Mesenchymal stem cells: Immunomodulatory capability and clinical potential in immune diseases

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Received 13 August 2014; revised 29 November 2014; accepted 15 December 2014
Available online 24 February 2015

Abstract

Mesenchymal stem cells (MSCs) represent a heterogenous population of adult, fibroblast-like multi-potent cells. MSCs have drawn much attention during the last decade in the field of regenerative medicine, mainly due to their capacity to differentiate into specific cell types, abundant production of soluble growth factors and cytokines, and hematopoiesis supporting properties. In addition, MSCs can migrate to the sites of inflammation and hold potent of immunomodulatory and anti-inflammatory effects through cell and cell interactions between MSCs and lymphocytes or production of soluble factors. Therefore, the application of MSCs in many disease situations is full of possibilities for future clinical treatment. Phase III clinical trials have been run using MSCs for treatment of Graft versus Host Disease (GVHD), and MSCs product approval has been achieved for pediatric GVHD treatment in Canada and New Zealand (Prochymal®; Osiris Therapeutics). In addition, hundreds of clinical trials are being run using MSCs for treatment of several immune mediated diseases, including GVHD, aplastic anemia (AA), Crohn’s disease (CD), rheumatoid arthritis (RA), and multiple sclerosis (MS). In this review we mainly focus on immunomodulation potential of MSCs and promising therapeutic application of MSCs in immune mediated diseases. Furthermore, we emphasize that biological effectiveness of MSCs will be one of most important standards to determine the dose of MSCs infusion.

Keywords: MSCs; Immunomodulatory; Cell infusion; Biological effectiveness

1. Introduction

Friedenstein was the first person to describe the isolation of clonogenic, proliferating fibroblastic MSCs from rat bone marrow (BM). And they showed that colony-forming unit fibroblasts (CFU-Fs) derived stromal cells can serve as feeder layers for the culture of hematopoietic stem cells (HSCs) and can differentiate into osteocytes, chondrocytes and adipocytes [1,2]. Besides BM, MSCs can also be isolated from adipose tissues [3], fetal liver [4], cord blood and mobilized peripheral blood [5], fetal lung [6], placenta [7], umbilical cord [8,9], dental pulp [10], synovial membrane [11], periodontal ligament [12], endometrium [13], trabecular and compact bone [14,15] (Fig. 1).

Increased evidences have shown that under appropriate culture conditions, MSCs are capable of differentiating into mesodermal, endodermal and even ectodermal cells. MSCs are capable of secreting growth factors and immunoprotective cytokines which have been used in the field of cell and organ transplantation. Most importantly, MSCs are safe, do not form teratoma, and can be used for tissue regeneration and repair [16,17]. And easy isolation, large quantity expansion and multipotential differentiation of MSCs make them ideal candidate for stem cell-based therapy and their application as...
gene carriers. Another intriguing feature of MSCs is that they are able to escape immune recognition and inhibit immune responses. Therefore, MSCs will be a very promising tool for immunomodulatory cell therapy in immune mediated diseases. At the time of writing, there are currently 423 clinical trials using MSCs registered at clinical-trials.gov. The clinical trials have been run for tissue repair including cardiac ischemia, limb ischemia, amyotrophic lateral sclerosis, diabetes, ischemic stroke, osteoarthritis, liver cirrhosis, and liver failure and so on. More clinical trials have been run for immune mediated diseases including GVHD, CD, MS, respiratory distress syndrome, AA, and RA (www.clinicaltrials.gov). In fact, immune mediated diseases are actually the largest kind of diseases to be clinically studied now. In addition, MSCs can differentiate into tissues of ectodermal, including skin, neurons. Furthermore, MSCs can differentiate into tissues of endodermal including lung, hepatocytes, renal, and pancreatic β-cells, endothelial cells.

2. Definition of MSCs

Pittenger et al. firstly defined MSCs by their ability to proliferate in culture with an attached fibroblast-like morphology, by the presence of a consistent set of cell surface protein markers, and by their extensive consistent differentiation to multiple lineages mesenchymal tissue under certain controlled in vitro conditions [18]. However, to date because there is no specific or unique cell surface marker, so the definition of MSCs was always controversy. Therefore, currently MSCs have been defined by using a combination of cell surface phenotypic protein markers, plastic adherent fibroblast-like growth and functional properties. It is generally agreed that adult human MSCs express Stro-1 [19], CD105 (SH2) [20], CD73 (SH3/4) [21], CD44, CD71 (transferring receptor), CD90 (THY1), the ganglioside GD2 [22,23] and CD271 (low-affinity nerve growth factor receptor), as well as some cell adhesion molecules including intercellular adhesion molecule-1,-2 (ICAM-1,-2), integrins (α1, α2, α3, α5, α6, αV, β1, β3, β4) [24], activated leukocyte-cell adhesion molecule (ALCAM), lymphocyte function-associated antigen 3 (LFA-3), etc.
3), vascular cell adhesion molecule-1 (VCAM-1), and CD72 [18,25]. They also express human leukocyte antigen (HLA) class I but not class II molecules on cell surface [26,27]. Additionally, MSCs lack the expression of typical hematopoietic antigens CD11a, CD14, CD31, CD34 and CD45 [9,18], or co-stimulatory molecules CD40, CD80, and CD86 [28,29]. The International Society for Cellular Therapy (ISCT) has offered several minimal criteria to identify MSCs which are listed as: 1) Plastic adherent fibroblast-like growth while maintaining these cells in standard conditions. 2) Expression of CD73, CD90 and CD105 markers in at least 95% of cell population and lack expression of CD34, CD45, CD14, CD11b, CD19 or CD79α and HLA-II markers as measured by flow cytometry. 3) Differentiation capability into adipogenic, osteogenic and chondrogenic lineage cells in vitro [30]. Some markers, including GD2, nestin and CD271, have been used to investigate the function of certain tissue derived MSCs or different MSCs subpopulation [22,23,31,32]. For example, GD2+ umbilical cord derived MSCs are a subpopulation of MSCs with feature of primitive precursor cells and most multipotential cells [23]. And CD106+ placenta derived MSCs are the more mature and biological functional MSCs with feature of stronger immunomodulatory capability [33] and angiogenic potential (not published).

Numbers studies also showed that the MSCs have the capacity to differentiate into multiple mesenchymal tissues both in vitro and in vivo, including osteoblast [25,34], condrocyte [35,36], adipocyte [37,38], tendon [39,40], skeletal muscle cells [39], cardiomyocyte [41,42] and hematopoietic supporting stroma cells [43]. In addition, MSCs also have capability for differentiating into tissues of ectodermal, including skin [44], neurons [45]. Furthermore, MSCs can differentiate into tissues of endodermal including lung [46,47], hepatocytes [27,48], renal [49,50], and pancreatic β-cells [51,52], endothelial cells [53,54] (Fig. 1). Actually, the tissue repair capability of MSCs is mainly base on their multi-lineage differentiation potential.

