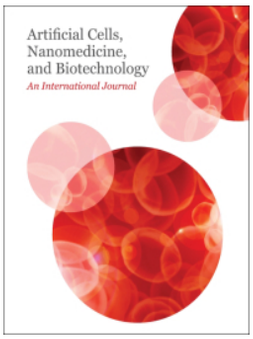

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REVIEW ARTICLE

Biotechnological and biomedical applications of mesenchymal stem cells as a therapeutic system

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Abstract

Mesenchymal stem cells (MSCs) are non-hematopoietic, multipotent progenitor cells which reside in bone marrow (BM), support homing of hematopoietic stem cells (HSCs) and self-renewal in the BM. These cells have the potential to differentiate into tissues of mesenchymal origin, such as fibroblasts, adipocytes, cardiomyocytes, and stromal cells. MSCs can express surface molecules like CD13, CD29, CD44, CD73, CD90, CD166, CXCL12 and toll-like receptors (TLRs). Different factors, such as TGF-β, IL-10, IDO, PGE-2, sHLA-G5, HO, and Galectin-3, secreted by MSCs, induce interaction in cell to cell immunomodulatory effects on innate and adaptive cells of the immune system. Furthermore, these cells can stimulate and increase the TH2 and regulatory T-cells through inhibitory effects on the immune system. MSCs originate from the BM and other tissues including the brain, adipose tissue, peripheral blood, cornea, thymus, spleen, fallopian tube, placenta, Wharton's jelly and umbilical cord blood. Many studies have focused on two significant features of MSC therapy: (I) MSCs can modulate T-cell-mediated immunological responses, and (II) systemically administered MSCs home in to sites of ischemia or injury. In this review, we describe the known mechanisms of immunomodulation and homing of MSCs. As a result, this review emphasizes the functional role of MSCs in modulating immune responses, their capability in homing to injured tissue, and their clinical therapeutic potential.

Keywords: bone marrow, cells, immunomodulatory, immune system, mesenchymal stem cells

Introduction

Mesenchymal stem cells (MSCs) are non-hematopoietic, multipotent progenitor cells, which exist in the bone marrow (BM)(Ben-Ami et al. 2011). They are responsible for the homing of hematopoietic stem cells (HSCs) and their self-renewal in the BM(Maitra et al. 2004). These cells are capable of differentiating *in vitro* and *in vivo* into more cells of mesenchymal lineage, as well as adipocytes, chondrocytes, osteocytes, tenocytes, fibroblasts, cartilage, bone, cardiomyocytes, skeletal myocytes, visceral cells, mesoderm, ectodermal cells (e.g. neurons), endodermal cells (e.g. hepatocytes), and stromal cells(Krampera et al. 2006a, Gebler et al. 2012, Wang et al. 2009).

In addition, MSCs have been found to supply cytokine and growth factor support for expansion of hematopoietic and embryonic stem cells(Aggarwal and Pittenger 2005). These cells, which are also well known as multipotent stromal or mesenchymal cells, were discovered by Friedenstein and his colleagues in 1970. MSCs are capable of dividing up to 50 times in about 10 weeks, *in vitro*(Lotfinegad 2014). The presence of non-hematopoietic stem cells in the bone marrow was first revealed by the observation of the German pathologist Cohnheim, 130 years ago(Chamberlain et al. 2007). This class of the multipotent progenitors were spindle-shaped, plastic-adherent, and non-phagocytic, with fibroblast-like morphology(Mohammadian and Shamsasenjan 2013).

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MSCs are well-known for the expression of surface markers such as:

CD105 (SH2), CD73 (SH3, SH4), stromal antigen-1, CD90, CD44, CD166 (VCAM), CD54, CD102 (ICAM-2), and CD49 (VLA) (Volarevic et al. 2011). Conversely, MSCs are distinguished from HSCs in that they lack the cell surface markers, CD11b, CD11c, CD14, CD19, CD31, CD34, CD45, CD79a, and the HLA-DR, lymphocyte function-associated antigen1(LFA1), erythrocytes (glycophorin A), platelet and endothelial cell markers. The commonly known phenotypes and markers are listed in Table I (Volarevic et al. 2011, Ghannam et al. 2010a, Shi et al. 2011). (Table I).

Table I. Phenotypes, lineage-specific and functional markers of MSCs (Krampera et al. 2006, Pountos et al. 2007, Bühring et al. 2007, Deans and Moseley 2000, Devine et al. 2002, Fickert et al. 2004, Jorgensen et al. 2004, Otto and Rao 2004, Pittenger and Martin 2004, Simmons and Torok-Storb 1991, Barry et al. 2001, Tse et al. 2003, Le Blanc et al. 2003, Xu et al. 2004, Vogel et al. 2003, Majumdar et al. 2003, Bruder et al. 1998, Gronthos et al. 1994, Potian et al. 2003).

