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Immunosuppressive Properties of Mesenchymal Stem Cells

Mohamed Abumaree · Mohammed Al Jumah · Rishika A. Pace · Bill Kalionis

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Abstract Mesenchymal stem cells (MSC) can be isolated from different adult tissues including bone marrow, adipose tissue, cord blood and placenta. MSCs modulate the immune function of the major immune cell populations involved in alloantigen recognition and elimination, including antigen presenting cells, T cells, B cells and natural killer cells. Many clinical trials are currently underway that employ MSCs to treat human immunological diseases. However, the molecular mechanism that mediates the immunosuppressive effect of MSCs is still unclear and the safety of using MSC in patient needs further confirmation. Here, we review the cytokines that activate MSCs and the soluble factors produced by MSCs, which allow them to exert their immunosuppressive effects. We review the mechanism responsible, at least in part, for the immune suppressive effects of MSCs and highlight areas of research required for a better understanding of MSC immune modulation.

Keywords Stem cells · Immunosuppression · Mesenchymal stem cells · Immune modulation

M. Abumaree · M. Al Jumah
King Saud Bin Abdulaziz University for Health Sciences/
King Abdullah International Medical Research Center,
King Abdulaziz Medical City, National Guard Health Affairs,
P.O. Box 22490, Riyadh 11426, Mail Code 1515, Saudi Arabia

R. A. Pace · B. Kalionis
Department of Obstetrics and Gynaecology, Royal Women's Hospital, University of Melbourne,
Parkville, Victoria, Australia 3052

R. A. Pace · B. Kalionis (✉)
Department of Perinatal Medicine Pregnancy Research Centre,
Royal Women's Hospital, University of Melbourne,
Parkville, Victoria, Australia 3052
e-mail: bill.kalionis@thewomens.org.au

Introduction

Stem cells fall into two broad categories; embryonic stem cells (ESCs) and adult stem cells (ASCs). ESCs are derived from the inner cell mass of the early embryo and are pluripotent. ESCs can differentiate into cell derivatives of the three germ layers: endoderm, ectoderm and mesoderm. ASCs can be obtained from a wide range of tissues but the most characterized source of ASCs is adult bone marrow. One important subset of ASCs is the mesenchymal stem cell (MSC). Friedenstein et al. [62] first described MSCs as spindle shaped cells derived from bone marrow that were able to adhere to plastic and form fibroblast colonies, which were called colony-forming unit fibroblasts (CFU-F). MSCs are multipotent cells able to differentiate into cell derivatives of the mesenchymal lineage, including adipocytes, osteocytes, chondrocytes and myocytes [6, 98]. However MSCs can "transdifferentiate" and thereby cross lineage barriers, differentiating into hepatocytes, neurons and astrocytes [140]. MSCs have been isolated from a range of adult tissues including liver, bone marrow, dental pulp, adipose-tissue, endometrium, muscle, amniotic fluid, placenta and umbilical cord blood.

There is much debate in the literature about the real nature of cells termed MSCs since heterogeneous populations of cells isolated using a variety of methods have been termed MSCs. There is no single, specific marker to identify authentic MSCs, however the International Society for Cellular Therapy has provided minimum criteria to identify MSCs; MSCs must be plastic-adherent, more than 95% of the population must express CD105, CD73 and CD90, and lack the expression of CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA class II as measured by flow cytometry. MSCs must also be able to differentiate to osteocytes, adipocytes and chondrocytes in vitro [58].

In many tissues, MSCs reside in a perivascular niche. Indeed, a sub-population of perivascular MSCs are thought to be pericytes or contractile cells surrounding the endothelium in blood vessels [44, 46]. Other avascular sources of MSCs have been identified including the amniotic and chorionic mesoderm of the fetal membranes [144, 199].

Despite the absence of definitive markers for MSCs, the heterogeneous nature of MSC populations and variations in the differentiation potential, MSCs remain very attractive sources of stem cells for the treatment of immune disorders since their efficiency in treating graft versus host disease (GVHD) is established [103, 183]. However, the immune properties of MSCs are also critical for their efficiency in regenerative medicine applications. Thus, the mechanism of their action is now under intense investigation. MSCs exert strong anti-inflammatory and immunosuppressive effects on the main immune cell subsets through their production of various soluble factors.

Immune Tolerance of Mesenchymal Stem Cells

Immunosuppressive Characteristics of Mesenchymal Stem Cells

Several studies have confirmed the immunosuppressive characteristics of MSCs. These cells express major histocompatibility complex (MHC) class I but not MHC class II. Mouse and human MSCs derived from bone marrow (BMSCs), fetal membrane, placenta (pMSCs), amniotic MSCs, dental pulp (DP-MSCs) or umbilical cord, express MHC class I but not MHC class II antigens [24, 32, 36, 49, 77, 79–81, 85, 108–110, 144, 164, 182, 197]. However, recent studies involving MSCs derived from bone marrow, placenta and umbilical cord have demonstrated that the expression of MHC class II by MSC can be upregulated by IFN-γ in vitro and in vivo [31, 49, 55, 106, 158, 184]. The up-regulation of MHC class II by IFN-γ does not elicit alloreactive lymphocyte proliferative responses [106, 145, 184]. These data are controversial, because the stimulation of MSCs with high-dose of IFN-γ can induce the proliferation of allogeneic T cells [30, 31, 168]. In addition, high levels of IFN-γ decrease the expression of MHC-II on MSCs thereby causing loss in the ability of MSCs to act as antigen presenting cells [30]. Thus, it is possible that MSCs can change their immune suppressive functions according to their microenvironments. Further studies are required to determine why MSCs apparently exhibit multiple roles i.e. they can act as immune suppressors or stimulators and their expression of MHC-II can either increase or decrease following IFN-γ stimulation. The immunosuppressive effect of MSCs is independent of the presence of MHC class I and II molecules, since MSC devoid of expressing of these molecules are able to inhibit the activation of T lymphocytes [97, 145]. HLA-G, a nonclassical MHC class I, is also involved in immunomodulation by MSC [125]. Dendritic cells, natural killer cells (NK) and T cells express receptors that interact with both the membrane-bound and the soluble isoform of HLA-G, which are expressed by human MSCs. The soluble isoform HLA-G5, secreted by MSC after IL-10 stimulation, can inhibit the cytolytic activity of NK and CD8+ cytotoxic T lymphocytes (CTL) shifting the T cell response to Th2 cytokine types and inducing the expansion of regulatory T cells [163]. In addition, fetal liver MSCs express the membrane-bound HLA-G1 isoform, which is directly involved in the inhibition of T cell activation [67].

