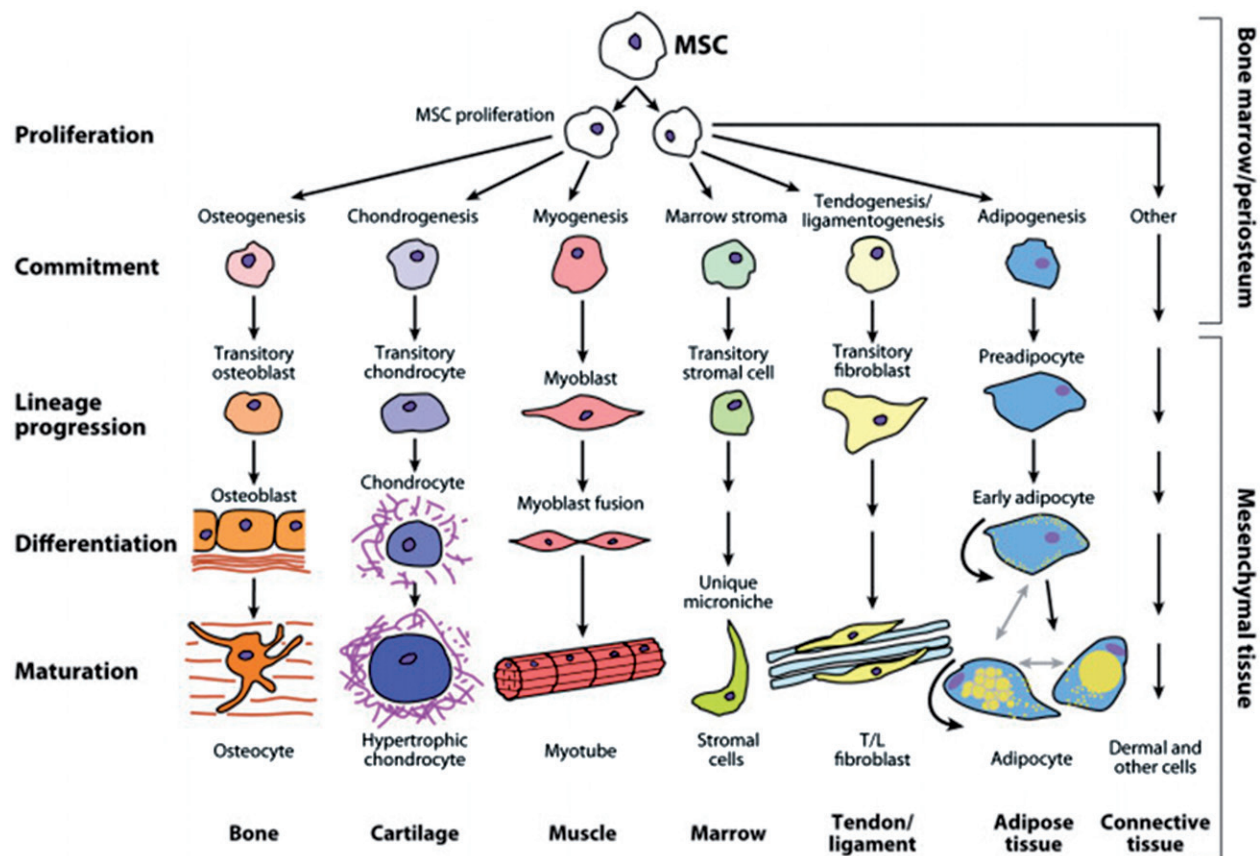


Figure 1. Msc differentiating to the variety of cell lineages.