	Positive in MSCs	Negative in MSCs
Hematopoietic receptors		CD1a (T6) CD14 (Lipopolysaccharide receptor) CD34 CD45 (Leukocyte common antigen) CD133 (AC133)
Adhesion molecules	CD44 (Hyaluronate receptor) CD50 (Intercellular adhesion molecule 3) CD54 (Intercellular adhesion molecule 1) CD56 (Neural cell adhesion molecule) CD58 (Lymphocyte function-associated antigen 3) CD62L (L-selectin) CD102 (intercellular adhesion molecule 2) CD106 (Vascular cell adhesion molecule-1) CD164 (Sialomucin) CD166 (Activated leukocyte cell adhesion molecule)	CD15 (Lewis Ag) CD31 (Platelet Endothelial Cell Adhesion Molecule-1) CD33 (Sialoadhesin) CD62E (E-selectin) CD62P (P-selectin) CD144 (Calherin 5)
Integrins	CD29 (Very late antigen β) CD49a (Very late antigen a1) CD49b (Very late antigen a2) CD49c (Very late antigen a3) CD49e (Very late antigen a5) CD49f (Very late antigen a6) CD61 (Vitronectin R βchain, GPIIb/IIIa) CD104 (β4 integrin)	CD11a (Lymphocyte function-associated antigen-1 α) CD11b (Macrophage-1 antigen) CD11c (Complement receptor type 4 a chain) CD18 (Lymphocyte function-associated antigen-1 β) CD49d (Very late antigen a4) CD51 (Vitronectin R a chain)
Growth factors and Cytokines	CD71 (Transferrin receptor) CD72 (Lymphocyte receptor) CD109 (platelet activating factor) CDw119 (Interferon γR) CD120 a & b (Tumor Necrosis factor-α 1&2 R) CD121 a & b (Interleukin-1R a&b chain) CD123 (Interleukin-3R) CD124 (Interleukin-4R) CD126 (Interleukin-6R) CD127 (Interleukin-7R) CD140a (Platelet derived growth factor receptor a) CD140b (Platelet derived growth factor receptor b) CD172a (Signal regulatory protein a) FGFR (Fibroblast growth factor receptor) CD271 (Low affinity nerve growth factor receptor) EGFR-1 (epithelial growth factor receptor-1)/ HER-1(human epidermal growth factor receptor-1) BMP R1 (Bone morphogenic protein receptor 1A) CD271 (Low affinity nerve growth factor receptor)	CD25 (Interleukin-2R) CD114 (Granulocyte-colony stimulating factor receptor) CD122(Interleukin-2R- β) HB-EGF EGFR-4(epithelial growth factor receptor-4)/ HER-4(human epidermal growth factor receptor-4)
Other Markers	CD9 (Tetraspanin) CD13 (Aminopeptidase N) CD59 (Protectin) CD73 (Ecto-5'-nucleotidase)(SH3/SH4) CD90 (Thy-1 glycoprotein) CD95 (Fas) CD105 (Endoglin) (TGFβ R/SH2) CD146 (MUC18,Mel-CAM, S-endo) CD157 (BP-3 or Bone Marrow Stromal cell antigen-1) SH3 (Src homology 3) D7-FIB STRO-1 MHC class I, HLA-A,B,C (human leukocyte antigen) SSEA-3,4 CXCL12 (SDF-1)	CD3 (CD3 complex) CD10 (CALLA) CD19 (B-lymphocyte Surface Antigen B4) CD30 CD30L (CD153) CD40 CD40L (CD154) CD80 (B7-1) CD83 (HB15a) CD86 (B7-2) CD235a (Glycophorin A) FasL (CD95L) TRAIL (tumour necrosis factor-related apoptosis-inducing ligand) TRAIL-R (tumour necrosis factor-related apoptosis-inducing ligand receptor) CXCR4 (CD184) MHC class II (HLA-DR) B2 microglobulin

It is believed that MSCs are remnants of embryonic stem cells which remain in the adult human body, and express embryonic stem cell markers including: HOX, SSEA-1, Nanong, Oct-4, Rex-1 and GATA-4(Krampera et al. 2006b, Lotfinegad 2014). In addition to the BM, MSCs originate from other sources, including the liver, lung, brain, adipose tissue, peripheral blood, cornea, synovium, thymus, dental pulp, periosteum, tendon, spleen, fallopian tube, placenta, amniotic fluid, Wharton's jelly and umbilical cord blood(Lotfinegad 2014). *In vitro* and *in vivo*, MSCs release IL-6, IL-7, IL-8, IL-10, IL-11, IL-12, IL-14, IL-15, sHLA-G5, PGE2, M-CSF, IDO,TGF-β, hepatocyte growth factor (HGF), inducible nitric oxide synthase (iNOS), Galectin-3, and hemooxygenase (HO). The potential for self-renewal and multipotency are the hallmarks of MSCs (Mohammadian and Shamsasenjan 2013, Shi et al. 2011, Moriscot et al. 2005). Pevsner-Fischer *et al*. displayed that cultured MSCs express toll-like receptor (TLR) molecules 1 to 9. Activation of MSCs by TLR ligands provoked IL-6 secretion and NF-kB nuclear translocation(Yagi et al. 2010, Pevsner-Fischer et al. 2007).

It has been identified that TLRs mediate responses of bone marrow-derived progenitor cells. A new study has described the significance of TLRs in migration and immune regulation of MSCs(Yagi et al. 2010, Pevsner-Fischer et al. 2007, Nagai et al. 2006, Ryan et al. 2007). It is predicted that MSCs constitute about 0.001% of mononucleotide cells in the BM, while their proportion declines with age(Mohammadian and Shamsasenjan 2013, Kitoh et al. 2004, Mueller and Glowacki 2001).

This review presents the immunomodulatory mechanism of MSCs on immune cells. In addition, homing of MSCs and the current uses of these cells in medicine are discussed briefly.

Immunomodulatory effects of MSCs on immune cells

It has been agreed that the potential of MSCs to modulate immune responses is due to both cell-cell interactions and paracrine effects(Lotfinegad 2014). MSCs can down-regulate the strength of an immune response by influencing both natural and adaptive immunity(Ben-Ami et al. 2011). MSCs can inhibit innate immune system cells (DCs, NK, monocyte and neutrophil) and adaptive immune system cells (B, TH1 and T- CTL). MSCs also induce stimulation of the TH2 and regulatory T-cells by the inflammatory microenvironment.

