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Concise Review: Mesenchymal Stem Cells and Translational Medicine: Emerging Issues

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ABSTRACT

Mesenchymal stem cells (MSCs) are emerging as a promising therapeutic approach of cell-based therapy for a wide range of autoimmune disorders and degenerative diseases. In preclinical and clinical studies, MSCs have been shown to be highly efficient in treating graft-versus-host disease, systemic lupus erythematosus, multiple sclerosis, type 1 diabetes, myocardial infarction, liver cirrhosis, inflammatory bowel disease, and other disorders. The underlying therapeutic mechanisms of MSCs include their homing efficiency to the tissue injury sites, their differentiation potential, their capability to produce a large amount of trophic factors, and their immunomodulatory effect. Because tissue damage sites are complicated milieus with distinct types of inflammatory cells and factors, available data have demonstrated that the properties of MSCs could be fundamentally influenced by the inflammatory elements. Thus, an understanding of the interaction between MSCs and the inflammatory microenvironment will provide critical information in revealing the precise in vivo mechanisms of MSC-mediated therapeutic effects and designing more practical protocols for clinical use of these cells. STEM CELLS TRANSLATIONAL MEDICINE *2012;1:51–58*

INTRODUCTION

Stem cells are considered the master cells, capable of both self-renewal and multilineage differentiation. Recent investigations have identified them as a potentially novel cell therapy for regenerative medicine largely because of their ability to differentiate into many functional cell types. It is anticipated that stem cell therapy could solve many medical challenges facing humanity, increase our knowledge of pathogenesis, allow us to screen for new drugs for safety and effectiveness, and treat a variety of diseases. It is highly expected that detailed investigations of stem cell biology and clinical applicability will result in revolutions in medical technologies.

Most early work on stem cells was carried out with pluripotent embryonic stem (ES) cells derived from inner cell mass of blastocyst embryo, which, however, introduced a series of ethical problems in clinical applications. To avoid such ethical issues and create histocompatibility, new technologies have enabled tissue cells to become induced pluripotent stem (iPS) cells [1]. One characteristic of ES cells and iPS cells is their ability to form teratomas, which, in turn, is a major concern for future clinical application [2, 3]. Moreover, it is likely that iPS cells are more tumorigenic than ES cells [4]. The teratoma-forming property of stem cells is considered a major obstacle for biomedicine by the U.S. Food and Drug Administration (FDA) [5].

In almost all tissues, there are mesenchymal stem cells (MSCs) that are responsible for regeneration and cellular homeostasis. These cells were first isolated and characterized by Friedenstein et al. in 1974 [6]. MSCs are spindle-shaped, fibroblast-like multipotent stem cells. In the last decade, MSCs were successfully isolated from various tissues. The most intensely studied MSCs are those derived from bone marrow (BM). The BM-MSCs are nearly 10% of the hematopoietic stem cells (HSCs) in number, and they are always regarded as a component of the HSC niche. In addition to BM-MSCs, MSCs from other sources, such as umbilical cord and adipose tissue, are also able to be expanded in vitro rapidly with sustained stable phenotype and differentiation potential toward several mesenchymal lineages, such as fat, cartilage, and bone [7].

The physiological role of MSCs is elusive because of their low frequency in tissues and lack of specific surface markers for identification. In the last few years, several studies have demonstrated the in vivo characteristics of MSCs. Sacchetti et al. and Crisan et al. revealed that MSCs are likely linked to $CD146^{+}$ $CD45^{-}$ perivascular pericytes, which are capable of producing angiopoietin-1, an important molecule in HSC microenvironment [8, 9]. Additionally, MSCs have