In vitro and *in vivo*, MSCs release IL (Interleukin)-6, IL-7, IL-8, IL-10, IL-11, IL-12, IL-14, IL-15, sHLA (soluble human leukocyte antigen)-G5, PGE2 (prostaglandin E2), M-CSF (macrophage colony-stimulating factor), IDO (Indole 2,3-dioxygenase), TGF- β (transforming growth factor- β), HGF (hepatocyte growth factor), iNOS (inducible nitric oxide synthase), Galectin-3, and HO (hemoxygenase). Pevsner-Fischer et al. displayed that cultured MSCs express TLR (Toll like receptor) molecules 1–9. Activation of MSCs by TLR ligands stimulate IL-6 secretion and NF κ B nuclear translocation (Pevsner-Fischer et al. 2007, Yagi et al. 2010). It is identified that TLRs mediate responses of bone marrow-derived progenitor cells. A recent study described the significance of TLRs in migration and immune regulation of MSCs (Nagai et al. 2006, Pevsner-Fischer et al. 2007, Ryan et al. 2007, Yagi et al. 2010).

Medical applications of MSCs

Stem cells in common and MSC in particular, due to their significant potential in proliferation and differentiation, are considered as perfect candidates for regenerative medicine applications (McTaggart and Atkinson 2007). Major role of MSCs is correlated to their various therapeutic properties: sustained self-renewal and expansion, multipotentiality, anti-inflammatory and immunomodulatory effects, secretion of mediators that initiate or support tissue renovation, and tissue substitution (Caplan and Dennis 2006, Du et al. 2013, Waszak et al. 2012). One of the most significant properties that

make MSCs a special tool for cell based therapeutic approaches is their ability to escape from immune rejection; therefore, HLA-matching is not that much important for their implantation and HLA-mismatched donors can be chosen too (Dazzi and Marelli Berg 2008, Siegel et al. 2009). Besides, the anti-inflammatory activity of MSCs resulted in the production of anti-inflammatory macrophages, which are important in increasing tissue repair (Kim and Hematti 2009).

The proof-of-principle essential to utilize of MSCs *in vivo* has been demonstrated by a series of trials: (I) MSCs might engraft into mouse tissues after transplantation and show a site-specific differentiation, which is due to their exclusive immunological properties that permit engraftment with no rejection; (II) in humans, autologous *in vitro* expanded MSCs could be transplanted intravenously with no toxicity; (III) co-transplantation of autologous MSCs with HSCs lead to improved HSC engraftment; and (IV) allogeneic transplantation of MSCs reduced the frequency and intensity of acute and chronic graft versus host disease (GVHD) (Gebler et al. 2012, Sato et al. 2010, Tolar et al. 2010).

Mesenchymal stem cells (MSCs) have been brought into the clinic for numerous reasons: for differentiation and repairing injured tissues, for increasing hematopoietic engraftment following transplant via the production of growth factors (116 117), as well as for immunosuppressant in GVHD (Koç et al. 2000, Lazarus et al. 1995). Some of the other considerable therapeutic area include ischemic cardiac disease (Beyth et al. 2005), chronic obstructive pulmonary disease Crohn's and Behç

et al.'s disease (Du et al. 2013, Mazaheri et al. 2012), autoimmune diseases (Corcione et al. 2006, Sotiropoulou et al. 2006), damaged liver and kidneys (McTaggart and Atkinson 2007), bone disorders (e.g., osteogenesis imperfecta) (Sillence et al. 1978, Horwitz et al. 1999, 2001, 2002), neurological defects (Nauta et al. 2006), metachromatic leukodystrophy, and Hurler's disease (Groth and Ringdén 1984, Krivit et al. 1999). Moreover, MSCs also have therapeutic potential used in treating pulmonary fibrosis and acute renal nephropathy, and also in inhibiting the progress of diabetes. MSCs transplantation promotes the development and expansion of B cells and renal glomeruli as well as decreasing collagen deposition and inflammation in fibrosis (Lee et al. 2009, Vija et al. 2009) (Urban et al. 2008). Furthermore, MSCs infusion can be very useful in cord blood transplantation where the restricted amount of stem cells delays engraftment and favors graft rejection. Cell therapy approach has also been utilized as GVHD prophylaxis in HSC transplantation. The therapeutic efficiency was related to reduced antigen-specific Th1/Th17 cell expansion, increased production of IL-10 and generation of CD4⁺, CD25⁺, and FoxP3⁺ Treg cells with the ability to suppress self-reactive T effector responses (Ghannam et al. 2010b, Angoulvant et al. 2004).