Innate immune system cells

Natural killer cells

Natural killer cells **(**NK cells) are the main effector cells in inherent immunity, and are commonly thought to play a basic role in antiviral responses(Yagi et al. 2010). MSCs hinder the proliferation of IL-2-induced NK cells, which is mostly mediated by the soluble immunosuppressive factors, transforming growth factor-ß (TGF-ß), soluble human leukocyte antigen-G (sHLA-G), prostaglandin E2 (PGE2) and indoleamine2,3- dioxygenase, in addition to cell-cell contact(Ben-Ami et al. 2011, Gebler et al. 2012, Lotfinegad 2014, Yagi et al. 2010, Spaggiari et al. 2008, Gonen-Gross et al. 2010, Abdi et al. 2008). MSCs can exert more influence on innate immunity during their inhibition of the cytotoxicity of NK cells by down-regulating the expression of NKp30, NKp44, NKG2D and DNAM-1-activating receptors on these cells, and also by inhibiting proliferation and inducing suppression of IFN-γ(Ben-Ami et al. 2011, Spaggiari et al. 2008, Spaggiari et al. 2006). Several studies have demonstrated that MSCs suppress NK cell proliferation and IFN-γ production driven by IL-2 or IL-15, but only partially inhibit the proliferation of activated NK cells(Aggarwal and Pittenger 2005, Shi et al. 2011, Ryan et al. 2007, Sotiropoulou et al. 2006, Rasmusson et al. 2003, Maccario et al. 2005). In contrast, Krampera *et al*. described that NK cells cultured for 4–5 days with IL-2 in the presence of MSCs showed reduced cytolytic potential against K562 cells, and this suppressive effect might be attributed to the IFN-γ produced by NK cells(Shi et al. 2011). Recently, Prigione *et al*. discovered that the inhibitory effect of MSCs on the proliferation of invariant NK T (iNKT, Vα24 + Vß11+) and γδT(Vδ2+) cells in the peripheral blood is mediated by secreting prostaglandin E2 (PGE2), before IDO and TGF-β1. On the other hand, cytokine production and cytotoxic activity of the cells were only moderately affected by MSCs. Vδ2 + cells also function as expert antigen-presenting cells for naive $CD4^+$ T cell response, and MSCs do not restrain antigen processing/presentation of activated Vδ2 + Tcells to $CD4^+$ T-cells. (Figure 1)(Shi et al. 2011, Prigione et al. 2009).

Dendritic cells

Dendritic Cells **(**DCs) participate with a key function in the beginning of primary immune responses, which depend on the maturation and activation steps of DCs. Immature DCs function as guards in peripheral tissues, by increased antigen uptake and processing, with low capability to stimulate T-cells(Yagi et al. 2010, Banchereau and Steinman 1998, Mellman and Steinman 2001). In the past, MSCs hampered the *in vitro* maturation of monocytes and hematopoietic progenitor cells into DCs, in addition to down-regulating the cell surface expression of MHC class II, CD11c, CD83 and co- stimulatory molecules on mature DCs(Ben-Ami et al. 2011, Jiang et al. 2005).

MSCs may also regulate immune reaction during interaction with DCs. MSCs could inhibit differentiation of monocytes into DCs; however, they could also inhibit the maturation of DCs, giving rise to immature DCs that could consequently render T-cells anergic. MSCs have also been shown to modify the cytokine secretion profile of DCs to up-regulate regulatory cytokines, for example IL-10, and down-regulate inflammatory cytokines like IFN-γ, IL-12, and TNF-α, and induce further anti-inflammatory effect or tolerant DC-phenotypes(Abdi et al. 2008, Ryan et al. 2005, Nauta et al. 2006). Spaggiari *et al*. confirmed that MSCs powerfully inhibit the maturation and functioning of immunomodulators of mesenchymal stem cell monocyte-derived DCs, by interfering selectively on the generation of immature DCs by means of inhibitory mediator MSC-derived PGE2, but not IL-6. On the other hand, the fundamental mechanism

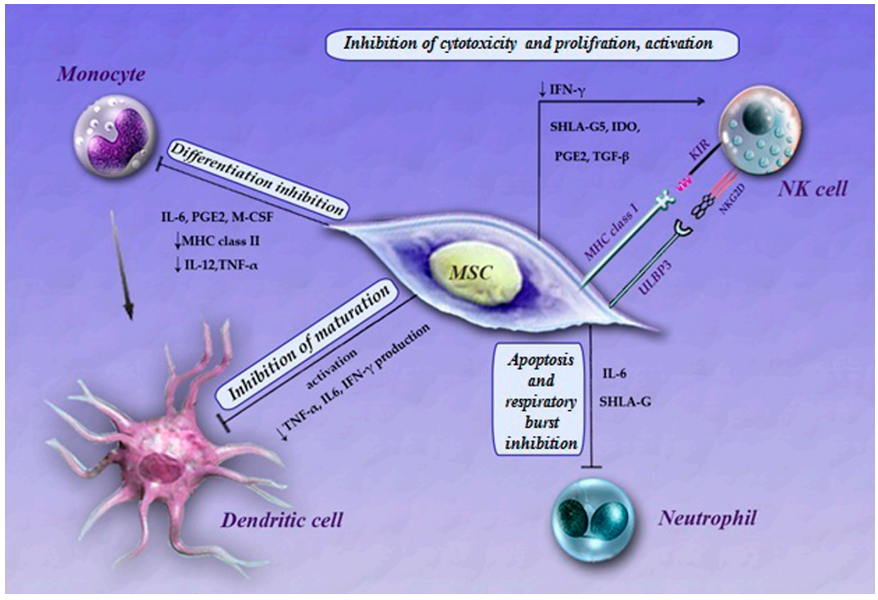

Figure 1. Effects of Mesenchymal stem cells (MSCs) on the innate immune system. MSCs exert an influence on a variety of cells of the immune system. Mechanisms governing these interactions include secretion of soluble paracrine factors by MSCs and direct cell–cell contact between MSCs and innate immune cells. Abbreviations: IFN gamma (interferon γ), IDO (indoleamine 2,3-dioxygenase), IL-2 (interleukin 2), IL-6 (interleukin 6), prostaglandin E2 (PGE2), transforming growth factor beta (TGFβ) TNF-α (tumor necrosis factor α), soluble human leukocyte antigen-G5 (sHLA-G5) M-CSF (monocyte- colony stimulating factor), MHC (major histocompatibility complex), KIR (killer inhibitory receptor), NK(natural killer cell), PD-1(programmed death 1), PD-L1(programmed death ligand1).

in the up-regulation of PGE2 in monocyte–MSC co-cultures remains unclear. Ramasamy *et al*. showed that the cell cycle in DCs was arrested in the G0/G1 phase upon contact with MSCs. A new study has reported that MSCs isolated from human adipose tissue are more potent immunomodulators for the differentiation of human DCs than MSCs derived from the BM (Shi et al. 2011, Spaggiari et al. 2009, Ramasamy et al. 2007, Ivanova-Todorova et al. 2009). One more MSC-secreted factor, IL-6, has been reported to be involved in the inhibition of the differentiation of monocytes to DCs, diminishing their stimulatory capacity on T-cells(Ghannam et al. 2010b, Jiang et al. 2005, Djouad et al. 2007).