Mesenchymal Stem Cells Suppress the Immune Response of Allogenic Lymphocytes

In a mixed lymphocyte reaction, MSCs derived from bone marrow of baboons or human inhibit the proliferative response from allogeneic lymphocytes (Fig. 1) [15, 55]. In addition, human BMSCs can actively suppress the proliferation of T cells stimulated by anti-CD3 or anti-CD28 antibodies [184]. Both murine and human BMSCs inhibit the proliferation of lymphocyte stimulated by anti-CD3 or with IL2, IL7 or IL15 in vitro [20, 162]. This inhibitory effect is partially mediated by IFN-γ [162]. Similarly, human pMSCs and amniotic membrane mesoderm stem cells (AMSCs) suppress the proliferation of allogeneic lymphocytes [11, 32–34, 85, 109, 189]. Furthermore, fetal liver MSCs do not elicit alloreactive T-cell proliferative responses but can inhibit mitogen-stimulated lymphocytes [67, 72]. Similarly, adipose derived MSCs can inhibit T cell proliferation [42]. Moreover, dental pulp MSCs (DP-MSCs) can suppress the proliferation of peripheral blood mononuclear cells [182]. The inhibitory effect of MSCs on the proliferation of lymphocytes is ratio-dependent [53, 109, 119, 145, 189].

Mesenchymal Stem Cells Modulate the Functions of Immune Cells

Several studies show that MSCs can modulate the functions of both T and B lymphocytes. MSCs can inhibit the production of TNF-α and IFN-γ by CD4+ (helper T cells) and CD8+ cytotoxic T cells, while they can upregulate the expression of IL-10 and restore the secretion of IL-4 by CD4+ and CD8+ T cells [200] (Fig. 1). In addition, fetal liver MSC can down-regulate IFN-γ production and also can increase IL-10 secretion in activated T cells [67]. Similarly, adipose derived MSCs can enhance the secretion of IL-4, IL-5, and IL-10 by T cells [42]. In contact cultures, human MSCs also suppress the ex vivo expan-

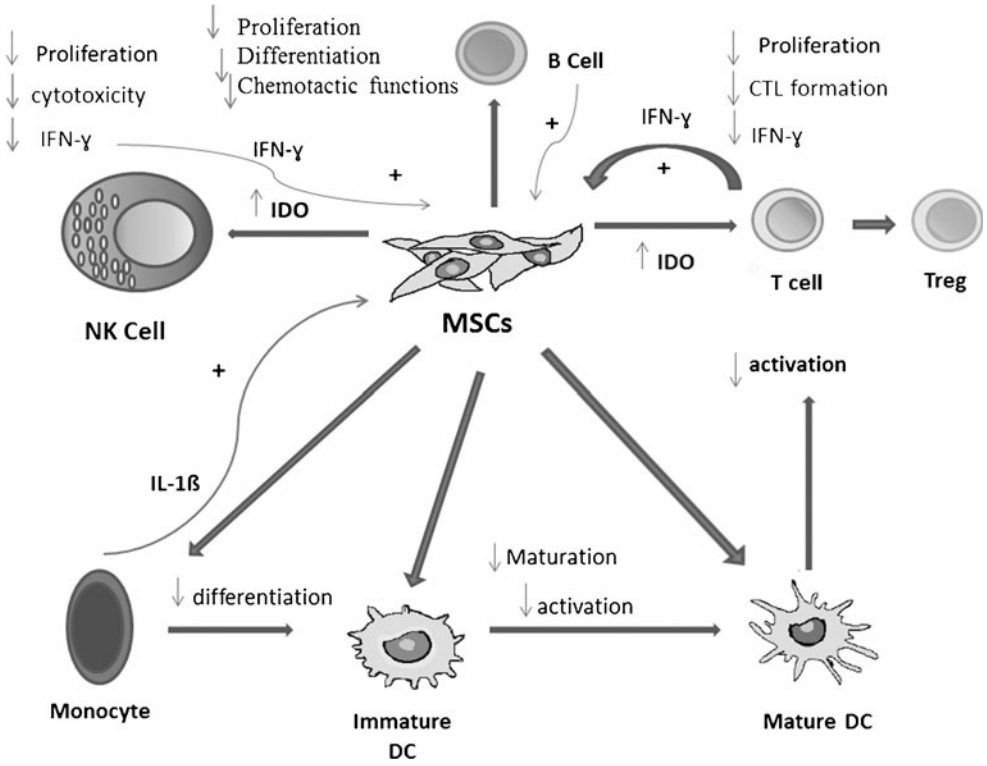

Fig. 1 Immunomodulation properties of MSCs on immune cells including T cells, NK cells, B cells, monocyte and dendritic cells (DCs)

sion of γδ T cells without affecting their cytotoxic activity [138].

Additionally, BMSCs can selectively suppress the proliferation of T and B lymphocytes by a cell-to-cell contact mechanism via the PD-1 (programmed death 1) inhibitory molecule and its ligands PD-L1 and PD-L2 [7, 191]. Moreover, BMSCs suppress the immune response of B cells stimulated by anti-CD40 or IL-4 [68]. This inhibitory effect of BMSCs on B cells has also been confirmed by other studies in which human BMSCs were shown to suppress the proliferation, differentiation and chemotactic functions of B cells [5, 43]. Similarly, human placental MSCs can also suppress the immune functions of different populations of immune cells including CD4+ and CD8+ T cells [32].

$CD8^+$ cytotoxic T lymphocytes (CTL) and the natural killer (NK) cells are effector cells displaying cytotoxic activities that can eliminate cancer or infected cells. CTLs are activated upon interaction with peptides expressed on MHC class I molecules. Human BMSCs can be recognized as targets by pre-activated alloreactive CTLs, and they are able to suppress the differentiation of CTL precursors into CTL effectors through secretion of suppressive factors [4, 151]. The inability of MSCs to activate CTL precursors in order to induce their differentiation into CTL effectors was evaluated by the absence of lysis of allogeneic targets [4, 151]. However, this suppression mechanism of MSCs on CTL is time and dose-dependent [4, 151]. The addition of MSCs to mixed lymphocyte culture on day 0, significantly inhibited the lysis of target cells by CTL, but the lysis of target cells by CTL was slightly reduced when MSCs were added on day 3 [4, 151]. In addition, when MSCs were added in the cytotoxic phase of the mixed lymphocyte culture, no significant inhibition of CTL mediated cytotoxicity was seen [4, 151]. Similarly, it was found that the increase in MSC concentration inhibited CTL-mediated cytotoxicity [4, 151]. Moreover, it has been shown that MSC are not lysed by CTLs [4, 151, 152]. This is a surprising result because MSCs express HLA class I antigens, which are targets for CTL lysis [107]; therefore it is important to investigate the mechanism by which MSCs escape the cytolytic effects of CTL.