Table 1. Treatment of diseases by mesenchymal stem cells in animal models

Disease	Species	Administration route	Mechanism of MSC effects	Cell source	Reference
Systemic lupus erythematosus	Mouse	Tail vein	Suppression of Th17 cells and increase of $CD4^+CD25^+Foxp3^+$ Treg cells	Murine bone marrow-derived MSCs	[15]
Rheumatoid arthritis	Mouse	Intraperitoneal	Decreased Th1 and Th17 cell expansion and induction of de novo generation of $CD4^+CD25^+Foxp3^+$ Treg cells	Human adipose-derived MSCs	[97]
Autoimmune type 1 diabetes	Mouse	Tail vein	Decreased Th1 cell expansion and induction of de novo generation of $CD4^+CD25^+Foxp3^+$ Treg cells	Murine bone marrow-derived MSCs	[18]
Hematopoietic system defects	Mouse	Tail vein	Provide critical growth factors and/or adhesion receptors	Human bone marrow-derived MSCs	[98]
Graft-versus-host disease	Mouse	Tail vein	Decreased expression of inflammatory cytokines, such as TNF-α, IFN-γ, and IL-12	Murine adipose-derived MSCs	[99]
Graft-versus-host disease	Mouse	Tail vein	Cytokine-induced nitric oxide production by MSCs Suppressed T cell proliferation	Murine bone marrow-derived MSCs	[14]
Myocardial infarction	Rat	Monolayered MSC transplantation	Secretion of a large amount of angiogenic and antiapoptotic cytokines	Rat adipose-derived MSCs	[100]
Myocardial infarction	Pig	Transendocardial	Stimulation of endogenous cardiac stem cells	Human bone marrow-derived MSCs	[101]
Parkinson's disease	Rat	Intranasal delivery to brains	Decreased production of inflammatory cytokines	Rat bone marrow-derived MSCs	[102]
Spinal cord injury	Rat	Transplantation of 3D scaffold with MSCs	Deposition of fibronectin and decreased expression of TNF-α and IL-1	Rat bone marrow-derived MSCs	[22]
Inflammatory bowel disease	Mouse	Intraperitoneal	Decreased colonic myeloperoxidase activity and neutrophil infiltration	Human ESC-derived MSCs	[19]
Liver fibrosis	Mouse	Tail vein	Increased expression of MMP-9 and MMP-14 and decreased expression of TGF-β1	Murine bone marrow-derived MSCs	[103]
Lung injury	Mouse	Jugular vein	IL1RN expressed by MSCs antagonized IL-1a function and release of TNF-α from activated macrophages	Murine bone marrow-derived MSCs	[23]
Acute lung injury	Mouse	Tail vein	Inhibition of Th2-mediated allergic airway inflammation and promotion of a Th1 phenotype in antigen-specific $CD4^+$ T lymphocytes through an IFN-γ-dependent process	Murine bone marrow-derived MSCs	[24]
Bone fracture	Mouse	Tail vein	Contribution to the callus initiation by expressing BMP-2, and decreased levels of TNF-α and IL-1	Murine bone marrow-derived MSCs	[104]
Corneal abrasion	Mouse	Intraperitoneal or intravenous	Secretion of the anti-inflammatory protein TSG-6	Murine bone marrow-derived MSCs	[21]
Skin wound	Mouse	Tail vein	Suppression of Th17 cells and increased IL-10 expression	Human gingiva-derived MSCs	[105]
Skin wound	Mouse	Intradermal	Immunosuppressive effect and release of tissue repair cytokines	Murine bone marrow-derived MSCs and fibroblasts	[106]

Abbreviations: 3D, three-dimensional; BMP, bone morphogenetic protein; IFN-γ, interferon-γ; IL, interleukin; IL1RN, interleukin 1 receptor antagonist; MMP, matrix metalloproteinase; MSC, mesenchymal stem cell; TGF, transforming growth factor; Th, T helper; TNF-α, tumor necrosis factor α; Treg, regulatory T cells; TSG-6, tumor necrosis factor-inducible gene 6 protein.

also been identified as $nestin^+$ cells in bone marrow, which play a critical role in constructing the HSC microenvironment [10].

MSCs hold great potential for the treatment of various degenerative diseases and immune disorders, largely because of their differentiation potential and immunoregulatory capacity. In vitro expanded MSCs have already been administered in vivo in both animals in preclinical models and patients in clinical settings, demonstrating promising clinical utilities. Unlike ES or iPS cells, MSCs have no ethical issues and have a low risk of forming teratomas; however, they are not completely free from malignancy potentials [11]. Nevertheless, pilot studies have demonstrated that MSCs are largely safe in vivo, and they are currently the most widely used stem cells in clinical settings.

