Immunomodulatory properties of human adult and fetal multipotent mesenchymal stem cells

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Abstract

In recent years, a large number of studies have contributed to our understanding of the immunomodulatory mechanisms used by multipotent mesenchymal stem cells (MSCs). Initially isolated from the bone marrow (BM), MSCs have been found in many tissues but the strong immunomodulatory properties are best studied in BM MSCs. The immunomodulatory effects of BM MSCs are wide, extending to T lymphocytes and dendritic cells, and are therapeutically useful for treatment of immune-related diseases including graft-versus-host disease as well as possibly autoimmune diseases. However, BM MSCs are very rare cells and require an invasive procedure for procurement. Recently, MSCs have also been found in fetal-stage embryo-proper and extra-embryonic tissues, and these human fetal MSCs (F-MSCs) have a higher proliferative profile, and are capable of multilineage differentiation as well as exert strong immunomodulatory effects. As such, these F-MSCs can be viewed as alternative sources of MSCs. We review here the current understanding of the mechanisms behind the immunomodulatory properties of BM MSCs and F-MSCs. An increase in our understanding of MSC suppressor mechanisms will offer insights for prevalent clinical use of these versatile adult stem cells in the near future.

Keywords: mesenchymal stem cells, bone marrow, fetal, multilineage differentiation, immunomodulation, T lymphocytes, natural killer lymphocytes, dendritic cells, major histocompatibility complex (MHC) molecules

1. Mesenchymal stem cells: Definition and functional capacity

Human mesenchymal stem cells (MSCs) are a population of multineage progenitor cells with the ability to differentiate into multiple mesenchymal lineages such as chondrocytes, osteoblasts, or adipocytes [1,2]. The initial isolation of MSCs was from the bone marrow (BM) based on plastic adherence of the cells as opposed BM hematopoietic cells which can be cultured in suspension [3]. Increasingly, MSCs have been reported to be isolated from a number of other organs in the adult [4-7] and fetal-stage tissue [8-13]. Due to the difficulty in comparing the various methods used to isolate BM and tissue MSCs, a recent movement to define these progenitor cells have proposed a minimal criteria for MSCs in terms of trilineage mesodermal differentiation capacity and expression of a specific panel of cell surface marker including being positive for CD73, CD90, and CD105; and negative for hematopoietic markers such as CD14 or CD11b, CD34, CD45, and CD19 or CD79a [14]. The ease of isolation of MSCs along with reports of differentiation into extra-mesodermal cell types has made MSCs a popular choice for cell therapy for preclinical and clinical trials of a variety of diseases [15,16].

2. Immunomodulatory Properties of Adult and Fetal-stage MSCs

One important reason for the abundant number of clinical studies using adult BM MSCs is the immunomodulatory properties of these cells [17-20]. As with organ transplantation, a critical issue in stem cell therapy is the rejection resulting from immune incompatibility between donor and recipient. BM MSCs' immunomodulatory properties appear to obviate this major obstacle for cell therapy [21]; moreover, these immunosuppressive effects allow for an even wider range of disease indications for these progenitor cells, including use for immune-related diseases [4,22-26]. BM MSCs appear to be poorly immunogenic [27], since they constitutively express low levels of major histocompatibility complex (MHC) class I...
molecules and no MHC class II molecules. Moreover, BMMSCs do not express co-stimulatory molecules such as CD40, CD80, or CD86 which are involved in the activation of T cell for transplant rejection [18,28,29]. Several studies show that differentiated and undifferentiated BMMSCs have suppressive effects on alloantigen- and mitogen-stimulated lymphocyte proliferation in *in vitro* studies using mixed lymphocyte reactions (MLR), with a concomitant reduction in the production of proinflammatory cytokines such as interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α) [17,18,30]. Thus, the clinical indications for human BMMSCs are considerably wider than other human stem cells, ranging from cell replacement for degenerative diseases—common indications for stem cell therapy—as well as immune-related diseases including autoimmune diseases and transplantation rejection [4,22-26].

While the differentiation plasticity and immunomodulatory properties of adult BMMSCs have brought much excitement in terms of prevalent clinical use for these progenitor cells, the fact remains that these cells are very rare, with cell numbers and proliferative capacity further decreasing with age [31,32]. In addition, an invasive procedure in terms of BM aspiration is needed to obtain BMMSCs. Thus, investigators have worked to identify other abundant and easily attainable sources of MSCs for therapeutic use. While many other adult tissues appear to harbor MSCs as well [4], the problems of requiring invasive procedures to obtain these relatively rare cells remain. A number of labs have thus turned to using discarded post-partum fetal-stage tissue for isolation of progenitor cells, since fetal umbilical cord blood is known to be a good source for the hematopoietic stem cell, one type of highly used stem cells. Known to be important in mediating the fetomaternal tolerance of pregnancy, fetal-stage extra-embryonic tissues are easily accessible mediators of actions of F-MSCs with subpopulations of leukocytes, and mechanisms of actions—when investigated—are reviewed.