NK cells which are constitutively cytotoxic against cells cannot lyse MSCs which are derived from human bone marrow or placenta [32, 151]; however IL-2–activated NK cells can lyse MSCs [143, 167]. Furthermore, NK cells activated with IL-2 and IL-15 showed a strong capacity to lyse adipose tissue-derived MSC [78]. However, data on the susceptibility of MSC for lysis by cytotoxic cells is contradictory as it has been discussed. Additionally, a recent study showed that allogeneic adipose tissue-derived MSC are highly susceptible for cytotoxicity-mediated lysis by $CD8^+$ T cells and NK cells [47]. Therefore, more research is needed to investigate the susceptibility of MSC for lysis by immune cells since it is essential for the efficacy and the safety of MSC therapy. Confirmation that MSCs are lysed by

immune cells would indicate that MSCs should be removed shortly after their infusion into patients; thus the usefulness of MSCs therapy will be debatable. However, MSCs appear to have a transient effect on the inflammatory milieu in graft versus host disease and MSC can have long lasting effects by passing on some of their effect to other cell types, such as regulatory T-cells [37, 70]. This suggests that if MSCs are lysed shortly after infusion, this would not prevent the long term effectiveness of MSCs.

Human BMSC can inhibit NK cell proliferation and NK cell-mediated cytolysis induced by IL-2 [1]. This inhibitory effect is due to the down regulation of the surface expression of the activating NK receptors (NKp30, NKp44, and NKG2D) on NK cells [166]. Human BMSC can also inhibit NK cell production of IFN-γ [1]. However, another study has reported that human BMSCs can significantly increase the secretion of IFN-γ by NK cells [143]. This discrepancy was attributed to the different effects that MSCs could have on NK cells and this may depend on whether NK cells are triggered by IL-2 or not [143]. Another possibility is that the ratio of NK cells to BMSCs, which is used in different experimental settings, may have different activation or inhibitory effects on NK cells by MSCs. There is difficulty in determining in vivo whether one, or many, NK cells interact simultaneously with an individual stem cell or vice versa.

It is obvious that MSCs can modulate the functions of the major immune cells including T, B and NK cells. However, the mechanisms by which MSCs use to modulate the immune functions of lymphocytes are still unclear. Therefore, more research is required to characterize the immunosuppressive markers which are secreted or expressed by lymphocytes following MSCs stimulation

Soluble Factors Secreted by Mesenchymal Stem Cells

The immunosuppressive function of MSCs is mediated by soluble factors, which are produced following the activation of MSCs by immune cells in co-culture systems. The interaction between monocytes and human BMSCs, activates BMSCs to secrete inhibitory molecules that inhibit alloreactive T cells [73]. This cellular communication is not contact-dependent, but rather is mediated by soluble factors including IL-1β [73]. In addition, it has been found that IL-1β secreted by monocytes and/or IFN-γ produced by activated T lymphocytes or NK cells can activate MSC [73, 107]. Moreover, murine BMSCs can induce the hyporesponsiveness of alloreactive T lymphocytes through the production of soluble factors [57]. However, the identity of the soluble factors produced by the activated MSC or the mechanism through which these cells act is still unclear.

As far as the mechanism underlying the immunosuppressive function of MSCs is concerned, several reports suggest that cell-cell contact is not a compulsory requirement for MSCs to suppress the immune response of immune cells such as T-cells [57, 73]. Therefore, MSCs must produce soluble factors mediating their immunosuppressive function on immune cells (Table 1 and Fig. 2).

Soluble factors produced by MSCs (pMSCs, BMSCs and DP-MSCs) in cell culture include stem cell factor (SCF), IL-6, IL-8,IL-10, IL-12, IFN-γ, PGE_2 (prostaglandin E_2), vascular endothelial growth factor (VEGF), macrophage colony-stimulating factor (M-CSF), hepatocyte growth factor (HGF) and transforming growth factor -β1 (TGF-β1) [1, 84, 109, 182, 198].

Among these factors with immunosuppressive functions are TGF-β1 and HGF, which have been studied extensively [32, 53]. A unique role for TGF-β has been excluded, and more likely TGF-β acts in synergy with HGF [53]. TGF-β1 and HGF mediate the immunosuppressive functions of BMSCs and pMSCs on T-cell proliferation [32, 53]. Blocking studies with anti-TGF-β1 and anti-HGF antibodies suggest that these cytokines work in a synergistic manner because T-cell proliferation is fully restored when both blocking antibodies are used [53]. Similarly, the addition of neutralizing antibodies to TGF-β and IL-10 partially reversed the immunosuppressive function of human pMSCs on the proliferation of T cells [32]. In addition, the blocking of PGE2 by indomethacin (prostaglandin inhibitor) partially restored the proliferation of T cells in presence of BMSC; thus suggesting that this cytokine may mediate the immunosuppressive function of MSCs [1]. The role of PGE_2 in mediating the immunosuppressive functions of BMSCs was further confirmed [165].

Table 1 Soluble factors mediating the immunosuppressive functions of mesenchymal stem cells (MSCs)

Immunomodulatory effects	Mechanisms
Inhibition of lymphocyte proliferation	1. synergistic effects of TGF-ß1 and HGF
	2. PGE_2
	3. IL-10
Inhibition of monocytes differentiation into macrophages or dendritic cells	M-CSF

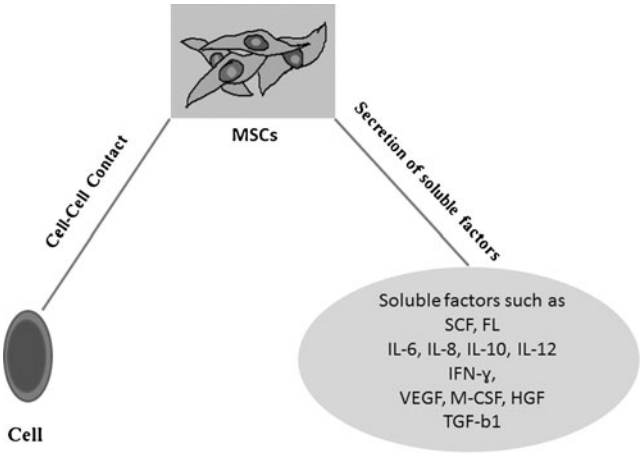

Fig. 2 Mesenchymal stem cells mediate their immunosuppressive modulation by cell-cell contact mechanism or by secreting soluble factors

MSCs are reported to mediate a potent inhibition on dendritic cell differentiation via PGE_2 [165].