Myeloid DCs are the main potent antigen-presenting cells, important in the induction of immunity and tolerance. Through maturation, immature DCs acquire the expression of co-stimulatory molecules and up-regulate the expression of MHC class I and class II molecules collectively, with further cell surface markers such as CD11c, CD80, CD83 and CD86. I*n vitro*, MSCs inhibit the maturation of monocytes and the development of $CD34^+$ hematopoietic progenitor cells into DCs, as shown by a decline in cell surface expression of MHC class II and co-stimulatory molecules, in addition to a reduced production of IL-12 and TNFα. This outcome is at least partly mediated through the production of IL-6 by activated MSCs or PGE-2, which are directly responsible for blocking DC maturation. These results propose that MSCs might regulate DC maturation to an anti-inflammatory or regulatory phenotype responsible for a satisfactory T-cell response(Aggarwal and Pittenger 2005, Ghannam et al. 2010a, Jiang et al. 2005, Spaggiari et al. 2009, Djouad et al. 2007). The effect of MSCs is controlled toward 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. DCs which are produced in the presence of MSCs secrete low levels of IL-12 and TNF-α, but elevated levels of IL-1β, IL-10; in addition, they express low levels of MHC class II surface antigens. Most recent studies propose that antigen processing and presentation by MHC class II surface antigens are impaired(Gebler et al. 2012, Nauta et al. 2006, Zhang et al. 2004). For the first time, Di Nicola *et al*. showed the repression of cell-mediated immune connections by co-culturing DCs, irradiated allogenic lymphocytes or phytohemaglutinin (PHA)-stimulated T-cells with irradiated MSCs, in a mixed lymphocyte reaction (MLR)(Lotfinegad 2014). They found that MSCs delayed the up-regulation of CD1A, CD40, CD80 (B7-1), CD86 (B7-2) and HLA-DR through DC maturation, even as CD83 increased. Significantly, DCs isolated from cultures that were co-cultured with MSCs showed a decreased potential to activate $CD4^+$ cells in the presence of MLCs(Aggarwal and Pittenger 2005, Maccario et al. 2005, Jiang et al. 2005, Zhang et al. 2004, Le Blanc and Ringden 2007, Beyth et al. 2005). In the presence of MSCs, IL-10-secreting plasmacytoid DCs, characterized by the expression of the BDCA4 antigen, increased after stimulation by lipopolysaccharide(Aggarwal and Pittenger 2005, Le Blanc and Ringden 2007). $CD14^+$ monocytes activate MSCs to secrete soluble factors as well as IL-1β that inhibit alloreactive T-cells. (Figure 1) (Le Blanc and Ringden 2007, Groh et al. 2005).

Neutrophils

Neutrophils are the first cells that arrive at inflammatory tissue, and these cells secrete cytokines. One more MSC-produced factor, IL-6, has been shown to be engaged in the inhibition of monocyte differentiation to DCs, diminishing their stimulation capacity on T-cells. Similarly, the production of IL-6 by MSCs has also been reported toward stoppage of apoptosis of lymphocytes and neutrophils(Ghannam et al.

2010b, Jiang et al. 2005, Djouad et al. 2007, Raffaghello et al. 2008, Xu et al. 2007). MSCs greatly inhibit the *in vitro* secretion of hydrogen peroxide in activated neutrophils, therefore these stem cells can potentially control the intensity of a respiratory burst upon inflammatory stimulation(Ben-Ami et al. 2011, Raffaghello et al. 2008). With respect to cells of the inherent immune system, MSCs can significantly decrease the power of the respiratory burst and apoptosis, which is a vital factor of the phagocytic role of neutrophils. This can be a serious process whereby MSCs can control the intensity of tissue injury following ischemic and ischemia/reperfusion damage(Mazaheri et al. 2012, Hirata et al. 1993). Hyperactivated T-lymphocyte helper 1 (Th1) produces proinflammatory cytokines such as IL-2, IL-6, IL-8, IL-17, TNF-α and IFN-γ. These cytokines stimulate neutrophils and activate monocytes. Activated monocytes stimulate Th1 differentiation by secreting IL-12, and the hyperfunction of neutrophils causes a tissue wound. Altogether, the connection between APCs, hypersensitivity of T-lymphocytes, and hyperactivity of neutrophils, might be the major cause for immune responses in Behcet's disease (BD). (Figure 1) (Mazaheri et al. 2012, Türsen 2012, Kapsimali et al. 2010, Tursen 2009, Hirohata and Kikuchi 2003).

Adaptive immune system cells

B-cells

MSCs are capable of modulating the immune response of B-cells. It has been demonstrated that in a co-culture method of stimulated B-cells and MSCs, the proliferation of B-cells as well as the secretion of antibodies (IgA, IgG, and IgM) were inhibited in plasma cells(Lotfinegad 2014, Corcione et al. 2006). In murine studies, MSCs have been stated to inhibit the proliferation of B-cells, stimulated through anti-CD40L and IL-4, or by pokeweed mitogen and protein A, as in Staphylococcus aureus(Nauta and Fibbe 2007, Schwartz et al. 2007, Glennie et al. 2005, Zhang et al. 2005, Tögel et al. 2005, Le Blanc et al. 2004a, Breitbach et al. 2007). Allogeneic MSCs have been revealed to restrain the proliferation, activation and IgG secretion of B-cells, as shown in BXSB mice that were utilized as an investigational model for human systemic lupus erythematous(Nauta and Fibbe 2007, Augello et al. 2005, Deng et al. 2005). Krampera *et al.* demonstrated that MSCs only decreased the proliferation of B cells in the presence of IFN-γ. The suppressive effect of IFN-γ was probably attributed to its capacity to stimulate the secretion of IDO by MSCs, which in turn suppresses the proliferative response of effector cells during the tryptophan pathway(Nauta and Fibbe 2007, Krampera et al. 2006a). Due to the fact that B-cell activation is mostly T-cell dependent, the influence of MSCs on the activity of T-cells might also not directly suppress B-cell functions. Additionally, MSCs have been shown to apply a direct influence on B-cells through cell to cell contact and during secretion of paracrine molecules(Corcione et al. 2006, Augello et al. 2005, Weil et al. 2011, Gerdoni et al. 2007). MSCs arrest B-cells in the G0/G1 phase of the cell cycle, without apoptosis(Mohammadian and Shamsasenjan 2013, Campagnoli et al. 2001). MSCs down-regulate the expression of the chemokine receptors CXCR4 and CXCR5, in addition to CCR7B, as well as lead to chemotaxis of CXCL12, the CXCR4 ligand, CXCL13 and CXCR5 ligand, suggesting that elevated numbers of MSCs influence the chemotactic properties of B- cells(Chamberlain et al. 2007, Volarevic et al. 2011, Shi et al. 2011, Abdi et al. 2008, Le Blanc and Ringden 2007, Corcione et al. 2006, Deng et al. 2005). These findings cannot support the potential therapeutic utilization of MSCs in autoimmune diseases, where the B-cells play a major role (Figure 2)(Le Blanc and Ringden 2007). Also, MSCs were