3. Interactions of human BMMSCs and F-MSCs with leukocyte subpopulations

3.1 Interactions with T Lymphocytes

Currently, the interactions of MSCs with T lymphocytes are the best studied. Many reports have shown that BMMSCs affect several properties of T cells, most prominently efficiently suppressing activated CD4+ T helper cell and CD8+ cytotoxic T cell (CTL) proliferation [19,29,58-60]. Activated T cells are arrested by BMMSCs in the G0/G1 phase of the cell cycle [61], but apoptosis is not induced [19,29]. Besides their ability to impair the proliferation of activated T cells, BMMSCs can prolong the survival of unstimulated T cells by rescuing the lymphocytes from activation-induced cell death by downregulation of Fas receptor and Fas ligand on T cells and inhibition of endogenous proteases involved in cell death [62]. Further studies have shown that BMMSCs reduce IFN-γ production by CD4+ Th1 cells and interleukin (IL)-17 release by CD4+ Th17 lymphocytes, whereas IL-4 secretion by CD4+ Th2 cells is augmented [58,63-66]. The cytolytic potential of CTLs can also be efficiently impaired by BMMSCs [67]. Recently, several studies investigated the impact of BMMSCs on T regulatory
lymphocytes (Tregs), a population of CD4+ CD25\textsuperscript{high} cells which play an important role in the induction of peripheral tolerance and the inhibition of proinflammatory immune responses \cite{68-70}. Many studies have shown that BMMSCs cultured with stimulated peripheral blood mononuclear cells (PBMCs) can induce the expansion of functional CD4+ CD25\textsuperscript{high} Foxp3\textsuperscript{*} Tregs \cite{58,66,67,71-75}. A number of mechanisms have been suggested—both cell-contact dependent and independent mechanisms—but there is no clear consensus as of yet; for example, transforming growth factor-\(\beta\) (TGF-\(\beta\)) has been cited as being involved in one study \cite{71} but not in another study \cite{72}. This discrepancy may be due to the subtle phenotypic variations induced in BMMSCs by the many methods available for isolation of these adult stem cells.

Several studies have attempted to delineate which specific molecules are involved in the immunomodulatory effect of BMMSCs on T-cell proliferation and effector functions. In the human system, the effects of BMMSCs on T cells are mainly mediated through cell-contact independent processes, implicating the importance of secreted factors \cite{76}. These molecules include IL-1\(\beta\) \cite{77}, TGF-\(\beta\) \cite{19,71,77}, hepatocyte growth factor (HGF)\cite{19}, prostaglandin E\textsubscript{2} (PGE\textsubscript{2})\cite{58,71,78,79}, indoleamine 2,3-dioxygenase (IDO)\cite{59,79-81}, heme oxygenase-1 (HO-1)\cite{82}, leukemia inhibitory factor (LIF)\cite{83}, insulin-like growth factor (IGF)\cite{84}, soluble human leukocyte antigen G5 (sHLA-G5)\cite{74,85}, galectin \cite{86,87}, and Jagged-1 \cite{88}. Most of the inhibitory soluble factors are not constitutively secreted, but can be induced by the interaction between activated effector cells and BMMSCs (Table 1).

F-MSCs also have been reported to have strong inhibitory effects on T lymphocytes. hWJ-MSCs display potent immunosuppressive properties on T cell activation in an antigen-independent manner \cite{51}, and can also suppress the proliferation of mitogen-stimulated rat splenocytes (xenograft model) or human PBMCs (alloimmune transplant model) in allogeneic MLR \textit{in vitro} \cite{51}. Furthermore, CD14\textsuperscript{*} monocytes promote the immunosuppressive effect of hWJ-MSCs probably via the IL-1\(\beta\)-PGE\textsubscript{2} axis. The inflammatory cytokine IL-1\(\beta\) produced by hPBMCs upon activation upregulates the expression of cyclooxygenase-2 (COX-2) and the production of PGE\textsubscript{2} by hWJ-MSCs \cite{89-92}. hP-MSCs can also suppress the proliferation of allogeneic T cells \cite{40,53,93}. These effects of hP-MSCs may involve the secretion of soluble factors TGF-\(\beta\) and IL-10 \cite{40,94}. Both hP-MSCs and hUCB-MSCs have been shown to increase the proportion of Tregs, which contributes to the suppression of T cell proliferation \cite{40,42}(Figure 1).

Interestingly, a number of reports have demonstrated that in \textit{in vitro} systems, pretreatment of BMMSCs and F-MSCs with the pro-inflammatory cytokine IFN-\(\gamma\) actually enhances their immunomodulation rather than decreases it \cite{40,59,95}. Some investigators have postulated that this may explain the \textit{in vivo} ability of MSCs to be effective against very inflammatory diseases such as graft-versus-host-disease (GVHD), in which the production of such activating cytokines as IFN-\(\gamma\) by T and natural killer lymphocytes (NKs) may actually promote MSC immunomodulation, subsequently suppressing the proliferation of CD4\textsuperscript{+}, CD8\textsuperscript{+} T cells, and NKs themselves \cite{59}. While this has not been proven in animal studies, pre-clinical and clinical data continues to reveal therapeutic efficacy after MSC administration, giving indirect evidence for this hypothesis. Interestingly, while IFN-\(\gamma\) pre-treatment of adult BMMSCs results in induction of IDO, a strong immunosuppressive enzyme \cite{59,80}, MHC II molecules—which can elicit inflammatory responses \cite{96}—are induced as well \cite{12,40}, but this does not appear to change the immunomodulatory effects of BMMSCs. It would be critical to elucidate this paradox to better understand why these progenitors possess such strong immunomodulatory properties inherently.