3. The safety of MSCs in clinical application

MSCs have been used in several approaches for regenerative cell therapy, as well as in the perspective of modulating immune response. Therefore, the biosafety features of MSCs need to be carefully investigated to exclude the occurrence of functional or genetic alterations before their release for clinical use. Bernardo et al. show that human BM-derived MSCs can be cultured long-term in vitro, without losing their morphologic, phenotypical, and functional characteristics. Moreover, MSCs propagated in culture continuously for up to 44 weeks maintained a normal karyotype [55]. Meza-zepeda et al. also report that adipose derived MSCs do not bypass senescence even after two months of post-senescence culture. MSCs show no evidence of transformation in vitro on the basis of re-entry into the cell cycle, mitotic index, acquisition of a rounded phenotype and loss of anchorage-dependence [56]. In addition, Poloni et al. show that human MSCs from BM, chorionic villi and amniotic fluid are not susceptible to transformation after extensive in vitro expansion [57]. Chen et al. reported that human umbilical cord MSCs (hUC-MSCs) maintain their biological character and function after long-term in vitro culturing (P15). Since hUC-MSCs can be safely expanded in vitro and are not susceptible to malignant transformation in serum-free medium [58]. Therefore, basically MSCs can maintain a stable immunophenotype and chromosome structure and will not be malignant transformation after long term in vitro culture expansion.

At the same time, increased evidences show that MSCs is also safe in vivo normal animal or animal disease model cell infusion therapy. Wang et al. evaluate the overall toxicity of hUC-MSCs in cynomolgus monkeys with repeated administrations and show that transplantation of hUC-MSCs did not affect the general health of cynomolgus monkeys [16]. Feng et al. evaluated the safety of human MSCs transplanted in cerebrom of Macaca fascicularis. Their results show that the transplantation of human MSCs in monkeys did not affect total IgM, IgG, CD3, CD4, or CD8 values. And transplantation of hMSCs to the cerebrum represents a safe alternative for clinical application of neurological disorders [59]. Francois et al. infused intravenously human MSCs to NOD/SCID mice with total body irradiation or local abdominal or leg irradiation and investigated the long term side-effect. Their results demonstrated that no tissue abnormality or abnormal human MSCs proliferation was observed at 120 days after irradiation. Meanwhile, These results showed that MSCs injection is safe and efficient for long-term treatment of severe complications after radiotherapy for patients refractory to conventional treatments [60].

Finally, human MSCs is also safe according to numerous clinical trial reports. Shi et al. assessed the safety and initial efficacy of UC-MSCs transfusions for acute-on-chronic liver failure (ACLF) patients associated with hepatitis B virus (HBV) infection. Their results suggest that UC-MSCs transfusions are safe in the clinic and may serve as a novel therapeutic approach for HBV-associated ACLF patients [61]. Wang et al. assess the safety and efficacy of human UC-MSCs in the treatment of rheumatoid arthritis (RA). Their results show that no serious adverse effects were observed during or after infusion. Furthermore, the treatment of UC-MSCs induced a significant remission of disease according to the 28-joint disease activity score [62]. Rodrigo et al. evaluates the safety and feasibility of intramyocardial MSCs injection in nine patients, shortly after AMI during short-term and 5-year follow-up. Their results suggest that intramyocardial injection of MSCs in patients shortly after AMI is feasible and safe up to 5-year follow-up [63]. Gupta et al. conducted a prospective double blind randomized placebo controlled multicenter study to determine the safety of BM-MSCs in patients with critical limb ischemia. Their results show that BM-MSCs are also safe when injected intramuscularly at a dose of 2 million cells/kg body weight [64]. In addition, Lee et al. performed a randomized pilot study to investigate the safety and efficacy of MSCs in patients with AMI. Their results showed that there was no treatment-related toxicity during intracoronary administration of MSCs. Meanwhile, no
significant adverse cardiovascular events occurred during follow-up [65]. Furthermore, Pak et al. evaluate the safety of adipose tissue derived MSCs (AT-MSCs) that was used for patients suffering from orthopedic conditions. Ninety one patients suffering from orthopedic conditions were treated with autologous AT-MSCs. AT-MSCs were injected with PRP into various joints (n = 100). No neoplastic complications were detected at any AT-MSCs implantation sites. Based on longitudinal cohort, the autologous and uncultured ADSCs/PRP therapy could be considered to be safe when used as percutaneous local injections [66]. Till now, scientists evaluate the safety of MSCs through three different level including in vitro culture expansion, animal disease model and clinical trials and get a conclusion that MSCs is safe cell. In addition, MSCs preparation and production must be manipulated in GMP or GTP laboratory and only qualified MSCs can be used for clinical application for safety and achieving ideal clinical effect.

4. Interaction between MSCs and immune cells

MSCs have also been shown to possess broad immunoregulatory capabilities and are capable of influencing both adaptive and innate immune responses. MSCs inhibit immune cells proliferation and maturation and suppress immune reactions both in vitro and in vivo in a non-MHC restricted manner [67]. Therefore, MSCs are considered to be hypoinmunogenic, displaying low expression levels of HLA class I, no expression of HLA class II, and no expression of costimulatory molecules, including CD40, CD80, and CD86 [28,68]. Basically, MSCs could exert widespread immunomodulatory effects on cells of both the innate and adaptive immune system. Ex-vivo expanded MSCs have also been showed to suppress the activity of a broad range of immune cells, including T cells, natural killer T (NKT) cells, dendritic cells (DCs), B cells, neutrophils, monocytes, macrophages and so on.