MSCs homing

Homing is the process by which cells migrate to, and engraft within. Although the homing of leukocytes to the inflammation sites is well studied, the process of progenitor cell homing to the sites of ischemia or damage is weakly identified (Imhof and Aurrand-Lions 2004, Luster et al. 2005). Homing involves a cascade of incidents begun to interactions between flowing cells and the vascular endothelium at the target tissue (Stage I). This procedure is mediated via "homing receptors" expressed on circulating cells that connect related endothelial co-receptors, causing in cell-tethering, and rolling contacts on the endothelial surface. This is typically followed by chemokine generated activation of integrin adhesiveness (Stage II), hard adhesion (Stage III), and extravasation (Stage IV) (Sackstein 2005, Yagi et al. 2010).

Integrins have been identified to play a significant role in cell adhesion, migration, and chemotaxis (Ridger et al. 2001, Werr et al. 1998). Integrin $\alpha 4/\beta 1$ -VCAM interaction has been known to regulate T cell and NK cell trafficking (Woodside et al. 2006). Integrin $\beta 1$ is involved in cell adhesion, which is essential for the anchorage of the engrafted cells. As expected, blockade of integrin $\beta 1$ reduces neutrophil migration into the lung through inflammation (Ridger et al. 2001, Yagi et al. 2010). Ruster et al. explained that MSCs interact with endothelial cells in an organized style, not only through integrin $\alpha 4/\beta 1$ -VCAM-1 interaction or integrin $\beta 1$, but also via the endothelial phenotype, P-selectin, MMP-2 production, and cytokines (Rüster et al. 2006). Fibronectin attaches extracellular matrix components like collagen, fibrin, and heparan sulfate proteoglycans. It plays a significant role in cell adhesion, growth, and migration as well as differentiation; and it is important in injury healing process. Integrin $\alpha 4/\beta 1$ -fibronectin interaction plays a significant role in transmigration of MSCs into the extracellular matrix (Ruoslahti 1984, Valenick et al. 2005).

Mesenchymal stem cells (MSCs) express chemokine receptors and ligands involved in cell migration, including CCR1, CCR2, CCR3, CCR4, CCR7, CCR8, CCR10, CCL2, CCL3, CCL4, CCL5, CCL7, CCL20, CCL26, CX3CL1, CXCL1, CXCL2, CXCL3, CXCL5, CXCL8, CXCL10, CXCL11, and CXCL12. In contrast, they do not express CXCR4, which suggests that CXCR4 can simply be significant for trafficking of mature stem cell population (Hoogduijn et al. 2010, Lotfinegad 2014, McTaggart and Atkinson 2007, Yagi et al. 2010). Stromal cell-derived factor 1 (SDF-1) which is formally intended Chemokine (C-X-C motif) ligand 12 (CXCL12) is a small chemokine that activates leukocytes and is frequently stimulated by pro-inflammatory stimuli like TNF- α or IL-1 (Fedyk et al. 2001). CXCR4 is the receptor for this chemokine and the SDF-1-CXCR4 interaction which is the main mechanism of homing, considered to be exclusive (Ma et al. 1998). MSCs considerably migrated in response to SDF-1 and CXCL12, constant with their expression of chemokine receptors CXCR4 or CX3CR1, respectively (Yagi et al. 2010).

As revealed in studies, on engraftment of hematopoietic stem/progenitor cells, interaction between CXCR4 and its ligand, SDF-1, co-operates a significant function in homing and mobilization (Chamberlain et al. 2007, Peled et al. 1999). Moreover, MSCs have an important role in co-transplantation of hematopoietic stem cells by producing SDF-1, Flt-3 ligand, and stem cell factor, together with expressing extra-cellular matrix proteins including fibronectin, laminin, and vimentin, which have a critical role in HSC homing in the bone marrow niche (Akbari et al. 2007, Delalat et al. 2009, Horwitz et al. 2011, Mohammadian and Shamsasenjan 2013).