### 3.2 Interactions with Dendritic Cells (DCs)

DCs are derived from monocytes and are potent antigen-presenting cells (APCs) that act by internalizing, shuttling, and presenting antigens to naïve T-cells, which then leads to T-cell activation. These key regulators of immunity display an extraordinary capacity to induce T cell responses and secrete a variety of cytokines; the differentiation status of DCs can influence whether its target lymphocyte—often T cells—will mount an effector versus a more immunomodulatory response \cite{97}. As such, studies have shown that BMMSCs inhibit the immunostimulatory capacity of DCs, supporting the development of a more tolerogenic population of DCs \cite{93,98,99}. BMMSCs markedly impair PBMCs differentiation into DCs and inhibit endocytosis and the production of IL-12 by DCs. In the presence of BMMSCs, the differentiation of CD14\textsuperscript{*} monocytes into DCs is impaired, and the monocytes retain high expression of CD14\textsuperscript{*}—a marker of immaturity for DCs—without the upregulation of CD1a, HLA-DR, or co-stimulatory molecules which prevent the DCs to efficiently induce T cell effector responses \cite{98}. In addition, BMMSCs also efficiently suppress the T cell-activating functions of DCs, including stimulation of T-cell proliferation, reduction of naïve CD4\textsuperscript{+} T lymphocytes polarizing into proinflammatory Th1 cells, and promotion of Th2 responses. BMMSCs can decrease TNF-\(\alpha\) secretion by DCs, which then leads to a reduced number of IFN-\(\gamma\)-producing Th1 cells. APCs generated in the presence of BMMSCs express low levels of IL-12, TNF-\(\alpha\), and MHC class II and high levels
of IL-1β and IL-10, regardless of CD86 expression [100]. BMMSCs also induce DCs to secrete IL-10, which favors IL-4-producing Th2 cells and Tregs [58]. Furthermore, BMMSCs impair the release of cytokines by activated DCs through PGE2 [58,99]. Both cell-to-cell contact and soluble factors such as IL-6 and macrophage-colony-stimulating factor (M-CSF) mediate the BMMSC-mediated inhibition of differentiation, cytokine production, and T-cell stimulatory capacity of DCs [98,101] (Table 1).

Interestingly, there are studies which show that BMMSCs itself can function as non-professional APCs. It has been reported that IFN-γ-stimulated BMMSCs can present exogenous antigens through upregulation of MHC class II molecules, which then results in activation of CD4+ T cells [28,102-104]. BMMSCs can also cross-present exogenous antigens to induce CD8+ T cell proliferation [105,106]. A few studies have shown that BMMSCs—similar to DCs—express high levels of toll-like receptors (TLRs), including TLR1, TLR3, TLR4, and TLR5. TLRs are receptors primarily expressed on APCs which recognize conserved pathogen-derived components. Triggering of TLR3, which binds double-stranded RNA, and TLR4, which binds lipopolysaccharide (LPS) and innate self antigens, on BMMSCs has been reported to suppress the immunomodulation of these cells through Notch/Jagged1 signaling, leading to production of pro-inflammatory mediators such as IL-1β, IL-6, and IL-8 [88,107-109]. However, another report showed that triggering of TLR on BMMSCs actually induces immunosuppression, which leads to the production of immunosuppressive kynurenines induced by IDO1. IDO1 can be induced by TLR3 and TLR4 signaling and this involves the activation of protein kinase R (PKR), an autocrine IFN-β signaling loop, and the activation of signal transducer and activator of transcription 1 (STAT1)/interferon regulatory factor 1 (IRF-1)[110]. These conflicting data regarding BMMSCs suppressing DC maturation and BMMSCs itself being an APC eliciting pro-inflammatory responses will require more research for clarification. One possible reason for these discrepant findings is that there is much heterogeneity between BMMSCs isolated from laboratory to laboratory. While the recent consensus of cell surface profile and tri-lineage mesodermal differentiation requirement has been extremely helpful to unify BMMSC phenotype [14], there still may exist epigenetic differences due to organ of origin and donor age, just to name a few variables. Moreover, the immunomodulatory properties of MSCs from different organs have not been much investigated, and one comparative study suggests that the MSC niche is unique in each tissue, which can contribute to functional differences [111]. Thus, it appears that studying the immunomodulatory behavior of MSCs derived from different origins would be important, and the accumulation

| Table 1 Human BMMSC-Derived Immunoregulatory Soluble Factors |
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| Leukocyte | Effects | Soluble Factors | References |
| T cells | Inhibition of T-cell proliferation, cytokine secretion and cytotoxicity | IL-1β | (77) |
| NKs | Inhibition of NK cell proliferation, cytokine secretion and cytotoxicity | TGF-β1 | (19,71,77) |
| NKs | Apoptosis of activated T-cells | HGF | (19) |
| DCs | Inhibition of DC maturation | PGE2 | (58,71,78,79) |
| DCs | Generation of CD4+ CD25high Foxp3+ Tregs | IDO | (59,79-81) |
| NKs | Inhibition of NK cell proliferation, cytokine secretion and cytotoxicity | HO-1 | (82) |
| NKs | Induction of CD4+ CD25high Foxp3+ Tregs | LIF | (83) |
| NKs | Generation of CD4+ CD25high Foxp3+ Tregs | IGF | (84) |
| NKs | Inhibition of NK cell proliferation, cytokine secretion and cytotoxicity | HLA-G5 | (74,83) |

Abbreviations: DCs, dendritic cells; NKs, natural killer lymphocytes; Tregs, T regulatory lymphocytes; IL-1β, interleukin-1β; TGF-β1, transforming growth factor-β1; HGF, hepatocyte growth factor; PGE2, prostaglandin E2; IDO, indoleamine 2,3-dioxygenase; HO-1, heme oxygenase-1; LIF, leukemia inhibitory factor; IGF, insulin-like growth factor; HLA-G5, human leukocyte antigen G5; CCL1, CC chemokine ligand 1; M-CSF, macrophage-colony-stimulating factor.
of such data will help to shed more light and clarity on discrepant findings of this field.