4.1. MSCs inhibit T cells proliferation and suppress allogeneic T-cell response

The main features of the T cell response is cell proliferation and cytokines secretion. Inhibit T cell proliferation is the most significant effect for MSCs. In vitro, MSCs are capable of suppressing T lymphocyte proliferation induced by mitogens [67,69,70], alloantigens [67,68,71,72], as well as activation of T cells by CD3 and CD28 antibodies [68]. Suppression of T cell proliferation by MSCs has no immunological restriction, similar suppressive effects being observed with cells that were autologous or allogeneic to the responder cells [28,67,72]. MSCs also modulate immune responses through the induction of regulatory T cells which are important in maintaining immune homeostasis and self-tolerance. MSCs have been reported to induce formation of regulatory T cells that were responsible for inhibition of allogeneic lymphocyte proliferation [70]. In addition, an increase in the population of regulatory T (Treg) cells has been demonstrated in mitogen-stimulated peripheral blood mononuclear cell (PBMCs) cultures in the presence of MSCs [73,74]. Yan et al. reported that MSC-exposed Treg cells are capable of more immunosuppressive than Tregs without coculturing with MSCs. And their results showed that programmed cell death 1 receptor/B7-H1 interactions and IL-10 might be responsible for the enhanced suppressive capability of MSC-exposed regulatory T cells [75]. However, depletion of regulatory T cells had no effect on the suppression of T cell proliferation by MSCs, and MSCs physically hinder T cells from the contact with antigen presenting cells (APCs) in a noncognate fashion [76]. Human adipocyte-MSCs undergo different modes of activation, when they were treated with mouse splenic T cell culture supernatant, compared to when they were stimulated with human PBMC supernatant. However, they still exerted an antiproliferative effect on mouse splenic T cells in vitro, primarily through COX-2 expression [77]. Human adipose-AT-MSCs obtained from kidney donors induced a 2-1-fold increase in the percentage of CD25(+) CD127(−) FoxP3(+) cells within the CD4(+) T cell population from allostimulated CD25(−) cells. And AT-MSCs induced Treg cells inhibited effector cell proliferation as effectively as natural regulatory T cells. The vast majority of cells within the induced Treg fraction had a methylated FOXP3 gene Treg-specific demethylated region indicating that they were not of natural regulatory T cells origin [78].

Although the exact mechanism underlying the immunosuppressive effects of MSCs is still not clear, most evidences supported that soluble factors are involved. These factors include prostaglandin E2 (PGE2) [73,79–81], indoleamine 2,3-dioxygenase (IDO) [82,83], hepatocyte growth factor (HGF) [84,85] and transforming growth factor (TGF)-β1 [69,86]. Additionally, it is well-established that IFN-γ plays an important role in the enhancement of MSCs suppressive activity [82]. Furthermore, increased evidences support that MSCs inhibit the proliferation and/or functions of CD4+ Th1 and Th17 cells, CD8+ T cells, and natural killer cells predominantly via the secretion of soluble factors including TGF-β1 and HGF [87–90]. In addition, MSCs play a key role in cytotoxic CD8+ T cells against intracellular pathogens. Schurch et al. reported that IFN-γ can promote the release of hematopoietic cytokines, including IL-6 from MSCs, which in turn reduced the expression of the transcription factors Runx-1 and Cebpα in early hematopoietic progenitor cells and increased myeloid differentiation and triggered the temporary activation of emergency myelopoiesis and promote clearance of the infection [91] (Fig. 2).

4.2. MSCs block natural killer T (NKT) cells proliferation and cytotoxicity

NKT cells are part of the innate immune system, and bridge the adaptive immune system with the innate immune system. Once activated, these cells can perform functions ascribed to both Th and Tc cells, involving the enhancement of cell mediated immune response [92]. In addition, NKT cells play a key role in the elimination of virus infected cells and tumor cells. MSCs alter the phenotype of NKT cells and suppress...
proliferation, cytokine secretion, and cytotoxicity against HLA-class I-expressing targets. Some of these effects require cell-to-cell contact, whereas others are mediated by soluble factors, including TGF-β1 and PGE2, suggesting the existence of diverse mechanisms for MSC-mediated NKT-cell suppression [84]. Spaggiari et al. also showed that MSCs can inhibit the IL-2-induced proliferation of unactivated NKT cells [93]. In addition, the results reported by Selmani et al. showed that MSCs inhibited iNKT (Vα24(+)/Vβ11(+)) and γδ T (Vβ2(+)) cell expansion from PBMC in both cell-to-cell contact and transwell systems. MSCs, through HLA-G5, affect innate immunity by inhibiting both NKT cell-mediated cytolysis and IFN-γ secretion [94]. Furthermore, Prigione et al. reported that MSCs inhibited IFN-γ production by activated Vα24(+) Vβ11(+) and impaired CD3-mediated proliferation of activated Vα24(+) Vβ11(+) and Vβ2(+) T cells, without affecting their cytotoxic potential [95]. Therefore, MSCs achieve inhibition of the NKT cells proliferation and immune regulatory function by involving multiple cytokines and signal pathway (Fig. 2).

4.3. MSCs affect B cells proliferation and maturation

B cells are a type of lymphocyte in the humoral immunity of the adaptive immune system specialized in antigen presentation and antibody production. Recent studies also showed that MSCs can inhibit several functions of B cells. Corcione et al. showed that B-cell proliferation was inhibited by MSCs through an arrest in the G0/G1 phase of the cell cycle. A major mechanism of B-cell suppression was soluble factors of MSCs production [96]. Furthermore, MSCs inhibited B-cell differentiation because IgM, IgG, and IgA production was significantly impaired. And CXCR4, CXCR5, and CCR7 in B-cell expression, as well as chemotaxis to CXCL12, the CXCR4 ligand, and CXCL13, the CXCR5 ligand, were significantly down-regulated by MSCs, suggesting that these cells affect chemotactic properties of B cells. In addition, MSCs also affect migrate to inflammatory regions under the guidance of cell adhesion molecules and receptors for inflammatory chemokines [97]. One recent study by Lee et al. showed that the conditioned medium of MSCs infected with a mycoplasma strain, Mycoplasma arginini, has marked inhibitory effects on Ig production by lipopolysaccharide/interleukin-4-induced B cells compared with mycoplasma-free MSC-CM [98]. Yan et al. found that BAFF in MSCs was expressed at a higher level after TLR4-priming, indicating that TLR4 and a downstream pathway play a role in BAFF secretion and thus exert an important function in B lymphocyte-related immune regulation [99]. Another recent study highlighted galectin-9 (Gal-9) strongly upregulated upon activation of the cells by IFN-γ. And their results showed that Gal-9 is a major mediator of the anti-proliferative and functional effects of MSCs not...
only on T cells but also on B cells. Moreover, Gal-9 and activated MSCs contribute to the suppression of antigen-triggered immunoglobulin release [100]. By contrast, Rosado et al. reported that BM-MSCs are able to promote in vitro proliferation and differentiation of transitional and naive B cells isolated from both healthy donors (HDs) and pediatric patients with Systemic Lupus Erythematosus (SLE) upon stimulation with CpG, soluble CD40L, anti-Ig antibodies and IL-2 [101]. Meanwhile, the results by our group show that treatment with UC-MSCs resulted in an increase of proliferation, differentiation of B cells into plasma cells and production of antibodies in vitro. And our results also showed that PGE2 partially mediated the immunosuppressive activity of MSC [102]. These conflicting results hinted that it is important to distinguish the direct action of MSCs on B cells from indirect effects mediated by other cell types contained in the different culture conditions.