Immunomodulatory effects of MSCs on immune system

It has been approved that the potency of MSCs to modulate immune responses is due to both cell-cell interactions and paracrine effects (Lotfinegad 2014). MSCs can reduce immune responses by influencing both natural and adaptive immunity (Ben-Ami et al. 2011). MSCs can inhibit innate immune system cells (DC, NK, monocyte, and neutrophil) and adaptive immune system cells (B, TH1, and T CTL) (Spaggiari et al. 2009).

Innate immune system cells

Natural killer cells

Natural killer cells (NK cells) are main effector cells of the innate immunity and are generally thought to play a basic role in antiviral responses (Yagi et al. 2010).

MSCs inhibit IL-2-induced NK cell proliferation, mostly via the soluble immunosuppressive factors, transforming growth factor- β (TGF- β), soluble human leukocyte antigen-G (sHLA-G), prostaglandinE2 (PGE2), and indoleamine 2,3-dioxygenase (IDO) in addition to cell-cell contact (Abdi et al. 2008, Ben-Ami et al. 2011, Gebler et al. 2012, Gonen-Gross et al. 2010, Lotfinegad 2014, Spaggiari et al. 2008, Yagi et al. 2010). Recently, Prigione et al. discovered that the inhibitory effect of MSCs on the proliferation of invariant NK T (iNKT, V α 24+V β 11+) and $\gamma\delta$ T(V δ 2+) cells in the peripheral blood is

mediated by secreting PGE₂, before IDO and TGF- β 1. On the other hand, cytokine production and cytotoxic activity of the NK cells only moderately affected by MSCs (Prigione et al. 2009, Shi et al. 2011).

MSCs may have more influence on the innate immunity by their inhibitory effects on natural killer cell cytotoxicity via down-regulating of NKp30, NKp44, NKG2D, and DNAM-1, by enhancing receptor expression on NK cells and also by inhibiting proliferation and suppressing of IFN- γ production (Ben-Ami et al. 2011, Spaggiari et al. 2006, 2008). Although several studies revealed that MSCs suppress NK cell proliferation and IFN- γ production (Aggarwal and Pittenger 2005, Maccario et al. 2005, Rasmusson et al. 2003, Ryan et al. 2007, Shi et al. 2011, Sotiropoulou et al. 2006), Krampera et al. described that NK cells which co-cultured with MSCs in the presence of IL-2 for 4–5 days had shown reduced cytolytic activity against K562 cell line and this suppressive effect might be attributed to the IFN- γ production by NK cells (Shi et al. 2011). General aspects of immunomodulatory effects of MSCs on NK cells are illustrated in Figure 1.

Dendritic cells

Dendritic cells (DCs), depending on their maturation and activation phase, have an important role in initiating of primary immune responses. Immature DCs have the ability of antigen up taking and processing and so they act as guard in peripheral tissues (Banchereau and Steinman 1998, Mellman and Steinman 2001, Yagi et al. 2010). MSCs may also regulate immune responses via interacting with DCs.

Myeloid DCs are the most potent antigen presenting cells which are essential in the induction of immunity and tolerance. During maturation, immature DCs acquired the expression of co-stimulatory molecules, and up-regulated the expression of MHC class I and class II molecules together with additional cell surface markers like CD11c, CD80, CD83, and CD86. MSC postpones the up-regulation of CD1A, CD40, CD80 (B7–1), CD86 (B7–2), and HLA-DR through DC maturation even as CD83 rose (Delalat et al. 2009, Ruoslahti 1984). *In vitro*, MSCs can inhibit the differentiation of monocytes and CD34⁺ hematopoietic progenitor cells into the DCs, via a declined cell surface expression of MHC class II, CD11c, CD83, and co-stimulatory molecules on mature DCs, in addition to a reduced production of IL-12 and TNF α ; and subsequently give rise to immature DCs which could consequently provide anergic T-cells. Ramasamy et al. explained that the cell cycle in DCs was arrested in the G0/G1 phase due to their contact with MSCs (Ma et al. 1998). This outcome is partly mediated by the production of IL-6 or PGE-2 by activating MSCs, which is directly responsible for blocking DC maturation (Aggarwal and Pittenger 2005, Djouad et al. 2007, Ghannam et al. 2010a, Jiang et al. 2005, Spaggiari et al. 2009). Spaggiari et al. confirmed that MSCs powerfully inhibited the maturation and function of monocyte-derived DCs by means of inhibitory mediator of MSCs derived, PGE₂ (Fedyk et al. 2001). IL-6 has been reported to be involved in the inhibition of monocyte differentiation to DCs as well as diminishing their stimulation capacity on T cells (Horwitz et al. 2011). These results suggest that MSCs might direct DC maturation to an anti-inflammatory or regulatory