Some studies have suggested that F-MSCs are poor APCs due to their low or limited expression of MHC class II and co-stimulatory molecules even after IFN-γ stimulation [40,112]. Recent studies have also investigated whether F-MSCs modulate DC phenotype and function. hAMSCs exert immunomodulatory effects on APCs, as demonstrated by their capacity to block maturation of monocytes into DCs [112]. They can prevent the expression of the DC lineage-specific marker CD1a and reduce the expression of HLA-DR, CD80, and CD83. This block in the monocyte-DC maturation process also results in impaired allostimulatory ability of these cells on allogeneic T cells [113,114]. Remarkably, hUCB-MSCs modulate DCs in a different way. hUCB-MSCs suppress the function of mature DCs by driving DCs to an intermediate maturation state and boosting IL-12 production by mature DCs [115]. These inhibitory mechanisms involve both cell-contact dependent as well as secretion of soluble factors [50] (Figure 1).

3.3 Interactions with Natural Killer Lymphocytes (NKs)

NKs are key players of the innate immune system and are important in targeting virus-infected cells and tumor cells. NKs are highly cytotoxic and secrete large amounts of proinflammatory cytokines such as TNF-α and IFN-γ [116,117]. Part of the innate immune system,
these cytotoxic lymphocytes are triggered to recognize and respond to MHC molecules signifying “self” versus “non-self”, rather than specific antigens which T and B lymphocytes of the adaptive immune system recognize. A few studies have shown that BMMSCs are able to suppress the proliferation and cytokine production of NKs [58,67,118]. The inhibition requires both cell-to-cell contact and soluble factors such as PGE2 and TGF-β [59,118]. BMMSCs can also modulate the cytotoxicity of NKs, reducing the levels of NK-secreted cytokines such as IFN-γ, IL-10, and TNF-α and this phenomenon also requires cell-cell contact [118,119]. However, stimulated NKs can efficiently lyse autologous and allogeneic BMMSCs [118,120,121]. The activating NK receptors NKp30, NKG2D, and DNAM-1 were involved in NK-mediated cytotoxicity against BMMSCs. IFN-γ-stimulated BMMSCs, on the other hand, were less susceptible to NK cell lysis as a consequence of the up-regulation of MHC class I molecules at the MSC surface [121]. Moreover, the secretion of soluble HLA-G (sHLA-G) by BMMSCs plays an important role in the inhibition of NK cytotoxicity and IFN-γ release [74]. First identified in choriocarcinoma and migratory trophoblasts, HLA-G (non-classical MHC I molecule) is thought to confer for the fetus a protective effect against the maternal immune system, including directly suppressing maternal NK cytotoxicity [122]. HLA-G can exist in several forms, with the best characterized being the complete transmembrane form (HLA-G1)—the predominant in vivo form—and one of the three soluble, truncated forms (HLA-G5 or sHLA-G) [123]. Unlike most MHC I molecules, HLA-G has very low polymorphism and its expression in the adult is highly restricted; however, in certain pathologic states including cancer and inflammatory diseases, expression can be induced [124]. The receptors for HLA-G include ILT-2, ILT-4, and CD94 and these receptors can be found on a number of leukocytes, most prominently being NKs [125] (Table 1).

F-MSCs can express surface molecule HLA-G, indicating potential tolerance-inducing properties [51,126]. We found that hP-MSCs are more resistant to stimulated-NK cytotoxicity than BMMSCs; moreover, hP-MSCs demonstrate enhanced suppressive effects towards NK in the presence of IFN-γ, and this is partially mediated through surface expression of HLA-G on hP-MSCs but not adult BMMSCs [127]. The placenta is known to have unique immunomodulatory interactions with maternal uterine NKs, which also have a different effector profile than peripheral blood NKs [128,129]. Thus, interactions of F-MSCs with NKs may be quite different than that found with BMMSCs, since NKs are one of the most important and predominant lymphocyte populations found during pregnancy. While such data is still scarce, research on F-MSCs interactions with this population of innate lymphocytes should yield interesting data, and perhaps even shed light on maternal-fetal immune mechanisms (Figure 1).

4. Clinical applications of adult and F-MSCs for GVHD

The majority of data on the immunomodulation of MSCs are in vitro in nature, however, a number of studies have been in vivo. One of the potentially lethal consequences after allogeneic HSCT is GVHD in which recipient cytotoxic T cells attack donor tissue, resulting in an immune-related complication which is associated with high morbidity and mortality [130]. Animal models of GVHD are one of the most commonly used disease models to validate BMMSC immune function in vivo, and these studies have demonstrated that BMMSCs do remain immunomodulatory in vivo [131-134]. Recent data has shown that the combination of BMMSCs and immunosuppressive drugs can prolong organ allograft survival [135,136]. Because of the profound immunomodulatory effect of BMMSCs shown in vitro and in vivo, co-transplantation of ex vivo-expanded BMMSCs with HSCs for GVHD has been recommended [22,26,137-145]. In addition, cytokines released by BMMSCs may promote homing or proliferation of HSCs and enhance HSCs engraftment [146-151]. Thus, based on the accumulated in vitro and animal studies, a number of clinical trials have been started to evaluate the potential of BMMSCs for the treatment of GVHD [22,26,137,140,152].

While there are in general fewer studies using F-MSCs as a cell therapy source, some pre-clinical studies have been conducted. Several animal studies show the prolonged survival of hAMSCs with no evidence of immunological rejection after xenogeneic transplantation into immunocompetent animals including rats [56,153-155] and swine [56]. Moreover, hAF-MSCs appear to be relatively resistant to rejection by the recipient—even with allogeneic cell transplantation—due to the expression of immunosuppressive factors such as CD59 (protectin) and HLA-G [156]. Co-transplantation of UCBHSCs along with F-MSCs can reduce potential GVHD in recipients [35], as well as enhance UCB cell engraftment and homing of CD34+ HSCs [157,158]. Therefore, F-MSCs appear to be a promising source for stem cell therapy of GVHD and likely other immune-related diseases.