4.4. MSCs modulate dendritic cells (DCs) generation and maturation

DCs are the main APCs in the mammalian immune system. Their main function is to present antigen material on the cell surface to the T cells. DCs affect significantly the balance between helper and regulatory T cell and establish tolerance to self antigen [103]. The presence of MSCs blocked the differentiation of peripheral and umbilical cord blood derived CD14+/CD1a− precursors into dermal/interstitial DCs [104]. Coculture of MSCs with DCs resulted in reduced expression of CCR7 by DCs following stimulation. Likewise, DCs matured in the presence of MSCs, showed significantly less migration to CCL19 [105]. Zhang et al. showed that MSCs inhibit in vitro apoptosis of resting and IL-8-activated inflammatory cells to migrate towards the site of inflammation. During the beginning phase of inflammation, neutrophils are one of the first-responders of inflammatory cells to migrate towards the site of inflammation.

4.5. MSCs preserve neutrophils viability and function

Neutrophils form an essential part of the innate immune system. They are differentiated from HSC in the BM. Neutrophil progenitors have a quite high proliferation rate and mature neutrophils have a very short lifespan. Neutrophils are one type of phagocytes and are found in the peripheral blood, tissues and BM. Neutrophils possess the capability of chemotaxis, phagocytosis and bactericide. During the beginning phase of inflammation, neutrophils are one of the first-responders of inflammatory cells to migrate towards the site of inflammation. MSCs inhibit in vitro apoptosis of resting and IL-8-activated neutrophils and reduce N-formyl-l-methionin-l-leucyl-l-phenylalanine (f-MLP)-induced respiratory burst while not affecting phagocytosis, expression of adhesion molecules, or the migration capability of neutrophils in response to classic stimuli. And further research showed that MSCs rescued neutrophils from apoptosis by constitutive release of IL-6 [110], Cassatella et al. reported that MSCs, upon TLR activation, may sustain and amplify the functions of neutrophils. Their results showed that TLR3-activated MSCs were powerful in preserving neutrophils viability and function, and a concerted action of endogenously produced IL-6, IFN-β, and GM-CSF determines most of the modulatory effects exerted by PMN by TLR3-activated MSC [111]. The results reported by Maqbool et al. also indicated MSCs rescue neutrophils from nutrient- or serum-deprived cell death [112] (Fig. 2). Therefore, neutrophils may be one of most important immune cells mediated the forward immunomodulatory of MSCs.

4.6. MSCs induces macrophage M1/M2 phenotype transformation

Macrophages are differentiated from monocytes residing in tissues. Macrophages play a key role in innate immune system. They are highly specialized in removal of dying or dead cells and cellular debris. And macrophage also is important immune effector cell involving cell mediated immune response. Increasing evidences have demonstrated that MSCs-mediated regulation of macrophages is critical for inflammation response and tissue injury repair. Nemeth et al. reported that injection of BM-MSCs can beneficially modulate the response of the host immune system to sepsis and significantly improve animal survival [113]. And their results suggest that the injected MSCs interact with circulating and tissue monocytes and macrophages and reprogram them. Treated monocytes and macrophages produce large amounts of IL-10, and the treatment decreases the amounts of circulating TNF-α and IL-6. Cao et al. transplanted mouse MSCs into the pancreas of the streptozotocin-treated hyperglycemic isogenic mice, resulting in a decrease in blood glucose due to a recovery in β cell mass. Their analysis suggest
that the grafted MSCs recruited M2 macrophages in a stromal cell-derived factor 1 (SDF-1)-dependent manner, which activates Wnt/β-catenin signaling in pancreatic ß cells to promote ß cell replication [114]. Another recent study demonstrated that mouse MSCs skewed macrophages towards an M2 phenotype in a cell contact-independent manner. MSCs exerted this effect through the inhibition of NF-κB p65 and the activation of STAT3 pathways [115]. In addition, preferential shift of the macrophage phenotype from M1 to M2 may be related to the immunomodulating characteristics of MSCs [116,117] (Fig. 3). Therefore, the discovery of monocytes and M1 macrophage transforming into M2 macrophage in presence of MSCs may be quite significant for inflammatory biology development and inflammatory disease treatment in future.

4.7. MSCs inhibit immune cells in vivo

The immunomodulatory capacity of MSCs has also been evaluated in vivo. First, in vivo administration of MSCs prolonged the survival of skin graft [72]. In addition, results demonstrated that MSCs do ameliorate mouse experimental autoimmune encephalomyelitis (EAE) [90]. Allogeneic MSCs improve the survival of corneal allografts without engraftment and primarily by secreting TSG-6 that acts by aborting early inflammatory responses [118]. AT-MSCs therapy efficiently ameliorates autoimmune diabetes pathogenesis in diabetic NOD/SCID mice by attenuating the Th1 immune response concomitant with the expansion/proliferation of Treg cells, thereby contributing to the maintenance of functional β-cells [119]. In established chronic colitis, therapeutic injection of activated macrophages by coculture with AT-MSCs alleviated its progression and avoided disease recurrence. And AT-MSCs protected from severe sepsis by reducing the infiltration of inflammatory cells into various organs and by downregulating the production of several inflammatory mediators, where AT-MSCs mediated macrophages derived IL-10 played a critical role [120]. In addition, administration of MSCs isolated from human BM, umbilical cord, or adipose tissue provoked a pronounced increase in alveolar macrophages and inhibited hallmark features of asthma, including airway hyperresponsiveness, eosinophilic accumulation, and Th2 cytokine production. Importantly, selective depletion of this macrophage compartment reversed the therapeutic benefit of MSCs treatment on airway hyperresponsiveness [121]. Lee et al. established one humanized mouse model by injecting isolated hUCB-derived CD34 + cells intravenously into immunocompromised NOD/SCID IL2γ null mice. After repeated intravenous injection of hPBMSCs or MRC5 cells into these mice, immunological alterations including T cell proliferation and increased IFN-γ, TNF-α, and human IgG levels, were observed. In contrast, hUCB-MSCs injection did not elicit these responses [122]. Meanwhile, Zanotti et al. reported that the use of encapsulated cells unequivocally demonstrates that MSCs do not require homing to specific organs or cell—cell contacts to control inflammation and their immunosuppressive action is based on the release of soluble factors that may act systemically [123]. In addition, anti-inflammatory is another important capability of MSCs and was confirmed in vivo too. Nemeth et al. showed that an intravenous injection of MSCs can beneficially modulate the response of the host immune system to sepsis and improve survival. And their results suggested that the injected MSCs interact with monocytes and macrophages in circulating and tissue and reprogram them. Treated monocytes and macrophages produce large amounts of IL-10, and the treatment decreases the amounts of circulating TNF-α and IL-6 [113]. This reduces harm caused by unbridled immune responses to the host tissues. Another recent study showed that systemic infusion of MSCs significantly ameliorated the clinical and histopathological severity of colitis, abrogating weight loss, diarrhea and inflammation, and increasing survival. And their results demonstrated that the therapeutic effect was associated with downregulation of the Th1-driven inflammatory responses. MSCs decreased a wide panel of inflammatory cytokines and chemokines and increased IL10, acting on macrophages [124]. Furthermore, systemic infusion of AT-MSCs on the activation state of macrophages inhibited colitis in mice, reducing mortality and weight loss while lowering the colonic and systemic levels of inflammatory cytokines [120]. However, ambiguous results were reported that intravenously infused C57BL/6 green fluorescent protein (GFP) MSCs home to the lungs in C57BL/6 recipient mice and induce an inflammatory response. This response was characterized by increased mRNA expression of monocyte chemoattractant protein-1 (MCP1), IL1-β, and TNF-α and an increase in macrophages in lung tissue after MSCs infusion [125]. These results of pre-clinical studies showed that MSCs possess broad immunomodulatory and anti-inflammatory activity in disease animal model in vivo and hinted us MSCs may be a promising candidate for potential clinical application in treating immune-based disorders in future.