phenotype which is responsible for a desired T-cell response (Aggarwal and Pittenger 2005, Djouad et al. 2007, Ghannam et al. 2010a, Jiang et al. 2005, Spaggiari et al. 2009).

The effect of MSCs is controlled through primary phases of DC maturation, as verified by alterations in the expression of the DC surface markers CD80, CD86, CD83, and the secretion of the polarizing cytokine IL-12. MSCs have been shown to modify the cytokine secretion profile of DCs. DCs which are generated in the presence of MSCs, secrete low levels of inflammatory cytokines like IFN- γ , IL-12, and TNF- α , high levels of regulatory cytokines like IL-1 β , IL-10 as well as low levels of MHC class II antigens; thus, induce further anti-inflammatory responses or generate tolerant DCs phenotype. Most recent studies suggest that antigen processing and presentation by MHC class II surface molecules is impaired in these DCs (Abdi et al. 2008, Nauta et al. 2006, Ryan et al. 2005).

CD14⁺ monocytes can activate MSCs to secrete soluble factors like IL-1 β which inhibit alloreactive T-cells (Groh et al. 2005, Le Blanc and Ringden 2007). Significantly, DCs which co-cultured by MSCs showed a decreased potential to activate CD4⁺ cells in mixed lymphocyte culture (MLC) (Aggarwal and Pittenger 2005, Beyth et al. 2005, Jiang et al. 2005, Le Blanc and Ringden 2007, Maccario et al. 2005, Zhang et al. 2004). A new study reported that adipose derived MSCs are more potent immunomodulators in human DCs differentiation than bone marrow derived MSCs (Peled et al. 1999).

Neutrophils

Neutrophils are the first cells which arrive to the inflammatory tissues and secrete cytokines MSCs may also induce its immunomodulatory effects by interacting with neutrophils (Ben-Ami et al. 2011, Raffaghello et al. 2008).

MSCs inhibit the *in vitro* secretion of hydrogen peroxide in activated neutrophils, therefore these stem cells can potentially control the intensity of a respiratory burst in inflammatory stimulation (Ben-Ami et al. 2011, Raffaghello et al. 2008). MSCs can decrease the intensity of the respiratory burst and apoptosis which is a vital factor of the phagocytic role of neutrophils. This may be a serious process whereby MSCs can control the intensity of tissue damage following ischemic and ischemia/reperfusion damage (Hirata et al. 1993, Mazaheri et al. 2012). In addition, the production of IL-6 via MSCs has been reported toward stoppage apoptosis of lymphocytes (Prigione et al. 2009) and neutrophils (Djouad et al. 2007, Ghannam et al. 2010a, Jiang et al. 2005, Raffaghello et al. 2008, Xu et al. 2007).

Adaptive immune system cells

B cells

B cells have a crucial role in adaptive immune system by differentiating to plasma cells and antibody secretion (IgA, IgG, and IgM). They also play a major role in autoimmune diseases (Le Blanc and Ringden 2007).

MSCs are capable of modulating the immune response of B cells. It has been demonstrated that in a co-culture of activated B-cells with mesenchymal stem cells, the B-cells proliferation as well as antibody secretion (IgA, IgG, and IgM) in plasma cells

were inhibited (Corcione et al. 2006, Lotfinegad 2014). MSCs arrest B cells in G0/G1 phase of the cell cycle and avoid apoptosis (Campagnoli et al. 2001, Mohammadian and Shamsasenjan 2013).