5. Conclusions

MSCs are multilineage progenitors which can be isolated from many adult organs as well as fetal-stage tissues. BMMSCs and F-MSCs have been reported to harbor strong immunomodulatory effects. While the data is still scarce regarding F-MSCs, several differences in the immune-suppressive properties between F-MSCs and adult BMMSCs have been found. Future investigations
on the molecular mechanisms underlying the immunomodulatory properties of both F-MSCs and adult BMMSCs would be important since these differences may have functional relevance to therapeutic use of both sources of progenitor cells.

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References
1. Pittenger MF, Mackay AM, Beck SC, Jaiswal RK, Douglas R, Mosca JD, Moorman MA, Simonetti DW, Craig S, Marshak DR. Multilineage potential of adult human mesenchymal stem cells. Science 1999, 284(5411):143-147.
2. Prockop DJ. Marrow stromal cells as stem cells for nonhematopoietic tissues. Science 1997, 276(5309):71-74.
3. Friedenstein AJ, Petrukova KV, Kurolesova A, Frolova GP. Heterotopic of bone marrow. Analysis of precursor cells for osteogenic and hematopoietic tissues. Transplantation 1968, 6(2):230-247.
4. Brooke G, Cook M, Blair C, Han R, Headwood C, Jones B, Kambouris M, Kollar K, McTaggart S, Pelekanos R, et al. Therapeutic applications of mesenchymal stromal cells. Semin Cell Dev Biol 2007, 18(6):846-858.
5. Zuk PA, Zhu M, Mizuno H, Huang J, Futrell JW, Katz AJ, Benhaim P, et al. Immunologic properties of differentiated and undifferentiated mesenchymal stem cells. Exp Hematol 2003, 31(10):890-896.
6. Di Nicola M, Carlo-Stella C, Magri M, Milanesi M, Longoni PD, Matteucci P, Grisanti S, Gianni AM. Human bone marrow stromal cells suppress T-lymphocyte proliferation induced by cellular or nonspecific mitogenic stimuli. Blood 2002, 99(10):3838-3843.
7. Le Blanc K, Tammik C, Rosendahl K, Ringden O, Zetterberg E. HLA expression and immunologic properties of differentiated and undifferentiated mesenchymal stem cells. Exp Hematol 2003, 31(10):890-896.
8. Yen BL, Huang HI, Chien CC, Jui HY, Ko BS, Yao M, Shun CT, Yen ML, Chen et al. Identification of mesenchymal stem/progenitor cells in human first-trimester fetal blood, liver, and bone marrow. Blood 2001, 98(8):2396-2402.
9. Donnenfeld E, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marinis F, Krause D, Deans R, Keating A, Prockop D, Horwitz E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 2006, 8(4):315-317.
10. Picinich SC, Mishra PJ, Mishra PJ, Glod J, Baneejee D. The therapeutic potential of mesenchymal stem cells. Cell- & tissue-based therapy. Expert Opin Biol Ther 2007, 7(9):965-973.
11. Giordano A, Galdensis U, Marino IR. From the laboratory bench to the patient's bedside: an update on clinical trials with mesenchymal stem cells. J Cell Physiol 2007, 211(1):27-35.
12. Bartholomew A, Sturgeon C, Satskis M, Ferrer K, McIntosh T, Patil S, Hardy W, Devine S, Ucker D, Deans R, et al. Mesenchymal stem cells suppress lymphocyte proliferation in vitro and prolong skin graft survival in vivo. Exp Hematol 2002, 30(1):42-48.
13. Le Blanc K, Tammik C, Rosendahl K, Zetterberg E, Ringden O. The minimal criteria for defining mesenchymal stromal cells. Cell- & tissue-based therapy. Expert Opin Biol Ther 2007, 7(9):965-973.
14. Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marinis F, Krause D, Deans R, Keating A, Prockop D, Horwitz E. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy 2006, 8(4):315-317.
15. Picinich SC, Mishra PJ, Mishra PJ, Glod J, Baneejee D. The therapeutic potential of mesenchymal stem cells. Cell- & tissue-based therapy. Expert Opin Biol Ther 2007, 7(9):965-973.
16. Giordano A, Galdensis U, Marino IR. From the laboratory bench to the patient's bedside: an update on clinical trials with mesenchymal stem cells. J Cell Physiol 2007, 211(1):27-35.
17. Bartholomew A, Sturgeon C, Satskis M, Ferrer K, McIntosh T, Patil S, Hardy W, Devine S, Ucker D, Deans R, et al. Mesenchymal stem cells suppress lymphocyte proliferation in vitro and prolong skin graft survival in vivo. Exp Hematol 2002, 30(1):42-48.
18. Le Blanc K, Frassoni F, Ball L, Locatelli F, Roelofs H, Lewis I, Lanino E, Sundberg B, Bernardos ME, Remberger M, et al. Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. Lancet 2008, 371(9624):1579-1586.
19. Jurewicz M, Yang S, Augello A, Godwin JG, Moore RF, Azzi J, Fiorina P, Atkinson M, Sayegh MH, Abdi R. Congenic mesenchymal stem cell therapy reverses hyperglycemia in experimental type 1 diabetes. Diabetes 2010, 59(12):3139-3147.
20. Nemat K, Leelahavanhkul A, Yuen PS, Mayer B, Pammelee A, Doi K, Robey PG, Leelahavanhkul K, Keller BH, Brown JM, et al. Bone marrow stromal cells attenuate sepsis via prostaglandin E2-dependent reprogramming of host macrophages to increase their interleukin-10 production. Nat Med 2009, 15(1):42-49.
21. Augello A, Tasso R, Negroini SM, Cancetta R, Peneo G. Cell therapy using allogeneic bone marrow mesenchymal stem cells prevents tissue damage in collagen-induced arthritis. Arthritis Rheum 2007, 56(4):1175-1186.
22. Le Blanc K, Rasmusson I, Sundberg B, Goetherstrom C, Hassan M, Uzunel M, Ringden O. Treatment of severe acute graft-versus-host disease with third party haploidentical mesenchymal stem cells. Lancet 2004, 363(9419):1449-1451.
23. Barry FP, Murphy JM, English K, Mahon BP. Immunogenicity of adult mesenchymal stem cells: lessons from the fetal allograft. Stem Cells Dev 2005, 14(3):252-265.
24. Majumdar MK, Keane-Moore M, Buayan D, Hardy WB, Moorman MA, McIntosh KR, Mosca JD. Characterization and functionality of cell surface molecules on human mesenchymal stem cells. J Biomed Sci 2003, 10(2):226-241.
25. Tse WT, Pendleton JD, Beyer WM, Egalka MC, Guinan EC. Suppression of allogeneic T-cell proliferation by human marrow stromal cells: implications in transplantation. Transplantation 2003, 75(3):389-397.
26. Ryushinokova E, Mosca JD, Zernetskina V, Majumdar MK, Begg CJ, Simonetti DW, Deans R, McIntosh KR. T cell responses to allogeneic human mesenchymal stem cells: immunogenicity, tolerance, and suppression. J Biomed Sci 2005, 12(1):47-57.
27. Stenderup K, Justesen J, Clausen C, Kassem M. Aging is associated with decreased maximal life span and accelerated senescence of bone marrow stromal cells. Bone 2003, 33(6):919-926.
28. de Braud F, Khayat D, Kroon BB, Valdagni R, Bruzzi P, Cascinelli N. Congenic mesenchymal stem cell lines: studies on cell surface molecules and functionality of cell surface molecules on human mesenchymal stem cells. J Biomed Sci 2003, 10(2):226-241.
29. Tse WT, Pendleton JD, Beyer WM, Egalka MC, Guinan EC. Suppression of allogeneic T-cell proliferation by human marrow stromal cells: implications in transplantation. Transplantation 2003, 75(3):389-397.
30. Ryushinokova E, Mosca JD, Zernetskina V, Majumdar MK, Begg CJ, Simonetti DW, Deans R, McIntosh KR. T cell responses to allogeneic human mesenchymal stem cells: immunogenicity, tolerance, and suppression. J Biomed Sci 2005, 12(1):47-57.
31. Stenderup K, Justesen J, Clausen C, Kassem M. Aging is associated with decreased maximal life span and accelerated senescence of bone marrow stromal cells. Bone 2003, 33(6):919-926.
32. de Braud F, Khayat D, Kroon BB, Valdagni R, Bruzzi P, Cascinelli N. Congenic mesenchymal stem cell lines: studies on cell surface molecules and functionality of cell surface molecules on human mesenchymal stem cells. J Biomed Sci 2003, 10(2):226-241.
35. In’t Anker PS, Scherjon SA, Kleijburg-van der Kerk C, Noort WA, Claas FH, Willemze R, Fibbe WE, Khanhi HHT: Amniotic fluid as a novel source of mesenchymal stem cells for therapeutic transplantation. Blood 2003, 102(4):1548-1549.