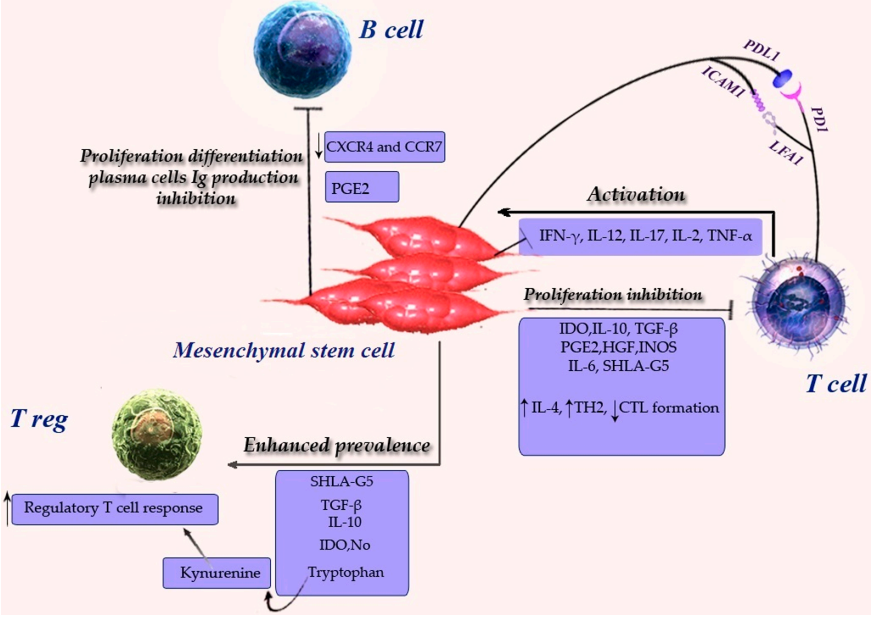

Figure 2. Effects of Mesenchymal stem cells (MSCs) on the adaptive immune system. These effects promote an overall anti-inflammatory and immunosuppressive state. Abbreviations: IFN gamma (interferon γ), IDO (indoleamine 2,3-dioxygenase), IL-2(interleukin 2), IL-4 (interleukin 4) IL-10 (interleukin 10), IL-6 (interleukin 6), IL-12 (interleukin 12), IL-17 (interleukin17),prostaglandin E2(PGE2), transforming growth factor beta (TGFβ), hepatocyte growth factor (HGF), induced nitric oxide synthases (iNOS), soluble human leukocyte antigen-G5 (sHLA-G5), ICAM 1(Intercellular adhesion molecule 1), LFA 1(Lymphocyte function-associated antigen-1), TH 2 (T helper 1), Treg (T regulatory).

observed to increase the CD40 expression and the ectopic hyperexpression of the CD40 ligand on the B-cells of BXSB mice(Shi et al. 2011, Deng et al. 2005).

T-cells

Mesenchymal stem cells are immunosuppressive by inhibiting the response of naive and memory T- cells in MLC, which are made by mitogens. Repression is MHC-free and mainly manifests if MSCs are added on the earliest day of the 6-day culture. The amount of restraint is dosage-dependent(Pevsner-Fischer et al. 2007, Tse et al. 2003, Le Blanc et al. 2003, Potian et al. 2003, Le Blanc and Ringden 2007). Manifest reserve is detected when more numbers of MSCs are present (MSC/lymphocyte ratio $>1/10$). In distinction, the adding of MSCs at a low ratio (1/100–1/10 000) frequently increases proliferation(Potian et al. 2003, Le Blanc and Ringden 2007, Le Blanc et al. 2003, Liu et al. 2004). Tse *et al.* demonstrated that nearness to MSCs was significant in suppressing T-cell responsiveness and recommended that direct interaction between lymphocytes and MSCs was more significant than soluble mediators in the immunosuppressive function of MSCs(Yagi et al. 2010, Tse et al. 2003). Krampera *et al.* stated that inhibition needs the presence of MSCs and MSC-T-cell interaction in culture(Yagi et al. 2010, Krampera et al. 2003).

Regulatory T cells

Although MSCs powerfully hamper T-cell proliferation, they can protect the role of $CD4^+$ $CD25^+$ $CD127^-$, forkhead box P3 $(FoxP3)^+$ regulatory T cells (Treg)(Le Blanc and Ringden 2007). MSCs raised the amount of $CD4^+$ $CD25^{high}$, $CD4^+$ $CTLA4^+$ and $CD4^+$ $CD25^+$ $CTLA4^+$ cells in IL-2-motivated lymphocytes and MLC(Aggarwal and Pittenger 2005, Maccario et al. 2005, Le Blanc and Ringden 2007). In contrast, the amount of $CD25^+$ and $CD38^+$ cells diminished in the presence of MSCs in mitogen-stimulated lymphocyte cultures (Figure 2)(Le Blanc and Ringden 2007, Groh et al. 2005). MSCs also generate bone morphogenic protein-2 (BMP-2), which mediates immunosuppression through the production of $CD8^+$ regulatory T cells(Le Blanc and Ringden 2007, Djouad et al. 2003).