Allogeneic MSCs have been shown to restrain the proliferation, activation, and IgG secretion of B cells in BXSB mice that are utilized as an investigation model for human systemic lupus erythematosus (Augello et al. 2005, Deng et al. 2005, Nauta and Fibbe 2007). Also, MSCs can cause an increase in the CD40 expression and CD40 ligand ectopic hyper expression in the B cells of BXSB mice (Deng et al. 2005, Shi et al. 2011). Krampera et al. demonstrated that MSCs decreased the proliferation of B cells in the presence of IFN- γ . The suppressive effect of IFN- γ is probably related to its ability to stimulate the secretion of IDO via MSCs, which in turn suppresses the proliferative response of effectors cells through the tryptophan pathway (Krampera et al. 2006a, Nauta and Fibbe 2007). MSCs down-regulated the expression of chemokine receptors CXCR4, CXCR5, and CCR7B; and decrease the chemotaxis of CXCL12 (CXCR4 ligand), CXCL13, and CXCR5 ligand, suggesting that elevated numbers of MSCs influence the chemotactic properties of B cells (Abdi et al. 2008, Chamberlain et al. 2007, Corcione et al. 2006, Deng et al. 2005, Le Blanc and Ringden 2007, Shi et al. 2011, Volarevic et al. 2011).

As B cell activation is mostly T cell-dependent, the influence of MSCs on T cells activity might also suppress B cells functions indirectly. In addition, MSC has a direct influence on B cell activity by cell contact and secretion of paracrine molecules (Augello et al. 2005, Corcione et al. 2006, Gerdoni et al. 2007, Weil et al. 2011). These findings cannot support the potential of therapeutic application of MSCs in autoimmune diseases, where the B cells play a major role (Le Blanc and Ringden 2007).

T cells

Human MSC limits the development of CD4⁺ and CD8⁺ T cells by soluble factors (Corcione et al. 2006, Di Nicola et al. 2002, Le Blanc and Ringden 2007, Potian et al. 2003, Tse et al. 2003). The suppressive factor is not constitutively produced by MSCs; since cell culture supernatants do not suppress T-cell proliferation (Augello et al. 2005, Le Blanc and Ringden 2007, Le Blanc et al. 2004, Maitra et al. 2004, Potian et al. 2003). Tse et al. displayed that nearness to MSCs significantly suppress T cell responsiveness which recommended that direct interaction between lymphocytes and MSCs was more significant than soluble mediators (Tse et al. 2003, Yagi et al. 2010). Krampera et al. also confirmed that immunosuppressive responses need MSC-T-cell interaction in culture (Krampera et al. 2003, Yagi et al. 2010).

Mesenchymal stem cells show immunosuppressive properties by inhibiting the response of naive and memory T cells in mixed lymphocyte culture (MLC) induced by mitogens (Koç et al. 2000). Suppression is MHC free (Nauta and Fibbe 2007) and mainly evident if MSCs is added on the earliest day of the 6-day culture. The suppression is appeared to be dosage dependent. Reserve manifests are detected when more numbers of MSCs are present (MSC:lymphocyte ratio >1:10). In contrast, adding of MSCs at a low ratio (1:100–1:10 000) increases proliferation (Le Blanc and Ringden 2007, Le Blanc et al. 2003, Liu et al. 2004, Potian et al. 2003).

MSCs may inhibit the cell division through the gathering of cells in the G0/G1 phase of the cell cycle. At the molecular level, cyclin D2 expression is down-regulated, whereas p27 expression is up-regulated; this might clarify why T cell proliferation, before activation, and IFN- γ secretion are affected by MSC (Glennie et al. 2005, Shi et al. 2011). A recent study demonstrated that B7-H4, a negative co-stimulatory molecule, is involved in the immunosuppressive effect of MSCs on T cell activation and proliferation by arresting the cell cycle and inhibition of the nuclear translocation of nuclear factor (NF)- κ B (Sensebe et al. 2010).