36. Bachmann MF, Kohler G, Ecabert B, Mak TW, Kopl M: Lymphoproliferative disease in the absence of CTLA-4 is not T cell autonomous. J Immunol 1999, 163(3):1128-1131.

37. Fukuchi Y, Nakajima H, Sugiyama D, Hirose I, Kitamura T, Tsuji K: Human placenta-derived cells have mesenchymal stem/progenitor cell potential. Stem Cells 2004, 22(5):649-658.

38. Wulf GG, Vierkamp V, Hemmerlein B, Haase D, Vehmeyer K, Pukrop T, Glass B, Emons G, Trumper L: Mesogenic, progenitor cells derived from human placenta. Tissue Eng 2004, 10(7-8):1136-1147.

39. In’t Anker PS, Scherjon SA, Kleijburg-van der Kerk C, de Groot-Swings GW, Claas FH, Fibbe WE, Khanhi HHT: Isolation of mesenchymal stem cells of fetal or maternal origin from human placenta. Stem Cells 2004, 22(7):1338-1345.

40. Chong CJ, Yen ML, Chen YC, Chien CC, Huang HL, Bai CH, Yen BL: Placenta-derived multipotent cells exhibit immunosuppressive properties that are enhanced in the presence of interferon-gamma. Stem Cells 2006, 24(1):2466-2477.

41. Chayevergato A, Bollini S, Pozzobon M, Callegari A, Gasparotto L, Taiani J, Ricciardi-Calazani F, Gerosa G, Vendramin I, et al.: Human amniotic fluid-derived stem cells are rejected after transplantation in the myocardium of normal, ischemic, immuno-suppressed or immuno-deficient rat. J Mol Cell Cardiol 2007, 42(4):746-759.

42. Hao L, Zhang C, Chen XH, Zou ZW, Zhang X, Kang PY, Liang X, Gao L, Peng XG, Sun AH: Human amniotic umbilical cord blood-derived stem cells suppress xenogeneic immune cell response in vitro. Croat Med J 2009, 50(4):351-360.