The role of other cytokines including IL-6 and M-CSF in mediating the immunosuppressive function of MSCs was also established. Both cytokines (IL-6 and M-CSF) play a major role in the development of antigen-presenting cells [84]. Blocking of the bioactivity of IL-6 and M-CSF failed to generate immature dendritic cells ($CD1a^+$ cells) and reduced the expression of CD14 by macrophages; thus suggesting that MSCs retain the monocyte or macrophage immunophenotype (CD14) via M-CSF or IL-6 [84]. The ability of IL-6 and M-CSF to restore dendritic cell differentiation was also examined. Neutralizing antibodies against IL-6 and M-CSF reduced the expression of CD14, but did not completely restore the acquisition of CD1a, suggesting that other soluble factors produced by MSCs may cooperate with IL-6 and M-CSF to inhibit DC differentiation [126]. This finding was further confirmed by [56] who reported the involvement of IL-6 in the immunoregulatory mechanism mediated by MSC through a partial inhibition of DC differentiation [56].

Whether the effects of MSCs on immune system cells are mediated by soluble factors, or cell–cell contact, or both, is still debatable. Nevertheless, it is very important to resolve this crucial issue in order to understand how different outcomes of the MSC interaction with dendritic cells are influenced by cell concentration and localization. Recently, the immunomodulatory effect of MSCs on dendritic cells during lipopolysaccharide (LPS) activation or antigen loading, was demonstrated to be dependent on cell–cell contact interactions, not on soluble factors (i.e., IL-6 and PGE2), as discussed above [3]. These controversial results are probably due to the ratio between MSC and dendritic cells (MSC dilution). Therefore, further studies are needed to determine the exact ratio between MSC and immune cells required to trigger the immunosuppressive effects of MSCs on immune cells via soluble factors, or cell-cell contact mechanisms, or both. Elucidating this issue is crucial for the efficient use of MSCs in regenerative medicine.

Mechanisms Mediating the Immunosuppressive Functions of MSCs

Several immunosuppressive mechanisms of mesenchymal stem cells have been reported as described below and shown in Table 2.

Role of Indoleamine 2,3-dioxygenase (IDO) in Mediating Immunosuppressive Functions of MSCs

A new immunoregulatory mechanism was described that involves tryptophan catabolism by the enzyme indoleamine 2,3-dioxygenase (IDO) [124]. In this mechanism, immune cells, such as macrophages, deplete tryptophan in the tissue or culture medium. Since, the uptake of tryptophan is crucial for cell proliferation, its depletion leads to termination of proliferation. MSCs derived from human bone marrow, placenta, umbilical cord, and DP-MSCs express

Table 2 Mechanisms mediating the immunosuppressive functions of mesenchymal stem cells (MSCs)

MSC immunomodulatory effects	Mechanisms
Inhibition of lymphocyte proliferation	1. IDO
	2. Nitric oxide
Induction of T lymphocyte anergy	Mediated by soluble factors and/or cell-cell contact
Induction of T lymphocyte apoptosis	1. IDO and IFN-γ
	2. HLA-G independent mechanism
Induction of regulatory T cells ($CD4^+CD25^+$)	Mediated by soluble factors and/or cell-cell contact
Modulating antigen presenting cell functions	1. Down-regulating MHC class II expression
	2. Down regulating the expression of costimulatory molecules CD80 and CD86
	3. Decrease the secretion of IFN-γ, TNF-α, IL-2 and IL-12

IDO, the activity of which is induced by IFN-γ [32, 49, 85, 121, 182]. Inhibition of IDO activity results in a partial but substantial inhibition of the immunosuppressive activity of both human BMSCs and pMSCs on the proliferation of T-cells [96]. IDO-mediated MSC inhibition of NK cell function was reported [166]. When NK cells were cultured with MSCs in the presence of an inhibitor which blocks the activity of IDO, the proliferation of NK cells was partially restored, whereas blockade of both IDO and PGE2 completely restored the proliferation of NK cells. Thus, both IDO and PGE2 act synergistically to mediate the inhibitory effects of MSCs on NK cell proliferation [166]. Moreover, the cytotoxic activity of NK cells is also completely restored when both IDO and PGE2 were inhibited in the coculture of MSCs and NK cells; thus further confirming the synergistic effect of IDO and PGE2 [166]. Furthermore, it was shown that the inhibition of IFN-γ results in a complete abrogation of the immunosuppressive activity of MSC confirming that the activity of IDO is induced by IFN-γ [96]. The requirement of IFN-γ to stimulate the production of IDO by human BMSCs and pMSCs and umbilical cord MSCs, which in turn inhibit the proliferation of lymphocytes, was confirmed by others [49, 85, 96]. IDO is not expressed constitutively by MSC, but rather it is induced by IFN-γ; thus confirming the necessity of IFN-γ in inducing the IDO mediated immunosuppressive effect of MSCs on lymphocyte proliferation [48, 85, 159]. However, another study contradicts this finding since human bone marrow MSC-mediated suppression of lymphocyte proliferation was not substantially reversed by either the addition of tryptophan or the addition of 1-methyltryptophan, a specific IDO inhibitor [184]. Recent research demonstrated that MSCs express IDO and this enzyme to a certain extent induces kidney allograft tolerance in mice through generation of regulatory T cells [64]. Whether MSC-associated immunosuppressive function is entirely dependent on IDO activity or not still unclear and therefore further studies are needed to confirm or exclude this immunosuppressive mechanism.

Induction of T Lymphocyte Anergy by MSCs

Naive T cells must receive two signals in order to be activated upon antigenic stimulation. The first signal results from the interaction between the T-cell receptor and the MHC molecules while the second signal is the co-stimulatory signal which results from the interaction between CD28 and B7 molecules. In the absence of costimulatory signal, the T cells become anergic, i.e., they cannot proliferate or secrete IL-2 upon antigenic stimulation. However, the addition of IL-2 can abrogate anergy. Human and mouse BMSCs do not express the co-stimulatory molecules CD40, CD80, and CD86, but they can render T lymphocytes anergic [53, 192]. Nevertheless, the removal of mouse BMSC from T cell co-culture could restore the production of IFN-γ but failed to reverse the proliferation of T cells despite the addition of exogenous IL-2 [68]. BMSCs were found to arrest T cells in the G0/G1 phase of the cell cycle. But this form of T-cell unresponsiveness, which is triggered by MSCs, is not the classical form of anergy since it is not reversed by exogenous IL-2, although T cells express IL-2 receptor; thus indicating that MSCs induce in a state of division known as "tolerance arrest" in T cells [68]. The lack of expression of costimulatory molecules by MSCs and their ability to induce anergy in T lymphocytes supports the use of MSCs as therapy in regenerative medicine.