T-helper and cytotoxic T-cells

The presence of signals that support the development of the Th1, such as CD3, CD28, IL-4, IL-2 and IL-12 stimulation, cause naive T-cells mature into IFN-γ-secreting cells. If MSCs are present in the culture, IFN-γsecretion is decreased. Hence, MSCs provoke a bias towards Th2 differentiation(Aggarwal and Pittenger 2005, Le Blanc and Ringden 2007). Mesenchymal stem cells suppress CD8 + T-cell-mediated lysis if added at the beginning of the MLC (Rasmusson et al. 2003, Le Blanc and Ringden 2007). Cytotoxicity was not affected if MSCs were added in the cytotoxic stage(Potian et al. 2003, Rasmusson et al. 2003, Maccario et al. 2005, Le Blanc and Ringden 2007, Angoulvant et al. 2004). Lysis was partly abrogated by the addition of IL-2. MSCs might hinder the afferent stage of alloreactivity and stop the growth of cytotoxic T-cells. When cytotoxic T-cells are activated, MSCs are not effective. *In vivo* studies are essential to clarify this point(Le Blanc and Ringden 2007, Angoulvant et al. 2004). Human MSCs limit the structure of $CD4^+$ and $CD8^+$ T cells by soluble factors(Tse et al. 2003, Potian et al. 2003, Le Blanc and Ringden 2007, Corcione et al. 2006, Di Nicola et al. 2002). The suppressive factor is not constitutively produced by MSCs, since cell culture supernatants do not suppress T-cell proliferation(Maitra et al. 2004, Potian et al. 2003, Le Blanc and Ringden 2007, Augello et al. 2005, Le Blanc et al. 2004b). This result may be characteristic of the inhibition of cell division, which is supported 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 with MSC(Shi et al. 2011, Glennie et al. 2005). Liu *et al.* clarified that the addition of antibodies specific to FasL and TGF-β1 satisfied suppression by MSCs in concanavalin A-stimulated MLC in a dose-dependent style, other than anti-IL-10, had no effect(Le Blanc and Ringden 2007, Liu et al. 2004). Mesenchymal stem cells may inhibit T-cell proliferation through the secretion of indoleamine 2, 3-dioxygenase (IDO). IDO is induced via IFN-γ, catalyzes the alteration of tryptophan to kynurenine, and inhibits T-cell responses through tryptophan diminution(Le Blanc and Ringden 2007, Munn et al. 1998).

Meisel *et al.*, using the Western blotting technique, revealed that human MSCs do not constitutively express IDO, but the expression is provoked by IFN-γ. IFN-γ also aroused IDO enzyme activity in dose-dependent behavior. Important IDO activity was detected in T-cells stimulated with mitomycin C-treated PBMC, in the presence of MSCs(Le Blanc and Ringden 2007, Meisel et al. 2004). PGE2, which is produced by cyclooxygenase (COX) enzymes, induces regulatory T-cells. (15-750). MSCs constitutively express COX-1 and COX-2 (Aggarwal and Pittenger 2005, Le Blanc and Ringden 2007, Arikawa et al. 2004) together. While purified T-cells were co-cultured by MSCs, both COX-2 and PGE2 production were boosted(Aggarwal and Pittenger 2005, Tse et al. 2003, Le Blanc and Ringden 2007). Inhibitors of PGE2 synthesis restored the majority of the proliferation of phytohemaglutinin-activated (PHA) lymphocytes co-cultured with MSCs. Tse *et al.* studied alloreactive lymphocytes in contrast to mitogen-stimulated cultures. They set up that neither MSC production of IL-10, TGFb1, and PGE2, nor tryptophan reduction, was responsible for the suppression in MLC(Aggarwal and Pittenger 2005, Tse et al. 2003). Di Nicola *et al.* recommended that HGF worked synergistically through TGF-β1, to challenge T-cell detection by simultaneous neutralization of HGF and TGF-β1 in the later study restoring T-cell proliferation(Yagi et al. 2010, Di Nicola et al. 2002). One more statement exhibited that quantitative real-time PCR confirmed important HGF mRNA up-regulated by IFN-γ and TNFα(Yagi et al. 2010, English et al. 2007). NO (nitric oxide) stops the proliferation of T-cells by suppressing the phosphorylation of signal transducer and activator of transcription-5 (STAT5), a transcription factor vital for T-cell activation and proliferation(Shi et al. 2011, Bingisser et al. 1998). Ding *et al.* reported that matrix metalloproteinases (MMPs), in particular MMP-2 and MMP-9, produced

by MSCs, mediate the suppressive activity of MSCs through diminution of CD25 expression on responding T-cells within a model of allogeneic islet transplant(Ding et al. 2009). In an experimental model of arthritis, MSCs reduced antigen-specific Th1/Th17 cell expansion and reduced the production of cytokines released via Th1/Th17 cells, for example IFN-γ and IL-17, and caused the Th2 cells to raise production of IL-4 and IL-10 in lymph node joints(Aggarwal and Pittenger 2005, Shi et al. 2011, Krampera et al. 2003, Zappia et al. 2005). Conversely, a new study reported that MSCs might provoke apoptosis in activated T-cells[$CD3^+$ and bromodeoxyuridine $BrdU^+$], but not in the resting T-cells[$CD3^+$ and $BrdU^-$]; this leads to clear reduction of delayed-type hypersensitivity (DTH) response *in vivo* with inducing NO production(Lim et al. 2010). A recent study demonstrated that the negative co-stimulatory molecule B7-H4 was involved in the immunosuppressive effect of MSCs on T-cell activation and proliferation by the generation of cell cycle arrest and the inhibition of nuclear translocation of the nuclear factor (NF)-kappa B(Sensebe et al. 2010). MSCs inhibit Th17 differentiation from naive T-cells. MSCs can also decrease the expression of major histocompatibility complex class E (MHC class E) (Mazaheri et al. 2012, Ghannam et al. 2010b). Conversely, in one study, it was found that CD25 and CTLA-4 (cytotoxic T lymphocyte-associated antigen-4) surface expression, and Foxp3 mRNA levels, were not dependent on whether $CD4^+$ T-cells were cultured in the presence of MSCs(Krampera et al. 2006b). Furthermore, MSCs have also been reported to influence the cytokine secretion profile of the different T-cell subsets, since their addition to an *in vitro* activated T-cell culture leads to reduced production of the pro-inflammatory cytokines: IFN-γ, TNF-α, IL-6, IL-17, and enhanced levels of anti-inflammatory cytokines, for example IL-4 and IL-10. On the whole, these outcomes could show a probable MSC-mediated alteration in Th1/Th2 balance(Zappia et al. 2005, Kong et al. 2009). MSCs can hamper T-cell proliferation by engaging the inhibitory molecule programmed death 1(PD-1) to its ligands PD-L1 and PD-L2, thus producing soluble factors that suppress T-cell proliferation (such as TGF-β or IL-10) and during interaction through DCs(Volarevic et al. 2011, Nauta and Fibbe 2007, Volarevic et al. 2009). MSCs increase Th2 and IL-4 production, regulatory T-cell response and decrease activation by foreign antigen, cytotoxic T-cells and IFN-γ production(Weil et al. 2011). The generation of HLA-G5 by MSCs has more lately been revealed to suppress T-cell proliferation, in addition to cytotoxicity of NK cells T-cells, and to increase the generation of regulatory T (Treg) cells. Cell contact between MSCs and activated T-cells stimulated IL-10 production, which was necessary to induce the release of soluble HLA-G5. (Figure 2) (Ghannam et al. 2010a, Selmani et al. 2008, Nasef et al. 2009).