43. Ilancharan S, Michalska A, Sugiya D, Hirose I, Kitamura T, Tsuji K: Human amniotic fluid-derived stem cells have characteristics of multipotent stem cells. Cell Profil 2007, 40(1):75-90.

44. Kim J, Lee Y, Kim H, Hong KJ, Kwon HC, Kwon HC, Kim SK, Cho DJ, Kang SG, You J, et al.: Immune properties of umbilical cord blood-derived mesenchymal stem cells with cells involved in alloantigen-specific immune response and promote endogenous repair in animal models of multiple sclerosis. J Immunol 2009, 182(10):5994-6002.

45. Krampepa M, Cosmi L, Angeli R, Pasini A, Liotta F, Andreini A, Santarlasci V, Mazzinghi B, Pizzolo G, Vinante F, et al.: Human mesenchymal stem cells inhibit the response of naive and memory antigen-specific T cells to their cognate peptide. Blood 2003, 101(9):3722-3729.

46. Glennie S, Sorensen J, Dyson PJ, Lam EW, Dazzi F: Bone marrow mesenchymal stem cells induce division arrest anergy of activated T cells. Blood 2005, 105(7):2821-2827.

47. Benvenuto F, Ferrari S, Geroldi E, Guandalini F, Frassoni F, Pistoa V, Mancardi G, Uccelli A: Human mesenchymal stem cells promote survival of T cells in a quiescent state. Stem Cells 2007, 25(7):1753-1760.

48. Zhou L, Chong MM, Littman DR: Plasticity of CD4+ T cell lineage differentiation. Immunity 2009, 30(6):646-655.

49. Bailo M, Soncini M, Vertua E, Signoroni PB, Sanzone S, Lombardi G, Arienti D, Calamani F, Zatti D, Paul P, et al.: Inducing proliferation of human amniotic epithelial (HAE) stromal cells for cell therapy. Stem Cells Dev 2000, 9(3):269-286.

50. Wang M, Yang Y, Yang D, Luo F, Liang W, Guo S, Xu J: Dose-dependent immunomodulatory effect of human stem cells from amniotic membrane: a comparison with human mesenchymal stem cells from adipose tissue. Tissue Eng 2007, 13(6):1173-1183.

51. Weiss ML, Anderson C, Medicetty S, Seshareddy KB, Weiss RJ, VanderWerff I, et al.: Mechanisms of foxp3+ T regulatory cell-mediated suppression. Exp Hematol 2009, 37(9):1265-1277.

52. Weiss ML, Medicetty S, Bledsoe AR, Rachakatla RS, Choi M, Merchav S, Li H, Niederkorn JY, Neelam S, Mayhew E, Word RA, McCulley JP, et al.: Prostaglandin E2 and transforming growth factor beta 1 play non-redundant roles in human mesenchymal stem cell induction of CD4+ or CD8+ regulatory T cells upon mesenchymal stem cell-lymphocyte interaction. Haematologica 2007, 92(7):881-888.

53. Li C, Zhang Y, Xiao N: Human placenta-derived mesenchymal stem cells inhibit proliferation and function of allogeneic immune cells. Cell Tissue Res 2007, 330(3):437-446.

54. Wolbank S, Peterbauer A, Fahmer M, Hennetrichter S, van Grienven M, Stadler G, Reß H, Gabriel C: Dose-dependent immunomodulatory effect of human stem cells from amniotic membrane: a comparison with human mesenchymal stem cells from adipose tissue. Tissue Eng 2007, 13(6):1173-1183.
lymphocyte and natural killer function and to induce CD4 + T cells. J Immunol 2009, 182(4):2143-2148.

84. Gieseke F, Schutt B, Viebahn S, Koscielniak E, Friedrich W, Handgretinger R, Muller I: Human mesenchymal stem cells inhibit mature dendritic cells. Exp Hematol 2009, 37(5):682-689.

85. Rasmusson I, Ringden O, Sundberg B, Le Blanc K: Mesenchymal stem cells inhibit differentiation and function of monocyte-derived dendritic cells. Blood 2005, 105(10):4120-4126.

86. Groh ME, Maitra B, Szekely E, Koc ON: Toll-like receptors and their ligands control mesenchymal stem cell functions. Exp Hematol 2009, 37(8):1059-1068.

87. Bouchet S, Gorin NC, Thierry D, Groh ME, Maitra B, Szekely E, Koc ON: Interferon-gamma-stimulated monocyte-derived dendritic cells. Exp Hematol 2009, 37(8):1059-1068.

88. Liotta F, Angeli R, Cosmi L, Fili L, Manuelli C, Frosali F, Mazzinghi B, Maggi L, Spaggiari GM, Abdelrazik H, Becchetti F, Moretta L: MSCs inhibit monocyte-derived DC maturation and function by selectively interfering with the generation of immature DCs: central role of MSC-derived prostaglandin E2. Blood 2009, 113(1):6576-6583.

89. Chen K, Wang D, Du WT, Han ZB, Ren H, Chi Y, Yang SG, Zhu D, Bayard F, Gieseke F, Bohringer J, Bussolari R, Dominici M, Handgretinger R, Muller I: Human mesenchymal stem cells inhibit lymphocyte proliferation by mitogens and alloantigens by different mechanisms. Exp Cell Res 2005, 305(1):33-41.

90. Cutler AJ, Limbani V, Girdlestone J, Navarrete CV: Dendritic cells in the T-cell areas of lymphoid organs. Immunol Rev 1997, 156:25-37.

91. Chen et al.: Mesenchymal stem cells inhibit T cell allo-responses via the TH2 pathway: relevance to tissue engineering human heart valves. Tissue Eng 2006, 12(8):2263-2273.