Induction of T Lymphocyte Apoptosis by MSCs

Several studies contradict each other as to whether MSCs inhibit the proliferation of lymphocytes by apoptotic mechanisms or not. Human BMSCs inhibit the proliferation of T cells by inducing apoptosis in T cells via a mechanism involved IDO and IFN-γ [141]. A recent study demonstrated that fetal liver MSCs can inhibit T cell proliferation by inducing apoptosis in T cells through a HLA-G independent mechanism [67]. In contrast, other studies have reported that human BMSCs and pMSCs inhibit the proliferation of T cells by a non-apoptotic mechanism since the proliferation of T cells efficiently resumed when re-stimulated with cellular or humoral activators in the absence of MSCs [32, 43, 53, 96, 192]. The non-apoptotic mechanism mediating the immunosuppressive effect of MSCs on lymphocytes was confirmed by others [32, 43, 96].

Induction of Regulatory T Cells ($CD4^+CD25^+$) by MSCs

Regulatory T cells ($CD4^+CD25^+$) represent specialized subsets of T cells with the capacity to suppress T cell responses and they are involved in both autoimmune reactions and graft rejection. In a mixed lymphocyte reaction, the co-culture of human BMSC or pMSCs with naïve T cells causes an increase in the number of regulatory T cells [1, 32, 66, 116]. In contrast, [17] ruled out this role for regulatory T cells in mediating the immunosuppressive function of MSCs [17]. They reported that the immunosuppressive function of mouse BMSCs does not require $CD4^+/CD25^+$ regulatory T cells since their depletion before antigenic stimulation does not affect MSC-inducing suppression [17]. But, a recent in vivo study demonstrated that the treatment of systemic lupus erythematosus (SLE) patients with autologous human BMSC increased the number of circulating regulatory T cells [28]. This finding was also confirmed by another study, which demonstrated

that kidney allograft tolerance could be induced in mice through the generation of regulatory T cells [64]. The discrepancies between these data suggest that MSCs may contribute to the expansion of the existing regulatory T cells without inducing new regulatory cell populations from the progenitor naive T cells.

Role of Mesenchymal Stem Cells on the Antigen Presenting Cells

Human BMSCs have a reversible inhibition effect on the differentiation of monocytes ($CD14^+$) into immature dendritic ($CD1a^+$) cells [84]. MSCs can down-regulate the expression of MHC class II and the costimulatory molecules CD80 and CD86 and decrease the secretion of IFN-γ, TNF-α, IL-2 and IL-12 by mature dendritic cells [84]. These dendritic cells have a reduced capacity to activate T-cell proliferation in a mixed lymphocyte reaction [84]. Moreover, human BMSCs can prevent the differentiation of $CD34^+$ progenitors and monocytes into dendritic cells [84]. Another study revealed that MSCs can block the differentiation of monocytes into dendritic cells and can impair their antigen-presenting ability; this results from blocking monocytes entering the G1 phase of the cell cycle with a progressive number of cells accumulating in the G0 phase [149]. Recently, the immunosuppressive effect of MSCs on the differentiation of monocytes into dendritic cells has also been confirmed. MSCs derived from human amniotic membranes and human bone marrow can block the differentiation and maturation of monocytes into dendritic cells by blocking the expression of CD1a and reducing the expression of CD80, and CD83 [118, 165]. This blockage of monocyte maturation resulted in impaired allostimulatory ability of these cells on allogeneic T cells and failure of these cells to produce IL-12 [118, 165].

Whether naive T cells diverge into Th1 or Th2 effector T cells depends on the cytokine environment, such as IL-12 and the type and the activation state of dendritic cells. Therefore, insufficient production of IL-12 and decreased expression of both MHC class II and costimulatory molecules of dendritic cells upon treatment with MSCs may modulate the balance between Th1 and Th2 cells in favour of the latter. Although the direct effect of MSCs on T cells can be found in the mixed lymphocyte reaction, the change in the morphology of dendritic cells and the decrease in the secretion of IL-12 may suggest that MSCs can have a direct immunosuppressive effect on dendritic cells, which consequently regulate the expansion of T-cells. Therefore, MSCs may modulate the immune system by acting directly on T cells and also at the first step of the immune response through the inhibition of dendritic cell differentiation and maturation. This immunosuppressive effect of MSCs on dendritic cells may be clinically relevant. Dendritic cells are the gatekeepers to the immune system of the human body, thus it seems likely that by suppressing the function of dendritic cells through the limitation of antigen uptake or processing or presentation, it could significantly reduce the likelihood of graft rejection. More importantly, the effects of MSCs on dendritic cells are reversible and thus avoid the complications of long-lasting hypoimmune competence following transplantation.

Secretion of Nitric Oxide by Mesenchymal Stem Cells

Nitric oxide (NO), which is produced by nitric oxide synthase (NOS) inhibits T-cell proliferation [2]. The production of NO by mouse BMSCs is involved in the suppression of T cells [161]. Recently, NO was shown to mediate human adipose-derived stem cells suppression of lymphocyte proliferation [48]. Therefore, these studies suggest that NO, which is produced by MSC, may be one of the mediators that suppress the immune system.

The Immunosuppressive Capability of MSCs In Vivo

The immunosuppressive capacity of MSCs in vivo has been addressed by various studies. Intravenous injection of MSCs prolongs the survival of an allogenic skin graft in baboons [15]. Similarly, the injection of mice with murine BMSCs promotes the survival of allogeneic skin grafts in mice [190]. In addition, MSCs are not rejected when implanted in various allogeneic immunocompetent mice [57]. However, the subcutaneous injection of melanoma cells led to tumor growth in allogeneic recipients only when MSCs were co-injected [57]. Although the potential side effects of immunosuppression induced by MSCs have to be considered in further clinical studies, the usefulness of MSCs for various therapeutic applications still remains of great interest. Recently, it was demonstrated that mice infused with murine MSCs prolonged the survival time of skin transplants [18]. The immunosuppressive effect of human MSCs on the severity of bleomycin-induced inflammation and fibrosis in an animal model was also evaluated. The presence of transplanted MSCs decreased the neutrophil infiltration and significantly reduced the inflammation as well as the severity of lung fibrosis in mice treated with allogeneic or xenogeneic placenta-derived cells [27].