Homing of MSCs

Homing is the procedure by which cells migrate to, and engraft within, the tissue in which they are able to apply local, efficient effects. While the homing of leukocytes to places of inflammation is well studied, the methods of progenitor cell homing to places of ischemia or damage are weakly recognized(Imhof and Aurrand-Lions 2004, Luster et al. 2005). Homing engages a cascade of incidents begun with shear-resistant adhesive 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 involve related endothelial co-receptors, causing in cell-tethering and rolling contacts on the endothelial surface. This is characteristically pursued via chemokine-generated activation of integrin adhesiveness (Stage II), hard adhesion (Stage III) and extravasation (Stage IV)(Yagi et al. 2010, Sackstein 2005). MSCs expressed chemokine receptors for homing of immune cells such as: CCR1, CCR2, CCR3, CCR4, CCR7, CCR8, CCR10, CCL2, CCL3, CCL4, CCL5, CCL7, CCL20, CCL26, CX3CL1, CXCL1, CXCL2, CXCL3, CXCL5, CXCL8, CXCL10, CXCL11 and CXCL12, but not CXCR4, suggesting that CXCR4 can simply be significant for the trafficking of mature stem cell populations and receptor tyrosine kinase growth factor receptors such as platelet-derived growth factor (PDGF) and insulin-like growth factor1(IGF-1)(Lotfinegad 2014, Yagi et al. 2010, McTaggart and Atkinson 2007, Hoogduijn 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 α4/β1-VCAM contact has been known to regulate T-cell and NK trafficking(Woodside et al. 2006). Integrin β1 engages cell to-cell adhesion, which can be essential for the anchorage of the engrafted cells. As expected, blockade of integrin β1 reduces neutrophil migration to the lung through inflammation(Yagi et al. 2010, Ridger et al. 2001). Ruster *et al*. explained that MSCs react in an organized style through endothelial cells, not only through integrin α4/β1-VCAM-1 interaction or integrin β1, but also via the endothelial phenotype, P-selectin, MMP-2 production, and cytokines(Rüster et al. 2006).

Fibronectin attaches extracellular matrix constituents like collagen, fibrin and heparan sulfate proteoglycans. It plays a significant role in cell adhesion, growth, migration, as well as differentiation, and it is significant for the injury healing processes. Records of previous studies show that contact between integrin α4 and β1-fibronectin plays a significant role in transmigration of MSCs into the extracellular matrix(Ruoslahti 1984, Valenick et al. 2005). Stromal cell-derived factor 1 (SDF-1), which is formally identified as chemokine (C-X-C motif) ligand 12 (CXCL12), is a minute chemotactic cytokine that activates leukocytes and is frequently stimulated through proinflammatory stimuli like TNF-α or IL-1(Fedyk et al. 2001). The receptor for this chemokine is CXCR4 and the SDF-1-CXCR4 communication is regarded to be private (Ma et al. 1998).

Interaction between SDF-1 and its ligand CXCR4 cooperates a significant function in homing, bone marrow retention and mobilization, as shown in studies on engraftment of hematopoietic stem/progenitor cells(Chamberlain et al. 2007, Peled et al. 1999). MSCs migrated considerably in response to SDF-1 and CX3CL, consistent with their corresponding expression of chemokine receptors CXCR4 or CX3CR1. Unexpectedly, Basic Fibroblast Growth Factor (bFGF) might have contrasting effects on MSC migration, depending on the concentration(Yagi et al. 2010). MSCs have an important role in co-transplantation by hematopoi-

etic 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 function in HSC homing in the bone marrow niche(Mohammadian and Shamsasenjan 2013, Horwitz et al. 2011, Delalat et al. 2009, Akbari et al. 2007).