92. Groh ME, Maitra B, Szekely E, Koc ON: Human mesenchymal stem cells require monocyte-mediated activation to suppress allogeneic T cells. Exp Hematol 2005, 33(8):928-934.

93. Groh ME, Maitra B, Szekely E, Koc ON: Human mesenchymal stem cells inhibit T cell allo-responses via the TH2 pathway: relevance to tissue engineering human heart valves. Tissue Eng 2006, 12(8):2263-2273.

94. Rasmusson I, Ringden O, Sundberg B, Le Blanc K: Mesenchymal stem cells inhibit lymphocyte proliferation by mitogens and alloantigens by different mechanisms. Exp Cell Res 2005, 305(1):33-41.

95. Ryan JM, Barry F, Murphy JM, Mahon BP: Interferon-gamma does not break, but promotes the immunosuppressive capacity of adult human mesenchymal stem cells. Clin Exp Immunol 2007, 149(2):353-363.

96. Jones EY, Fugger L, Strominger JL, Siebold C: MHC class II proteins and disease: a structural perspective. Nat Rev Immunol 2006, 6(4):271-282.

97. Steinman RM, Pack M, Inaba K: Dendritic cells in the T-cell areas of lymphoid organs. Immunol Rev 1997, 156:25-37.

98. Jiang X, Zhang Y, Liu B, Zhang SX, Wu Y, Yu XD, Mao N: Human mesenchymal stem cells inhibit differentiation and function of monocyte-derived dendritic cells. Blood 2005, 105(10):4120-4126.

99. Beelen E, de Groot-Swings GM, Fibbe WE, Kanhai HH, Scherjon SA, Rasmusson I, Ringden O, Sundberg B, Le Blanc K: Mesenchymal stem cells induce apoptosis of activated T cells. Exp Hematol 2005, 33(8):928-934.

100. Lanz TV, Tritschler I, Koppel A, Tolosa E, Opitz CA, Litzenburger UM, Lutz C, Rameshwar P: Antigen-presenting property of mesenchymal stem cells occurs during a narrow window at low levels of interferon-gamma. Blood 2009, 113(1):1545-1555.

101. Groh ME, Maitra B, Szekely E, Koc ON: Toll-like receptors and their ligands control mesenchymal stem cell functions. Stem Cells 2009, 27(1):7963-7973.

102. Groh ME, Maitra B, Szekely E, Koc ON: Toll-like receptors and their ligands control mesenchymal stem cell functions. Stem Cells 2009, 27(1):7963-7973.

103. Liotta F, Angeli R, Cosmi L, Fili L, Manuelli C, Frosali F, Mazzinghi B, Maggi L, Spaggiari GM, Abdelrazik H, Becchetti F, Moretta L: MSCs inhibit monocyte-derived DC maturation and function by selectively interfering with the generation of immature DCs: central role of MSC-derived prostaglandin E2. Blood 2009, 113(1):6576-6583.

104. Chan WK, Lau AS, Li JC, Law HK, Lau YL, Chan GC: MHC expression kinetics and immunogenicity of mesenchymal stem cells after short-term IFN-gamma challenge. Exp Hematol 2008, 36(1):154-1555.

105. Groh ME, Maitra B, Szekely E, Koc ON: Toll-like receptors and their ligands control mesenchymal stem cell functions. Stem Cells 2009, 27(1):7963-7973.

106. Liotta F, Angeli R, Cosmi L, Fili L, Manuelli C, Frosali F, Mazzinghi B, Maggi L, Spaggiari GM, Abdelrazik H, Becchetti F, Moretta L: MSCs inhibit monocyte-derived DC maturation and function by selectively interfering with the generation of immature DCs: central role of MSC-derived prostaglandin E2. Blood 2009, 113(1):6576-6583.
152. Ringden O, Remberger M, Svahn BM, Barkholt L, Mattsson J, Aschan J, Le Blanc K, Gustafsson B, Hassan Z, Omazic B, et al: Allogeneic hematopoietic stem cell transplantation for inherited disorders: experience in a single center. Transplantation 2006, 81(5):718-725.

153. Kong XY, Cai Z, Pan L, Zhang L, Shi J, Dong YL, Yang N, Li Q, Huang XJ, Zuo PP: Transplantation of human amniotic cells exerts neuroprotection in MPTP-induced Parkinson disease mice. Brain Res 2008, 1205:108-115.

154. Zhao P, Ie H, Hongo M, Ota M, Konishi I, Nikiad T: Human amniotic mesenchymal cells have some characteristics of cardiomyocytes. Transplantation 2005, 79(5):528-535.

155. Kubo M, Sonoda Y, Muramatsu R, Usui M: Immunogenicity of human amniotic membrane in experimental xenotransplantation. Invest Ophthalmol Vis Sci 2001, 42(7):1539-1546.

156. Walther G, Gekas J, Bertrand OF: Amniotic stem cells for cellular cardiomypoplasty: promises and premises. Catheter Cardiovasc Interv 2009, 73(7):917-924.

157. Prather WR, Toren A, Meiron M: Placental-derived and expanded mesenchymal stromal cells (PLX-I) to enhance the engraftment of hematopoietic stem cells derived from umbilical cord blood. Expert Opin Biol Ther 2008, 8(8):1241-1250.

158. Hiwase SD, Dyson PG, To LB, Lewis ID: Cotransplantation of placental mesenchymal stromal cells enhances single and double cord blood engraftment in nonobese diabetic/severe combined immune deficient mice. Stem Cells 2009, 27(9):2293-2300.

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