Preclinical Studies with MSCs

A remarkable property of MSCs is their powerful capacity for regulating immune responses. As a result, current MSC-based therapy has mainly been applied to alleviating immune disorders. Various studies have evaluated the therapeutic effect of MSCs in preclinical animal models and demonstrated great clinical potential (Table 1). Some examples are discussed below.

Graft-versus-host disease (GvHD) is a severe complication following bone marrow and HSC transplantation. It has been shown that more than 40% recipients with bone marrow transplantation develop GvHD, and many of them are hard to treat even with steroids [12]. In recent years, MSCs have been successfully applied to treating GvHD in mouse models. One or two infusions of MSCs after bone marrow transplantation greatly improve the survival rate of GvHD mice and dramatically reduce immune cell infiltration in various organs. These studies also demonstrated that proinflammatory cytokines are critical in MSC-mediated immunosuppression in vivo, as elimination of interferon-γ (IFNγ) signaling diminishes the therapeutic effect of MSCs [13, 14].

Systemic lupus erythematosus (SLE) is a generalized autoimmune disease that can be mimicked with mice lacking a functional *fas* gene. The therapeutic effect of MSCs has been validated in the mouse model of SLE [15]. MSCs derived from $fas^{-/-}$ mice were partially deficient in abundance and stemness, as revealed by plating assay and induced differentiation toward adipocytes. Allogenic MSC administration largely reduces the production of autoantibodies in the sera and ameliorate renal dysfunction in those mice with active SLE symptoms [15].

In experimental autoimmune encephalomyelitis (EAE), an established animal model of multiple sclerosis (MS), MSCs also exhibited beneficial effects [16, 17]. Decreased immune cell infiltration and demyelination in the central nerve system were observed after systemic MSC infusion. Along with less $CD4^+$ T-cell migration, the plasma level of interleukin-17 (IL-17) was reduced. Notably, MSC injection at the peak of pathogenesis is more effective, whereas no improvement was observed in these studies if MSCs were injected at the disease-stable stages.

In the treatment of autoimmune type I diabetes, MSCs significantly delayed diabetes onset in non-obese diabetic (NOD) mice [18]. MSC infusion strikingly protected islets from destruction, as evidenced by insulin staining, lymphocyte infiltration, and islet morphology. In addition, hyperglycemia was reversed in 90% of diabetic mice receiving MSC treatment, and some of the mice remained normoglycemic for more than 2 months.

Recent studies have shown that human MSCs were effective in treating mouse inflammatory bowel disease (IBD) [19]. In this model, human ES cells were used to derive MSCs. These ES cell-derived MSCs possessed surface markers, morphology, and immunosuppressive capacity similar to those of BM-MSCs. After treatment with these MSCs, IBD animals exhibited much healthier appearance compared with control mice, as shown by significantly alleviated colon inflammation and body weight loss.

In addition to autoimmune diseases, MSCs are capable of producing trophic factors to help tissue repair. Investigations by the Prockop team have shown that human MSCs were effective in treating myocardial infarction [20] and cornea damage [21] through secretion of tumor necrosis factor-inducible gene 6 protein (TSG-6), which served to reduce inflammation and promote tissue reconstruction. A similar phenomenon has been reported with MSCs in treating other tissue injuries, such as spinal cord [22], lung [23, 24], and skin [25, 26]. Therefore, it is possible that MSC-derived soluble factors could replace MSCs in treating various diseases to evade the risk of cell-based therapies.

Clinical Applications of MSCs

The success of MSCs in modulating immune responses and promoting tissue repair in preclinical studies have prompted exploration of MSCs in clinical settings [14, 27–29]. Currently, there are 92 registered clinical trials evaluating the potential of MSC-based cell therapy worldwide (ClinicalTrials.gov, http://clinicaltrials.gov/). As shown in Table 2, 30 completed clinical trials have been announced, including phase III trials. Since 2008, several clinical trials have been carried out in the United States. With the advancement of preclinical research, more and more countries have recognized the good hope of MSC-based therapies and are participating in the expanding number of clinical trial registrations (35 in Europe, 22 in the United States, 18 in China, 5 in Korea, 4 in the Middle East, 3 in Canada, 2 in India, 1 in Africa, 1 in Japan, and 1 in Australia). It is anticipated that the completion of these trials will dramatically improve clinical applications of MSCs to treat various devastating diseases that affect human health.