MSCs may inhibit T-cell proliferation through the secretion of indoleamine 2,3-dioxygenase (IDO). IDO, which is induced by IFN- γ , can catalyze the alteration of tryptophan to kynurenine and also inhibit T-cell responses through tryptophan reduction (Le Blanc and Ringden 2007, Munn et al. 1998). Meisel et al. revealed that human MSCs do not express IDO constitutively, and the expression is stimulated by IFN- γ . IFN- γ stimulates IDO enzyme activity in a dose-dependent manner. The importance of IDO activity was identified in T cells stimulated by mitomycin C-treated PBMC in the presence of MSCs (Le Blanc and Ringden 2007, Meisel et al. 2004).

MSCs display their immunosuppressive potentials through the other mechanisms too. Matrix metalloproteinase (MMPs), particularly MMP-2 and MMP-9, are produced by MSCs and mediate the suppressive activity of MSCs through the reduction of CD25 expression on responding T cells (Ding et al. 2009). MSCs can inhibit T-cell proliferation by interacting of the inhibitory programmed death 1 (PD-1) molecule to its ligands PD-L1 and PD-L2, thus producing soluble factors (such as TGF- β or IL-10) that suppress T-cell proliferation (Nauta and Fibbe 2007, Volarevic et al. 2009, 2011). Recently, it has been revealed that the production of HLA-G5 by MSCs may suppress T-cell proliferation, as well as natural killer and T-cell cytotoxicity, and also may increase the generation of regulatory T (Treg) cells. Cell contact between MSCs and activated T cells stimulate IL-10 production, which is necessary to induce the release of soluble HLA-G5 (Ghannam et al. 2010a, Nasef et al. 2009, Selmani et al. 2008).

A recent study reported that MSCs might stimulate apoptosis in activated T cells [CD3⁺ and bromodeoxyuridine (BrdU)⁺], but not in the resting T cells [CD3⁺ and BrdU⁻]. *In vivo*, this may lead to the reduction of delayed-type hypersensitivity (DTH) response by inducing NO production (Lim et al. 2010). NO (nitric oxide) prevents the T cells proliferation by suppressing the phosphorylation of signal transducer and activator of transcription-5 (STAT5), an essential transcription factor for T cell activation and proliferation (Bingisser et al. 1998, Shi et al. 2011). Altogether, MSC increases TH2 generation, IL-4 production, regulatory T cell response, and also decrease activation by foreign antigen, cytotoxic T cell, and IFN- γ production (Weil et al. 2011).

T helper cells. The T helper cells (Th cells) are subpopulations of CD4⁺ T-cells that play an important role in the adaptive immune system and provide help to other cells of the immune system releasing cytokines or causing cell activation (Akbari et al. 2007).

Signals that support T-helper cell 1 (TH1) development such as CD3, CD28, IL-4, IL-2, and IL-12, can also cause naive T cells maturation into IFN- γ secreting cells. IFN- γ secretion decreases in the presence of MSCs in culture. Hence, MSCs stimulates a bias towards TH2 differentiation (Aggarwal and Pittenger 2005, Le Blanc and Ringden 2007). Furthermore, MSCs has also been reported to influence the cytokine secretion profile of the different T-cell subsets, since *in vitro*, their addition to an activated T-cell culture reduces production of the pro-inflammatory cytokines like IFN- γ , TNF- α , IL-6, IL-17, and increases anti-inflammatory cytokines like IL-4 and IL-10. Altogether, these findings could show a possible MSC-mediated alternation in Th1/Th2 balance (Kong et al. 2009, Zappia et al. 2005).

MSC inhibits naive T cells to differentiate into the TH17 (Meisel et al. 2004). MSC reduces antigen-specific Th1/Th17 cell expansion as well as cytokine (IFN- γ and IL-17) production by Th1/Th17 cells. MSCs also induce the Th2 cells to increase the production of IL-4 and IL-10 in lymph node joints (Aggarwal and Pittenger 2005, Krampera et al. 2003, Shi et al. 2011, Zappia et al. 2005). MSCs can also decrease the expression of major histocompatibility complex class E (MHC class E) on T-helper cells (Ghannam et al. 2010b, Mazaheri et al. 2012).