The therapeutic efficacy of MSCs in the murine model of multiple sclerosis (MS), experimental auto-immune encephalomyelitis (EAE), was reported [192]. In this model, MSCs decrease the clinical signs associated with demyelinisation (ataxia, paralysis of one or more members) when they are injected before or at the onset of the disease. On the other hand, no therapeutic effect was observed when the injection occurs after disease stabilisation. Another study showed that the intravenous injection of baboons with

autologous or allogenic baboon MSCs together with haematopoietic progenitor cells was not associated with toxicity and allowed a faster haematopoietic recovery [50]. Two other studies confirm these results. In murine models of allogeneic bone marrow transplantation, sublethally irradiated recipients received allogeneic bone marrow, with or without host or donor MSCs. The addition of host MSCs significantly enhanced the long-term engraftment associated with tolerance to host and donor antigens, but the infusion of donor MSCs was associated with significantly increased rejection of allogeneic donor bone marrow cells [127]. Similarly, in a mouse model of graft versus host disease (GVHD), the injection of donor MSCs had no beneficial effect on the incidence or severity of the GVHD, a major cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation [173]. The absence of an effect was not due to MSC rejection because they still could be detected in grafted animals, but rather to an absence of a suppressive effect on donor T cell division in vivo [173]. Thus, in these murine models, experimental data do not support a significant immunosuppressive effect of MSCs in vivo for the treatment of GVHD. However, a recent study showed that MSCs can reduce the severity of GVHD in an F1 model of acute GVHD [115]. In this model, the infusion of F1 mice with allogeneic BMSCs significantly alleviated tissue damage which was initiated by GVHD in the MSCs treated mice, and the proportion of CD4+/IL-4+IL-10+ Th2 cells in peripheral blood was higher in the MSC treated mice [115]. Therefore, the immunomodulatory effect of MSCs was possibly related to favouring type Th2 T cells subsets (CD4+/IL-4+IL-10+ Th2 cells) [115].

Evidence for Mesenchymal Stem Cells Escaping Recognition by Immune Cells

As we discussed in previous sections, MSCs possess immunosuppressive properties that might allow their successful use in cellular therapy. The evidence for MSC tolerance is increasing and comes primarily from the observation that mismatched MSCs can be grafted in vivo. Several studies have described the engraftment of mismatched MSCs in vivo [51, 82, 95, 120, 139, 142]. The systemic infusion of autologous and allogeneic bone marrow MSCs into baboons showed that these MSCs were distributed widely in several tissues including gastrointestinal, kidney, lung, liver, thymus, and skin [51]. Similarly, it was shown that human bone marrow MSCs could engraft in the myocardium of rats [95]. In addition, rat bone marrow MSCs also integrate into chick tissues including the heart, liver, and vertebral column [142]. Moreover, the engraftment of MSCs in the murine central nervous system [82, 120, 139] has been demonstrated. Human pregnancy itself provides strong evidence to support the immune escape of HLA-unrelated MSCs in transplantation. During pregnancy, cell trafficking occurs bi-directionally between fetus and mother; a natural situation that could be described as a long lasting transplantation process of fetal stem cells [23, 112, 181]. The semi-allograft fetal cells can survive in the maternal tissues for long period of time with apparent immune rejection. Fetal stem cells can engraft in maternal tissues such as marrow, liver, spleen, lungs, appendix where they remain throughout life without immune rejection [89, 129, 130, 160]. Fetal cell involvement in tissue repair after human pregnancy has also been proposed [39, 130, 160].

Hematopoietic stem cell transplantation (HSCT) further supports the immunosuppressive action of MSCs. The transplantation of HLA-unrelated MSCs into allogeneic hematopoietic stem cell transplantation recipients suggests that the cotransplantation of solid organs with MSC may facilitate engraftment through the non-specific immunosuppressive action of MSC rather than by the induction of specific tolerance to the transplanted organ [176]. However, it is debatable whether donor MSCs have a sustained engraftment potential in host bone marrow after allogeneic HSCT. Several studies have reported that marrow stroma remains of host origin after allogeneic HSCT in the majority of adults [9, 153, 172]. Moreover, recipient stroma was also detected in pediatric patients after allogeneic HSC transplantation [93]. However, a small number of donor MSCs were detected in a few patients who underwent allogeneic HSCT [38, 54, 146].

Humoral alloimmune mechanisms have also contributed significantly to MSC tolerance. Humoral alloimmune mechanisms are clinically important in solid organ transplantation, because HSCT could be associated with the formation of antibodies against HLA and minor histocompatibility complexes, which may lead to graft rejection; thus individuals, who are heavily immunosuppressed, can have antibodies mediating a humoral response against the stem cell graft; causing rejection [40, 69, 76, 100, 169, 170, 174]. Peripheral blood of HSCT patients receiving MSC was found to be associated with increased levels of alloantibodies [100]. In vitro studies also showed that MSCs stimulate B-cell antibody secretion [150]. However, [180] ruled out a significant role for alloantibodies in HSCT [180]. Bone marrow MSCs, which were infused into immunosuppressed patients, were shown not to be associated with alloantibodies [180]. This was further supported by the finding that MSCs are capable of suppressing the production of alloantibodies in vitro [41].

Blood group antigens, which are non-HLA antigens, could trigger the production of alloantibodies which may cause rejection [171]. However, human bone marrow MSCs do not express blood group antigens and therefore MSCs are not rejected as a result of antibody reaction against blood group antigens [180].

Collectively, the literature shows evidence that MSCs are capable of engrafting into recipients' tissues by modulating the immune response of the recipients.

How Far are We From the Clinical Application of MSC to Treat Immunomediated Diseases?

Cell based therapy using stem cells has been reported recently as a promising tool to treat many human diseases, such as hematological, oncology, immune related diseases. Currently, many stem cell centres use the hemopoietics stem cells in treating human diseases. However there is increasing shift to use MSC instead. This is mainly for the unique immunomodulatory properties that MSCs have displayed in many studies. MSC-based therapy may offer potential anti-inflammatory and immunomodulating effects in the treatment of a variety of inflammatory and autoimmune diseases [83].

Several studies have confirmed that MSCs could improve neurological defects through powerful immune controlling effects. MSCs are capable to modify the functions of several immune effector cells of the innate and adaptive immune systems, which have a role in the pathogenesis of autoimmune diseases [185]. The intravenous infusion of MSCs in mice with experimental autoimmune encephalomyelitis (EAE) revealed engraftment of MSCs into the secondary lymphoid organs, and this also induced peripheral T-cell tolerance to the immunising antigen myelin basic protein, thus leading to good clinical improvement, demyelination decrease, and the infiltration of the centre nervous system (CNS) by T cells and macrophages [192]. In addition, MSCs have the capacity for either stimulating or inhibiting myelin basic protein-specific T lymphocytes in a dose-dependent manner and modulate antigen-stimulated T cells to differentiate into either T helper type 17 or regulatory T cells, respectively, via pathways involving TGF-ß and IL-6 [113]. Subsequently, many studies have confirmed that human and mouse MSCs can improve the clinical progress in EAE, reduction demyelination, and stimulate tissue repair [10, 42, 65, 71, 148, 194]. However, few studies observed engraftment of MSCs into the CNS [87, 195]. In addition, limited evidence has demonstrated engraftment of human MSCs for an extended period of time in the murine CNS, and the immune-suppressive property of MSCs was also questioned when it was found that MSCs were rejected after in vivo infusion; possibly by a mechanism that involved activated NK cells and γδ T cells [60, 147, 167].