4.8. Factors affecting the immunomodulatory activity of MSCs

Evidences showed that inflammation environment can change the immunomodulation activity of MSCs. Inflamed
periodontal ligament stem cells showed significantly diminished inhibition of T-cell proliferation. In cocultures, stimulated PBMSCs showed significantly less induction of CD4+CD25 + FOXP3+ regulatory T cells and IL-10 secretion in the presence of inflamed compared with healthy periodontal ligament stem cells. Furthermore, suppression of Th17 differentiation and IL-17 production by inflamed periodontal ligament stem cells was significantly less than by healthy cells [126]. Waterman et al. have suggested that MSCs may polarize into two distinctly acting phenotypes following specific TLR stimulation, resulting in different immune modulatory effects and distinct secretomes. The TLR4-primed MSCs population exhibits a proinflammatory profile (MSC1) and the TLR3-primed MSCs population delivers anti-inflammatory signals (MSC2) [127]. Furthermore, Micro RNA expression level also is another important factor affect the immunomodulation capability. Reported results showed that miR-181a [128] and miR-155 [129] reduces the immunosuppressive capacity of inflammatory cytokine-activated MSCs. In addition, Evidence had also shown that different cell subsets show different immunomodulation activity. Yang et al. reported CD106+ chorionic villi (CV)-MSCs possess high immunomodulation activity, whereas CD106- CV-MSCs possess high colony formation capacity. In addition, the immunosuppressive activity of MSCs is highly related to their ability for the secretion of immunoregulatory cytokines and PGE2. In CD106+ MSCs, a list of genes was up regulated, including COX-2, IL-1a, IL-1b, IL-6 and IL-8 [33]. Recently, chemical that can correct the MSCs biological function was also reported. The research by Ma et al. showed that Immunomodulatory agent thalidomide corrects impaired MSCs function in inducing tolerogenic DCs in patients with immune thrombocytopenia. The thalidomide modulated MSCs from ITP patients induced mature DCs to become tolerogenic DCs. And the induction of tolerogenicity in DCs by MSCs was dependent on the expression of TIEG1 in DCs [130]. Furthermore, recent experiments clearly documented the inhibitory effect of gamma irradiation on proliferation of MSCs, but does not impair the immunosuppressive capacity of BM-MSCs in vitro and thus might increase the safety of MSC-based cell products in clinical applications [131]. Zhang et al. reported that MSCs from late passage displayed a stronger immunosuppressive activities. And their results also showed that increased interleukin-6 production may be a possible underlying mechanism for enhanced immunomodulatory ability of MSCs [132]. These results hinted that some growth factors, cytokines and chemicals may be used for correcting impaired MSCs function to benefit patients with MSCs deficiency in future.

4.9. The effect of immune cells against MSCs

The interaction between MSC and immune cells is usually bidirectional. Sotiropoulou tested the ability of different cytokines to induce NK cytotoxicity against MSCs, their results show that NK cells cultured for 4 days in IL-15—supplemented medium could effectively lyse MSCs. In addition, IL-2 and the combinations of IL-12/IL-15 and IL-12/IL-18 also resulted in induction of lytic activity against MSCs [84]. Another study by Spaggiari et al. indicated that the activated NK cells by IL-2 explosion, but not freshly isolated NK cells, displayed strong cytolytic activity. Meanwhile, their investigation showed that the expression of NKP30, NKG2D and DNAM-1 in NK cells involved in the lysis of MSCs [93]. In addition, Eugela et al. investigated the effect of Tregs against MSCs. Their results showed that kidney perirenal AT-MSCs and originating Tregs from healthy donors do not impair each other's suppressive effect on allo-reactivity [133]. Actually, There are still lots of work to do to clear the effect on MSCs by other immune cells now.

5. Therapeutic application of MSCs for immune diseases

Currently, there are many promising clinical trials using MSCs in cell-based therapies of numerous diseases. MSCs suppress T-cells, B cells and DCs function and represent a promising strategy for cell therapy of immune-mediated diseases. The immunomodulatory activities of MSCs provide a rational basis for their application in the treatment of immune-mediated diseases. Our analysis below will include the most frequently studied immune mediated diseases: GVHD, AA, MS, RA, CD and SLE.