Medical applications of MSCs

Stem cells in general and MSCs in particular, by their adaptable increase and differentiation potential, are considered perfect candidates for utilization in regenerative medical procedures(McTaggart and Atkinson 2007). One of the most significant properties that make MSCs a special device for cell-based therapeutic approaches, is their capability to escape from immune refusal; therefore, HLA-matching is not of much significance for their implant and HLA-mismatched donors can also be selected (Siegel et al. 2009, Dazzi and Marelli Berg 2008). Major roles of MSCs are correlated to their diverse therapeutic properties, like their anti-inflammatory and immunomodulatory effects, the secretion of mediators that initiate or support tissue renovation and tissue substitution with the potential of multipotent differentiation (Caplan and Dennis 2006, Waszak et al. 2012, Du et al. 2013). The major significant therapeutic areas comprise ischemic cardiac disease, graft-versus-host disease (GVHD), chronic obstructive pulmonary disease, Crohn's and Behcet's disease(Mazaheri et al. 2012, Du et al. 2013). MSCs infusion can also be very useful in cord blood transplantation where the restricted amount of stem cells delays engraftment and favors graft rejection. The cell therapy approach has also been utilized as prophylaxis in GVHD in HSC transplantation. The therapeutic efficiency was related to reduced antigen-specific Th1/Th17 cell expansion, increased production of IL-10 and generation of $CD4^+$,$CD25^+$,FoxP3 $^+$Treg cells via the ability to suppress self-reactive T-effector responses(Ghannam et al. 2010a, González et al. 2009). Growth of autoimmune diabetes results from immune cell dysfunction to maintain peripheral and central tolerance. MSCs can be useful in regulating Treg/auto reactive T-cell balance. The earliest proposed function of MSCs was the stimulation of the regeneration of endogenous insulin-secreting cells, and next, inhibition of the T-cell-mediated immune responses against newly produced beta cells(Urban et al. 2008). MSCs have been brought into clinical therapy for numerous reasons: to differentiate and repair injured tissues, to increase hematopoietic engraftment following transplant through the production of growth factors, and for immunosuppressant function in GVHD. Since the immunomodulatory methods vary between murine and human MSCs, animal forms cannot mimic the medical position(Lazarus et al. 1995, Koç et al. 2000). Recently studies in pathological models have also revealed that MSC can home in to damaged kidneys and make simple renovations(McTaggart and Atkinson 2007). The proof-of-principle essential to utilize of MSCs *in vivo* has been shown in a series of trials:(I) MSCs might engraft into mouse tissues after infusion and use a site-specific differentiation, which is due to their exclusive immunological properties that permit engraftment with no rejection; (II) in humans, autologous enlarged MSCs *in vitro* could be infused intravenously with no toxicity; (III) transplantation of autologous MSCs in arrangement by HSCs lead to improved HSC engraftment; and(IV) allogeneic transplantation of MSCs decreased the frequency and intensity of acute and chronic GVHD (Gebler et al. 2012, Sato et al. 2010, Tolar et al. 2010). Additionally, MSCs have been used for the conduct of different autoimmune diseases leading to the stimulation of T-cell tolerance and damaged pathogenic T and B cell responses. BM-derived MSCs can also suppress the proliferation of PBMCs, independent of their supply (autologous or allogeneic), subtype of autoimmune disease and form of conduct(MacDonald et al. 2011). In the case of tissue renovation, the anti-inflammatory activity of MSCs resulted in the production of anti-inflammatory macrophages, which were important for increasing tissue repair(Kim and Hematti 2009). Moreover, MSCs also have therapeutic potential in treating pulmonary fibrosis, acute renal nephropathy, and in inhibiting the progress of diabetes. MSC transplantation promotes the extension and growth of B-cells and renal glomeruli as well as decreasing collagen expression and inflammation in fibrosis(Lee et al. 2009, Vija et al. 2009). MSCs express high levels of arylsulfatase A and α-l-iduronidase. The absence of these enzymes cause breakdown to hydrolyze a different substrate, leading to its accumulation and the dysfunction of several organs, the most severe being mental retardation. The lack of arylsulfatase A is the cause of metachromatic leukodystrophy, and the deficit of α-l-iduronidase is the cause of Hurler's disease, disorders that can possibly be prevented via allogeneic hematopoietic stem cell transplantation (HSCT), which is just potential therapy(Groth and Ringdén 1984, Krivit et al. 1999). MSCs can be exploited to treat bone disorders (e.g., osteogenesis imperfecta). Five patients with osteogenesis imperfecta, treated with bone marrow transplantation, had donor osteoblast engraftment, novel dense bone shape, an augmentation in complete bone mineral content, increase in development rate and decreased frequencies of bone cracks. This proposes that HSCT leads to engraftment of practical MSCs. Gene-marked MSCs, to recognize the cells after infusion, were given to six children who had undergone HSCT for severe osteogenesis imperfecta(Sillence et al. 1978, Horwitz et al. 1999, Horwitz et al. 2001, Horwitz et al. 2002). A bone marrow biopsy demonstrated 0.3%–7.4% Y-chromosome-positive cells by fluorescent in situ hybridization (FISH),signifying engraftment of the donor MSCs. Lee *et al*. stated the case of a patient with acute leukemia, who accepted a peripheral blood stem cell graft collectively via MSCs since her HLA-haploidentical father was treated by regular immunosuppression(Le Blanc and Ringden 2007, Lee et al. 2002).

Conclusion

Mesenchymal Stem Cells (MSCs) have a capacity to home in and integrate into damaged tissues. MSCs provide immunomodulatory effects by paracrine and/or cell-cell contact that inhibit innate immune system cells (DCs, NK cells, monocytes and neutrophils) and adaptive immune system cells (B, TH1 and T CTL). Also, MSCs stimulate Th2 and regulatory T-cells by the inflammatory microenvironment.

Therefore, the use of MSCs could lead to various therapeutic possibilities such as supporting tissue regeneration and correcting inherited disorders. A rational understanding of the mechanisms of action of MSCs allows the translation of our basic knowledge of MSC biology into the design of new clinical therapies .The potential antiproliferative and immunomodulatory function of MSCs is being intensely studied by various groups, with the hope that MSCs may be developed as a therapeutic strategy for autoimmune disease, HSCT, BMT(Bone marrow Transplantation) and as a useful tool for cell-based therapy. Autologous transplantation of MSCs has a high ability to produce the desired results in clinical therapies, but it could induce tumors, because MSCs can undergo spontaneous transformation exhibiting a tumorigenic potential with immunosuppression effects. Also, allogeneic MSCs might have a potential risk of infections obtained from donors. The opportunity exists to utilize genetic engineering of MSCs to state particular factors for homing and therapy. Finally, clinical trials with MSCs will afford a rich resource of information that can be studied widely in the laboratory and will play an important role in clinical therapy. In the present review, the comprehensive definition, sources, markers, and receptors of MSCs, as well as the immunomodulatory effect of these cells on innate and adaptive immune system cells, homing to the damaged tissues and therapeutic aspects in a variety diseases, have been reviewed. We hope that using MSCs in the treatment of autoimmune diseases, BMT, HSCT and cell-based therapy will be investigated more in the near future.

Authors' contributions

AA, AR, and FSTM conceived of the study and participated in its design and coordination. AM, K S, SK, Mt, AS, VZ, and MGG participated in the sequence alignment and drafted the manuscript. All authors read and approved the final manuscript.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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