Regardless of whether MSCs incorporate into the CNS, MSCs in the periphery appear to prevent autoimmune disruption of the CNS and also support tissue repair in the CNS. Although stopping immune-mediated injury to the CNS should indirectly lead to axon sparing, many studies demonstrate that MSCs can directly defend neural tissues through paracrine mechanisms [65, 87, 185, 195]. In vivo studies, which employ neurological animal models, provided a direct a role for the neuroprotective effect of MSCs. MSCs can induce oligodendrogenesis [10, 42, 194], prevent neural cell apoptosis [35, 132, 187, 193], secret neurotrophic factors [42, 133], inhibiting oxidative stress [99] and modulating the activation of microglia [90, 132, 156]. Collectively, these studies provide a strong basis for the usage of MSCs in therapeutic trials for neurological diseases characterised by inflammation and neural damage, such as multiple sclerosis (MS).

Mesenchymal Stem Cells in Clinical Trials

Using stem cell therapy in treating wide range of human diseases is progressing. There are many-registered clinical trial exploiting MSC to investigate the possibility of the usefulness and the clinical applicability of MSC in treating or modulating the immunological diseases [94, 134]. Many unanswered questions and challenges remain before we can efficiently utilize MSC in clinical treatments. Although it seems that utilization of MSCs in treating human diseases is imminent, the experience which we gained from the gene therapy clinical trials suggests we may be ambitious in our time predictions.

Many reports have demonstrated the safety of using MSC in treating human diseases mostly with immune mediated pathogenesis. In multiple sclerosis patients, the potential therapeutic applications of autologous MSC in improving clinical manifestations of MS patients have examined by [[122], [122]]. Patients were injected intrathecally with autologous culture expanded MSCs and the feasibility of autologous MSC for treatment of MS patients has been demonstrated [122]. Another phase I/II open-safety clinical trial confirmed the clinical feasibility, the safety procedure, and the immunological effects of intrathecal and intravenous administrated autologous MSCs in patients with MS and amyotrophic lateral sclerosis (ALS) [86]. In addition, adipose tissue expanded MSCs, which known to have immune modulatory effects, were also demonstrated to be safe in treating three MS patients [88, 155]. Similarly, the feasibility of using MSCs, in treating human diseases, has also been demonstrated in Systemic Lupus Erythematosus (SLE). Reports indicate that allogenic MSC transplantation may be a feasible and safe salvage therapy in refractory SLE patients [111, 175]. A pilot study of 15 patients with refractory SLE who had transplantation of allogeneic mesenchymal stem cells demonstrated that MSCs could ameliorate disease activity, improve serologi-

cal markers and stabilise renal function; thus MSC transplantation appears beneficial in treatment of patients with SLE refractory to conventional treatment options [111]. Another study reported the usefulness of MSCs in SLE treatment. It has been found that a deficiency of bone marrow MSC/osteoblast function in an SLE mouse model could impair osteoblastic niche, which may correlate in part, to the difficulty of reconstructing immune homeostasis in treatment-refractory SLE [175]. In addition, it has been demonstrated that allogenic BMMSC transplantation conferred significant therapeutic effects on SLE mice and treatment-refractory patients by reconstructing the osteoblastic niche and restoring immune homeostasis [175]. Another study demonstrated the therapeutic effect of gingival-derived MSCs (GMSCs) in an experimental animal module of autoimmune colitis [196]. Systemic infusion of GMSCs in experimental colitis significantly ameliorated both clinical and histopathological severity of the colonic inflammation, restored the injured gastrointestinal mucosal tissues, reversed all symptoms, and suppressed the overall disease activity in mice [196]. The effect was mediated, in part, by the suppression of inflammatory infiltrates and inflammatory cytokines/mediators and the increased infiltration of regulatory T cells and the expression of anti-inflammatory cytokine IL-10 at the colonic sites [196].

MSCs have been widely used in hematopoietic stem cell transplantation as they possess many immunomodulatory properties. T-cell–depleted hematopoietic stem-cell transplantation (HSCT) from an HLA-haploidentical relative is a feasible option for children needing an allograft and lacking an HLA-compatible donor [8]. However, both primary and secondary graft failures are mainly mediated by host alloreactive T cells [59, 74, 136] . In addition, recipients of T-cell–depleted HSC transplants from an HLA-disparate relative are exposed to an increased risk of life-threatening infections, especially of viral origin, due to the delay in reconstitution of adaptive immunity [8, 93].

MSCs have been assessed in clinical trials for their capacity to improve engraftment in allogeneic stem cell transplantation. This is because MSCs are capable of contributing to hematopoiesis and results from animal models show that the cotransplantation of MSCs with HSCs can improve engraftment of HSCs [16, 128].

The feasibility of using cultured MSCs in patients was first demonstrated in patients with hematologic malignancies. A phase I clinical trial reported that there were no adverse reactions in patients with malignancies, who were intravenously infused with autologous BMMSCs that had been expanded in culture [101]. Furthermore, a phase I-II clinical trial reported the feasibility of intravenous-infused, culture-expanded autologous BMMSCs in myeloablative breast cancer patients, as evidenced by the rapid hematopoietic engraftment [91]. Moreover, the feasibility of using MSCs was demonstrated in patients undergoing myeloablative HSC transplantation for various hematological malignancies [102]. Cotransplantation of HLA-identical sibling culture-expanded BMMSCs with an HLA-identical sibling HSC transplant was reported to be feasible, seems to be safe, may also accelerate hematopoietic recovery and reduce the incidence of both acute and chronic graft-versus-host disease (GvHD) [102].