5.1. MSCs and GVHD

GVHD is a difficult and potentially lethal complication of hematopoietic stem cell transplantation (HSCT). This can occur in up to 30–50% of patients with HLA matched sibling transplant and even more frequently in HLA-mismatched unrelated donor transplants (60–80%) [134]. GVHD is normally treated with corticosteroid and other immunosuppressive therapy [135,136]. However, response of GVHD to steroid therapy is between 20% and 40%, mortality of GVHD with refractory to steroid therapy approaches 80% [137]. MSCs can be expanded in culture and possess complex and diverse immunomodulatory activity. Moreover, human MSCs carry low levels of class I and no class 2 HLA antigens, making them immunoprivileged and able to be used without HLA matching. Increased evidences have shown that MSCs may be promising cell product for GVHD treatment (Table 1). First clinical trial displayed that BM-MSCs have a potent immunosuppressive effect in vivo, and induced complete response (CR) of aGVHD that is refractory to conventional immunosuppressive therapy [138]. A later phase II clinical study from the same group involved 55 steroid-resistant patients with severe aGVHD. Treatment with HLA-identical and haploidentical sibling donor BM or third-party mismatched BM-MSCs induced a 70% initial response rate that was not related to age or HLA match. None of the patients had side effects either during or immediately after the MSCs infusion [139]. Ringden et al. injected MSCs to eight patients with steroid-refractory grades III–IV GVHD. GVHD disappeared completely in six of eight patients. Two died soon after MSCs treatment with no obvious response. Five patients are still alive 3 years post MSCs transplantation. Their survival rate was significantly better than that of 16 patients with steroid-
resistant biopsy-proven gastrointestinal GVHD, not treated with MSCs during the same period (P = 0.03) [140]. Herrmann et al. also undertook a phase I trial in patients suffering from steroid-refractory aGVHD and cGVHD utilizing BM-MSCs. The response rate overall for aGVHD was complete in seven, partial in four and no response in one patient. Two patients with cGVHD achieved CR with two partial responses (PR) and three with no response (NR). The survival for those with aGVHD who achieved a complete response compared with those who did not was significant (p = 0.03) [141].

Further research showed that MSCs infusions are safe and effective for children with steroid-refractory aGVHD, especially when applied early in the disease course [142]. In addition, Muroi et al. conducted a multicenter phase I/II study using BM-MSCs manufactured from healthy unrelated volunteers to treat steroid-refractory aGVHD. By week 4, 13 of 14 patients (92.9%) had responded to MSCs therapy with a CR (n = 8) or PR (n = 5). At 24 weeks, 11 patients (10 with CR and 1 with PR) were alive. At 96 weeks, 8 patients were alive in CR. Their results showed that third-party-derived BM-MSCs may be safe and effective for patients with steroid-refractory GVHD [143]. Meanwhile, Ringden et al. tested placenta derived MSCs (PDMSCs) for treatment of steroid-refractory aGVHD. Nine patients who had undergone HSCT and who had developed steroid-refractory grade III–IV aGVHD were treated by PDMSCs infusion. Their results showed that there was an overall response rate of 75% [144]. The results by Ringden et al. showed that MSCs derived from other tissue also can be tried to treat GVHD.

There have been several studies using MSCs as prophylaxis to prevent GVHD and promote HSCs engraftment and obtained useful and inspiring results (Table 2). In phase I studies, Lazarus et al. estimated the feasibility of transplanting autologous or allogeneic MSCs to improve engraftment of HSCs, as well as to reduce GVHD [145,146]. Kuzmina et al. accomplished a Phase II clinical trial and investigated that the prophylaxis of MSCs for aGVHD. Their results showed that the patients with BM-MSCs infusion have significant lower rate of grade II-IV aGVHD (5.3%) compared with patients without BM-MSCs infusion (38.9%) of patients (P = 0.002) [147]. Several researches have shown that MSCs from amnion, placenta, and umbilical cord can be potentially used for substituting BM-MSC in several therapeutic applications, including the treatment of GVHD [9,79,148]. Therefore, our group tested to cotransplant the culture-expanded UC-MSCs in 50 people with refractory/relapsed hematologic malignancy undergoing haplo-HSCT with myeloablative conditioning. Grade II-IV aGVHD was observed in 12 of 50 (24.0%) patients. cGVHD was observed in 17 of 45 (37.7%) patients and was extensive in 3 patients. The probability that patients would attain progression-free survival at 2 years was 66.0%. Our research indicated that MSCs cotransplantation with HSCs is effective in improving donor engraftment and reducing severe GVHD [149]. Meanwhile, our group observed that Patients with severe AA (n = 17) received haploidentical HSCT plus MSCs infusion. The 3-month and 6-month survival rates for all patients were 88.2% and 76.5%, respectively;
mean survival time was 56.5 months. Therefore, our results showed that Combined transplantation of haploidentical HSCs and MSCs on severe AA without an HLA-identical sibling donor was safe, effectively reduced the incidence of severe GVHD, and improved patient survival [150]. Then another clinical trial of AA investigated by our group and suggested that the modified conditioning regimen without high-dose immunosuppressive agents was sufficient to achieve sustained donor engraftment in which the third-party donor-derived UC-MSCs may play an important role [151]. Although cell dose is much less in our clinical trial (5 \times 10^5/kg) than in clinical trial (14 \times 10^6/kg) run by Le Blanc K et al., our clinical trial also achieved ideal therapeutic effect. This is also consistent to our recent data that show that PGE2 which plays a key role in immunomodulation was secreted much more in UC-MSCs than BM-MSCs. Therefore, PGE2 maybe can be using as a biological effectiveness to evaluate immunomodulation potency of MSCs (not published). These results showed that MSCs derived from kinds of tissue may be safe and effective for prevention of GVHD.

5.2. MSC and acquired AA

AA is mostly considered an immune-mediated BM failure syndrome, characterized by hypoplasia and pancytopenia with fatty BM and reduced angiogenesis. Previous investigations have demonstrated that acquired AA is manifested as abnormalities of HSCs/HPCs and hematopoietic microenvironment [152]. Lots of evidences have hinted that AA might be a syndrome characterized by stem/progenitor-cell disorders including HSCs/HPCs and BM-MSCs. BM-MSCs support hematopoiesis and regulate almost overall immune cells function to maintain the hematopoietic and immune homeostasis [97,139]. BM-MSCs can modulate the major immune cell functions including T cells, B cells, monocytes, DCs, NKTs and neutrophils [153,154]. BM-MSCs possess remarkable immunosuppressive properties on Th1, Th17 and CTLs. BM-MSCs inhibit the proliferation of T cells, IFN-\(\gamma\) and TNF-\(\alpha\) secretion by Th1 cells while promoting IL-10 production by Th2 cells and the expansion of Treg cells. However, recent researches showed that BM-MSCs from AA patients had poor proliferation and deficient immune suppression of MLR, PHA-induced T cell activation and IFN-\(\gamma\) release [155,156]. Our recent study showed that BM-MSCs from AA patients were reduced in suppressing the proliferation and clonogenic potential of CD4+ T cells while promoting Treg cells expansion. BM-MSCs were also defective to suppress the production of TNF-\(\alpha\) and IFN-\(\gamma\) by CD4+ cells. However, there was no significant difference in regulating the production of IL-4, IL-10 and IL-17 [157]. In addition, our research also showed that BM-MSCs from AA patients showed aberrant morphology, decreased proliferation and clonogenic potential and increased apoptosis than BM-MSCs from healthy controls. BM-MSCs from AA patients were susceptible to be induced to differentiate into adipocytes but more difficult to differentiate into osteoblasts. Consistent with abnormal biological features, a large number of genes implicated in cell cycle, cell division,
proliferation, chemotaxis and hematopoietic cell lineage showed markedly decreased expression in BM-MSCs from AA patients. Conversely, more related genes with apoptosis, adipogenesis and immune response showed increased expression in BM-MSCs from AA patients. The gene expression profile of BM-MSCs further confirmed the abnormal biological properties and provided significant evidence for the possible mechanism of the destruction of the BM microenvironment in AA [158].