Cytotoxic T cells. Cytotoxic T cells (CTL) are subpopulations of CD8⁺ T-cells that play an important role in the cellular immune system to kill cancer cells, infected cells or damaged cells (Akbari et al. 2007).

MSCs which co-cultured in mixed lymphocyte culture (MLC) suppress CD8⁺ T-cell activity. MSCs, if added by the start of the MLC, can suppress CD8⁺ T-cell mediated lysis (Le Blanc and Ringden 2007, Rasmusson et al. 2003). However, cytotoxicity is not affected if MSCs were added in the cytotoxic stage (Angoulvant et al. 2004, Le Blanc and Ringden 2007, Maccario et al. 2005, Potian et al. 2003, Rasmusson et al. 2003). Lysis was partly stopped by adding IL-2. MSCs might inhibit the afferent phase of alloreactivity and prevent the development of cytotoxic T cells (Angoulvant et al. 2004, Le Blanc and Ringden 2007). CD25 and CTLA-4 (cytotoxic T lymphocyte-associated antigen-4) surface expression, and Foxp3 mRNA levels, were not dependent forward when CD4⁺ T cells were cultured in the company with MSCs (Krampera et al. 2006a).

Regulatory T cells. The regulatory T cells (Tregs), are a subpopulation of T cells which modulate the immune system, maintain tolerance to self-antigens, and abrogate autoimmune disease. These cells generally suppress or downregulate induction and proliferation of effector T cells (Akbari et al. 2007).

While MSCs effectively inhibit T cells proliferation, they can protect the role of CD4⁺ CD25⁺ CD127⁺ FoxP3⁺ regulatory T cells (Treg). MSCs increase the amount of CD4⁺ CD25⁺, CD4⁺ CTLA4⁺ cells, and CD4⁺ CD25⁺ CTLA4⁺ cells in IL-2-stimulated MLC (Aggarwal and Pittenger 2005, Le Blanc and Ringden 2007, Maccario et al. 2005). In contrast, the amount of CD25⁺ and CD38⁺ cells decrease in the presence of MSCs in mitogen-stimulated lymphocyte cultures (Groh et al. 2005, Le Blanc and Ringden 2007). MSC also produces bone morphogenic protein-2 (BMP-2) which mediates immunosuppressive response through the production of CD8⁺ regulatory T cells (Djouad et al. 2003, Le Blanc and Ringden 2007).

Prostaglandin E2 (PGE2), which is produced by cyclooxygenase (COX) enzymes, induces the regulatory T cells. MSCs constitutively express COX-1 and COX-2 together. When purified T cells were co-cultured with MSCs, both COX-2 and PGE2 production were increased PGE2 synthesis inhibitors restored the majority of the proliferation of lymphocytes co-cultured by MSCs (Aggarwal and Pittenger 2005, Arikawa et al. 2004, Le Blanc and Ringden 2007).

Conclusion

Rational understanding of MSCs mechanisms of action allows us to translate our basic knowledge of MSC biology into the design of new clinical therapies. The anti-proliferative potential and immunodulatory function of MSCs has been studied by different groups, with the hope that MSCs may be developed as a new therapeutic strategy for autoimmune disease, Hematopoietic Stem Cell Transplantation (HSCT), Bone marrow Transplantation (BMT), and cell-based regenerative therapy. MSCs have the capacity of homing and integration into the damaged tissues. MSCs provide immunomodulatory effects on the immune system via paracrine and/or cell-cell interaction, which may inhibit innate and adaptive immune system cells. Therefore, employing MSCs could lead to various therapeutic possibilities such as supporting tissue regeneration and correcting inherited disorders. Autologous MSC transplantation may have a high capability to develop the desired outcome in clinical therapies.

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Declaration of interest

The authors declare that they have no competing interests.

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