Further studies have also confirmed the safety of cotransplantation of allogeneic or autologous culture expanded BMMSCs with HSCs in hematologic and non-hematologic malignancies patients. In a pilot study, cotransplantation of haploidentical BMMSCs and HSCs reconstituted haematopoiesis in three patients with previous graft failure/rejection; thus MSCs can enhance hematopoietic engraftment and donor chimerism with subsequent low probability of severe acute GVHD and infections [105]. A phase 1/2 pilot study reported that MSCs can reduce the risk of graft failure in haploidentical HSC transplant recipients [12]. This was shown by the cotransplantation of culture expanded BMMSCs in children undergoing transplantation of T cell depleted hematopoietic stem cells from an HLA disparate relative [12]. In a phase I-II trial, the safety and feasibility of haploidentical MSCs in a cohort of children undergoing unrelated donor umbilical cord blood transplantation (UCBT), was also evaluated [117]. They showed that infusion of ex-vivo culture- expanded haploidentical MSCs into UCBT recipients can be performed safely. Since haploidentical MSCs are allogeneic MSCs, these data support the use of allogeneic MSCs from unrelated donors, an approach that may help solve time and donor variability problems [8]. The cotransplantation of adipose tissue-derived mesenchymal stem cells (AMSC) from haploidentical donors, along with peripheral blood HSCs from HLA-matched siblings, into two patients with severe aplastic anaemia was reported to modulate host alloreactivity and/or promote better engraftment of donor hematopoiesis, reducing the risk of early graft failure seen in severe aplastic anemia (SAA) patients [61]. Another recent pilot study reported the safety of using HLA-mismatched nonmyeloablative (NMA) HCT with MSC co-infusion [14]. Another pilot study reported the efficacy of bone marrow allogeneic MSCs in treating patients with hemorrhagic cystitis, pneumomediastinum and perforated colon [154]. Finally, the feasibility of MSCs in improving human diseases was also demonstrated in fistula-in-ano disease. A phase II, randomized clinical trial reported the safety of using adipose-derived stem cells in inducing healing in patients with complex fistula-in-ano [63]. Collectively, the feasibility and safety of MSCs in treating human diseases is evident, but further studies are also necessary to validate the applications of MSCs in cellular therapy.

One of the most fascinating properties of culture expanded MSCs is their ability to modify the immune response of immune cells both in vitro and in vivo (as discussed above). Acute GVHD is a T-cell mediated process, occurring in few months following allogeneic transplant or a donor lymphocyte infusion; and steroid-refractory GVHD has an extremely poor prognosis [13, 131]. MSCs have potential in improving GVHD after allogeneic HSC transplantation [52, 92]. The potential of haploidentical MSCs infusion for the treatment of GVHD was first reported in a 9-year-old boy who received a matched unrelated donor HSC transplant for leukemia [104]. No alloreactivity was detected when patient's lymphocytes were cultured with donors MSCs before or after MSC transplantation [104]. A subsequent study confirms the potential for MSCs in treating GVHD [154]. Recently, culture expanded BMMSCs were administered to patients with steroid refractory GVHD in a multicenter, phase II trial [103]. Interestingly, in this study GVHD responses were independent of the source of MSCs; i.e. use of HLA-identical sibling, haplo-identical, and third-party HLA-mismatched donors showed similar results [103]. This will have major impact in future clinical trials because the generation of donor specific MSCs is time consuming, costly, and in many cases unfeasible because of the urgent need for use. The efficacy of MSCs in GVHD was also shown in patients with steroid-refractory acute GVHD, who received culture-expanded BMMSCs derived from unrelated HLA disparate donors [188].

The literature clearly shows intense efforts in utilizing MSC to treat human diseases with very encouraging results. Currently, more than 145-registered clinical trials are posted in the Clinical Trial web page. Most of these slide are phase I and II, eight trials are in phase III (http://clinicaltrials.gov/ct2/home).

Risk of Infection After Mesenchymal Stem Cell Transplant

MSCs with its unique immunosuppressive properties have the potential for use as a cell based therapy. However, immunemodulatory effects may interfere with the general immune responses to infections in transplant recipient patients, who are already immunocompromised. Therefore, patients are susceptible to bacterial, fungal and viral infections. For example, mycoplasma hyorhinis infection can dramatically increase the anti-proliferative effect of MSCs; thus demonstrating MSCs can be efficient vectors of mycoplasma infection, and emphasizing the importance of monitoring cell cultures for contamination [201].

The risk of transmitting viruses from culture expanded MSCs is also of particular concern especially in HSCT recipients, who have severe GVHD. In these individuals, GVHD-associated immunodeficiency compounds the effect of multiple immunosuppressive agents, and they are at particular risk of viral infection [75, 114, 177]. MSCs can be infected in vitro with both cytomegalovirus (CMV) and herpes simplex-1 (HSV-1), nonetheless MSCs cannot be infected with Epstein–Barr virus (EBV) in vitro [179]. Furthermore, it is unlikely that MSCs isolated from healthy seropositive donors contain CMV, HSV-1, HSV-2, EBV or varicella zoster virus (VZV) [179]. Therefore, MSC transplants from healthy seropositive donors to patients may appear to be safe. A preliminary study revealed that culture expanded BMMSCs and umbilical cord blood MSCs were not infected with human herpes virus type-6 (HHV-6); and therefore MSCs transplant are safe with respect to HHV-6 contamination [137].

Parvovirus B19 (B19) is a DNA virus with pronounced tropism for erythroid precursors and megakaryocytes that express the erythrocyte P antigen (globoside), which is known as the B19 receptor [25]. The virus can persist in the bone marrow, and is detected in healthy donor MSCs [29, 45, 157]. The B19 screening of MSCs used in treating GVHD patients showed that the virus can infect MSCs in vitro, but the immunocompromised recipients, who were infused with MSC infected B19, showed no clinical consequences [157, 178]. The etiologic agent of Kaposi sarcoma (KS), KS-associated herpes virus (KSHV),1 infects a number of cell types within KS lesions, including endothelial cells, monocyte-derived cells, and characteristic "spindle cells" that help define these tumors [19, 21, 22]. Within infected individuals, a variety of circulating bone marrow derived cells also can harbor KSHV DNA [26, 123, 186]. KSHV can infect primary human bone marrow cells [135]; thus demonstrating that MSCs are susceptible to KSHV infection.

In summary, since virus can infect MSC, viremia in the recipient may lead to infection of infused MSC and theoretical suppression of the immunomodulating effects and therefore, clinical trials are needed to elucidate these points.

Conclusion

MSCs exert their immunosuppressive functions by secreting soluble factors, such as cytokines, IDO, PGE2, NO following their activation by cytokines such as IFN-γ and IL-1β. However, the identity of the soluble factors produced by the activated MSC or the mechanism through which these cells act is still unclear. Upon activation, MSCs can modulate the immune functions of dendritic cells by causing inhibition of T cell proliferation, or by increasing the generation of regulatory T cells. However, these mechanisms are not

completely responsible for the immune suppressive effects of MSCs, because MSCs can function alone to modulate the functions of T cells without the need of dendritic cells. The immune suppressive activity of MSCs in vivo is still unclear, although there is increasing acceptance to use MSC in treating human diseases instead of using haematopoietic-derived stem cells. Future directions should be aimed at a better understanding of the factors involved in the immune modulation activity of MSCs.

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