MSCs may be a promising therapeutic candidate as a treatment for AA due to following two quite important facts, ① hematopoiesis supporting and potent immunosuppressive capability of MSC and ② biological characteristic difference and functional capability deficiency of BM-MSCs derived from patients with AA. However, till today there is just one clinical trials using MSCs alone was accomplished by Xiao et al. Xiao et al. investigated that the safety and efficacy post intravenous administration of MSCs to 18 patients with AA. BM-MSCs ((5.0−7.1) × 10^{5}/kg body weight) were injected intravenously to 18 patients, including 14 patients with non-severe AA and four patients with severe AA who were refractory to prior immunosuppressive treatment. Two patients had injection-related adverse events, including transient fever and headache. No major adverse events were reported during the follow-up period. An immunological analysis revealed an increased proportion of CD4^{+}CD25^{+}FOXP3^{+} regulatory T cells [159]. Therefore, their results showed that MSCs are safety and efficacy for AA treatment. In another recent study, Ozdogu H et al. summarized that the result of post-transplant treatment with MSCs of a 26-year-old patient with AA complicated by invasive sino-orbital aspergillosis. The patient was treated with MSCs to benefit from the dual effects of MSCs in immune reconstitution: suppression against alloreactive T cells and facilitation of the re-engraftment process. The patient did not develop acute or chronic GVHD. And the aspergillus infection healed completely. The engraftment failure was also ended without any complications [160]. In addition, there are several reports pointed that the patients achieved rapid hematopoietic engraftment of donor origin and lower rate of acute or chronic GVHD was observed post cotransplantation MSCs with HSCs [161,162]. BM-MSCs in patients with AA are abnormal. However, allogenic MSCs will be eliminated soon after transplantation. The efficacy of MSCs was mainly achieved through the secretion of couples of immune factors. Abnormal MSCs would not be replaced. So it is totally possible the efficacy of MSCs in clinical treatment is transient. Therefore, according to our understanding MSCs should be applied for couple of times to maintain the therapeutic effect. However, it is still need to be clear according to the controlled pilot or clinical trial.

5.3. MSCs and MS

MS is the most common neurological disease in young adults, affecting approximately two million people worldwide. MS is an autoimmune disorder of the central nervous system where myelin and oligodendrocytes are targeted by cell mediated and humoral immunity [163]. Currently there is still no effective choice for MS treatment. Given MSCs putative roles in immunosuppression and neural repair, they have also recently been proposed as treatment for MS. In addition, the results showed that patient MSCs exhibited phenotypic changes, distinct transcriptional profile and functional defects implicated in MSC immunomodulatory and immunosuppressive activity [164]. Currently, close to 17 clinical trials are registered to use MSCs therapy for the treatment of MS (http://www.clinicaltrials.gov/). MSCs have well been tolerated and were safe in patients with early phase clinical studies. Autologous MSCs were safely given to patients with secondary progressive MS. The efficacy results demonstrated the evidence of structural, functional, and physiological improvement after treatment in some visual endpoints is suggestive of neuroprotection [165]. Mohajeri et al. investigated the molecular mechanism of MSCs infusion for MS treatment. They found that the expression of FoxP3 after intrathecal injection of MSCs was significantly higher than the levels prior to treatment. Such significant enhanced expression of FoxP3 associated with clinical stability [166]. Findings from this pilot study further support the potential of MSCs for treatment of MS patients. A patient with MS was transplanted with multiple allogeneic hUC-MSC. The results also showed allogeneic hUC-MSC may be a safe, effective, and more practical source of stem cells for the treatment of MS [167]. However, obviously lots of effective trials still will be needed before MSCs can be used for MS clinical treatment in future.

5.4. MSCs and RA

RA is the commonest autoimmune joint disease that has achieved significant therapeutic advances in the past decades, but remains difficult to treat in a subset of cases. Therefore, Wang et al. firstly tried to treat RA by using MSCs infusion. In a clinical trial for RA treatment by Wang, 172 patients with active RA who had inadequate responses to traditional medication were enrolled. Patients were divided into two groups for different treatment: disease-modifying anti-rheumatic drugs (DMARDs) plus medium without UC-MSCs, or DMARDs plus UC-MSCs group (4 × 10^{7} cells per time) via intravenous injection. Their results showed that no serious adverse effects were observed during or after infusion. The serum levels of TGF-α and IL-6 decreased after the first UC-MSCs treatment (P < 0.05). The percentage of CD4^{+}CD25^{+}Foxp3^{+} regulatory T cells of peripheral blood was increased (P < 0.05). The therapeutic effects maintained for 3–6 months without continuous administration, correlating with the increased percentage of Treg cells of peripheral blood. Repeated infusion after this period can enhance the therapeutic efficacy. Therefore, treatment with DMARDs plus UC-MSCs may provide safe, significant, and persistent clinical benefits for patients with active RA [62]. In another recent phase I clinical trial by Liang et al., four patients with persistently active RA underwent MSCs transplantation. Three of four patients received a reduction in erythrocyte sedimentation rate, DAS-28, and visual analog scale pain score at 1 and 6 months.
after transplantation. No one had achieved the DAS-28-defined remission in the follow-up period. No serious adverse events were reported. Their results demonstrated that allogeneic MSCT is one of safe treatment choice for severe and resistant RA [168].

5.5. MSCs and CD

CD is a chronic inflammatory bowel disease characterized by a relapsing-remitting clinical behavior. The main feature of CD is intestinal inflammation. In recent years several groups tried to use MSCs to treat CD and obtained some promising results. The results of a phase I study showed that administration of autologous BM-MSCs appears safe and feasible in the treatment of refractory CD [169]. Ciccocioppo et al. enrolled 12 consecutive outpatients with CD refractory or unsuitable for current available therapies. Ten patients (two refused) received intrafistular MSCs injections. All patients who underwent MSCs infusion sustained complete closure (seven cases) or incomplete closure (3 cases) of fistula tracks with a parallel reduction of CD and perianal disease activity indexes, and rectal mucosal healing were induced by treatment. In addition, the percentage of mucosal and circulating Treg cells significantly increased during the treatment and remained stable until the end of follow up [170]. The results from two phase I/IIa clinical trial demonstrated that allogeneic AT-MSCs also is a simple, safe, and beneficial therapy for perianal fistula in CD patients [171,172]. In another phase 2 study, administration of allogeneic MSCs reduced CD activity index and CD endoscopic index of severity scores in patients with CD luminal refractory to biologic therapy [173].

5.6. MSCs and SLE

SLE is a common and potentially fatal autoimmune disease characterized by autoantibodies associated with multiorgan injury, including the renal, cardiovascular, neural, musculoskeletal and cutaneous systems. Although disease severity and organ involvement vary significantly among SLE patients, abnormalities of T and B lymphocytes are universal [174,175]. Conventional immunosuppressive therapies, such as cyclophosphamide and mycophenolate mofetil can control disease in most, but not all, patients with lupus nephritis. There is a subset of lupus nephritis patients whose disease either does not respond or relapses, and their prognosis remains poor. In addition, progressive immunosuppressive therapy may lead to the development of serious infection, cumulative drug toxicity, and an increased risk of cardiovascular disease and malignancy [176]. Recent research showed that there were abnormalities in actin cytoskeleton, cell cycling regulation, BMP/TGF-β, and MAPK signaling pathways in BM-MSCs from SLE patients [177]. Tang et al. found that activated NF-κB pathway in SLE derived BM-MSCs inhibits the BMP-2-induced osteoblastic differentiation through BMP/Smad signaling pathway, suggesting that the impaired osteoblastic differentiation may participate in the pathology of osteoporosis in SLE patients [178]. Another research also found that BM-MSCs from SLE patients exhibited senescent behavior and are involved in the pathogenesis of SLE. And numerous studies have shown that p16 [179], Wnt/β-catenin and p53/p21 pathway plays critical role in the senescent of SLE BM-MSCs [180–182]. A pilot single-center clinical studies reported the safety and efficacy of allogeneic BM-MSCs and UC-MSCs in treating drug-resistant SLE patients, and the clinical results have been encouraging [183]. In addition, Li et al. investigated that the roles of MSCs transplantation in SLE patients with refractory cytopenia. Thirty-five SLE patients with refractory cytopenia were enrolled in a MSCs transplantation trial. The results suggested that MSCs transplantation could reverse hematological aberration in SLE patients with refractory cytopenia, which might be associated with reconstitution of Treg and Th17 cells [184]. Wang et al. observed the long-term safety and efficacy of allogeneic MSCs transplantation in treatment-resistant SLE patients. Eighty-seven patients with persistently active SLE who were refractory to standard treatment or had life-threatening visceral involvement were enrolled. Allogeneic BM-MSCs and UC-MSCs were intravenously. These results showed that allogeneic MSCs transplantation resulted in the induction of clinical remission and improvement in organ dysfunction in drug-resistant SLE patients [185]. A recent multicenter clinical study by Wang et al. found that intravenous UC-MSCs transplantation resulted in clinical disease remission and systemic amelioration in lupus patients who are refractory to other. However, some patients had disease relapses after 6 months; therefore, they suggested that a repeated MSCs infusion is feasible and necessary after 6 months to avoid disease relapse [186].

5.7. MSCs and inflammatory disease

MSCs are also used in human clinical trials for the treatment of inflammatory. MSCs modulate inflammation by decreasing the immune cells and products of the inflammatory response [187]. Skrahin et al. accomplished an open-label phase 1 safety trial. They infused autologous MSCs as adjunct treatment in patients with multidrug and extensively drug-resistant tuberculosis. Their results showed that MSCs as an adjunct therapy are safe and can now be explored further for the treatment of patients with MDR or XDR tuberculosis in combination with standard drug regimens [188].

5.8. MSCs and other immune disease

Report showed that UC-MSCs could restore behavioral functions and attenuate the histopathological deficits of experimental autoimmune encephalomyelitis over the long term (i.e., 50 days) by suppression of perivascular immune cell infiltration and reduction in both demyelination and axonal injury in the spinal cord [189]. Zhang et al. tried to infuse UC-MSCs to treat patients with HIV-1-infected immunological nonresponders (INRs). Their results showed that all patients tolerated the UC-MSCs transusions well throughout the trial. The UC-MSCs transfusions preferentially increased circulating naive and central memory CD4 T-cell counts and restored HIV-1-specific IFN-γ and IL-2 production in the INRs. These enhancements in immune reconstitution were also associated
with the reduction of systemic immune activation and inflammation in vivo. The data suggested that MSCs transplantation may be used as a novel immunotherapeutic approach to reversing immune deficiency in HIV-1-infected INRs [190].

6. Perspective

MSCs have become a subject of clinical research interest due to their easy isolation and in vitro large scale cultivated amplification, attractive potential for multi-lineage differentiation and hematopoiesis supporting, growth factors production and cytokines secretion, and potential immunomodulatory capacity. In addition, MSCs is definitely safe and well-tolerated for use in cell therapy, which provide a striking candidate for degenerative diseases and immune mediated diseases. Increased clinical evidence suggests that MSCs may have great potential in the treatment and prevention of GVHD, AA, MS, CD, SLE and some other immune mediated diseases. Nevertheless, clinical trials yielded ambiguous results on the effects of MSCs. These ambiguous findings might result from insufficient standardization during the MSCs extraction, expansion and administration procedures and interindividual MSCs donor differences. Therefore, to obtain maximal clinical benefit, lots of problems, including tissue sources, numbers of cells, the optimal passage time in culture before use, cell subpopulation and standardized process of cell production, need to be solved before MSCs as a medicine applied widely to treat patients. In addition, it is absolutely important to optimize process of treatment and be able to effectively monitor and communicate the benefits and risks of a cell therapy to a patient. Furthermore, a clear and rigorous pharmacokinetics and pharmacodynamics model of the mechanism of action of transient cell therapies is absolutely necessary. Expanding our understanding of the molecular mechanisms governing immunomodulatory properties of MSCs will enable us to greatly improve their clinical efficacy. Most importantly, further well-designed, randomized and controlled clinical trials should be designed for better understanding of the underlying biology and utilizing MSCs therapy for immune mediated disease in the future. In addition, the cell dose that was using in clinical treatment is still totally different in different group study. We suggest that we should determine the MSCs cell dose according to the biological effectiveness of the MSCs. Meanwhile, it is really urgent to develop the biological effectiveness of various MSCs biological functions.

Conflict of interest

The authors wish to confirm that there are no conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Acknowledgments

This work was supported by The National Basic Research Program of China (973 Program) (2011CB964802), National Natural Science Foundation of China (81000196 and 81330015) and Tianjin Research Program of Application Foundation and Advanced Technology (12JCZDJC25000).

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