Along with a better understanding of the molecular mechanisms underlying the therapeutic effects of MSCs, more and more therapeutic utilities of MSCs have been tried for various human diseases [30]. For instance, MSCs have been successfully applied to revert GvHD in patients receiving bone marrow transplantation [31, 32], especially in patients diagnosed with severe steroid resistance [33–35]. Similarly, in SLE and Crohn's disease patients, both autologous and allogeneic MSCs were able to suppress inflammation and reduce damage to kidneys and bowel, supposedly by induction of regulatory T cells in patients [25, 36–38]. In the cardiovascular system, allogeneic MSCs have been shown to reverse left ventricle acute myocardial infarction [39, 40]. In hematopoietic stem cell transplantation, MSCs provided support for the growth and differentiation of hematopoietic progenitor cells in the bone marrow microenvironment [41, 42]. In the endocrine system, placenta-derived MSCs increase the levels of insulin and C-peptide and improve the renal function and cardiac function after infusion in diabetic patients [43]. Various clinical studies have been carried out with patients suffering from neurological disorders. It has been reported that BM-MSCs improve multiple system atrophy [44], MS, amyotrophic lateral sclerosis [45–47], and stroke, likely through immediately immunomodulatory effects [48]. In the digestive system, autologous BM-MSCs improved clinical indices of liver function in liver cirrhosis patients and liver failure patients caused by hepatitis B [49, 50]. BM-MSCs can also exert strong therapeutic effects on tissue repair in muscle skeletal and skin diseases, including muscle remodeling, regeneration of periodontal tissue defects, diabetic critical limb ischemia, bone damage caused by osteonecrosis, and burn-induced skin defects [51–53]. It is noteworthy that Prochymal, an allogeneic human BM-MSCs-based stem cell product by Osiris Therapeutics (Baltimore, MD, http://www.osiristx.com) has passed Phase III clinical trials in treating GvHD and Crohn's disease and become the only stem cell-based drug approved by the FDA [33, 54]. Taken together, these clinical trials are providing critical information for the development of stem cell-based clinical application.

Although there is a long way to go before MSCs can be used as a regular clinical therapy, available clinical information is encouraging. It seems that MSC treatments are quite safe as long as the cells are administered properly. Under treatment for GvHD, SLE, and liver failure, a few patients developed fever, chill, liver damage, and other side effects [25, 33, 49, 55]. With the maturation of isolation and culture technologies, allogeneic MSCs are becoming more popular than autologous BM-MSCs [36, 38, 56]. Among the allogeneic MSCs, human umbilical cord- and placenta-derived MSCs are the most investigated. In last few years, adipose tissue-derived MSCs have attracted great attention as they are easy to be derived autologously and have been shown to be effective in treating Hurler syndrome, metachromatic leukodystrophy, GvHD, and SLE [25, 43, 57]. These clinical trial results demonstrated that MSCs derived from various sources exert similarly therapeutic effects on immune disorders [31, 33]. Notably, MSCs derived from different sources are also capable of supporting regeneration of damaged tissues in myocardial, kidney, bone, and skin [15, 39, 53]. Moreover, to increase the number of MSCs at the damaged sites and the efficiency of differentiation, studies on liver cirrhosis, osteonecrosis, skin

Table 2. Examples of published clinical trials of mesenchymal stem cell-based therapy registered on ClinicalTrials.gov

Disease	Enrollment number	Trial design	Effects	Clinical trial phase	Cell mass (hMSCs/kg)	MSC source	Reference
GvHD	12	Systemic infusion (peripheral vein)	Reduced responses; decreased GvHD stages; no infusional or other identifiable acute toxicity	Phase II	2.0×10^6; 8.0×10^6	Allogeneic bone marrow-derived MSCs (Prochymal)	[32]
GvHD	32	Systemic infusion (peripheral vein)	Reduced responses; no infusional toxicities or ectopic tissue formations	Phase II	2.0×10^6; 8.0×10^6	Allogeneic bone marrow-derived MSCs (Prochymal)	[33]
Myocardial infarction	53	Systemic infusion (peripheral vein)	Reduced ventricular tachycardia episodes and pulmonary function; better global symptom score; no adverse events	Phase I	0.5×10^6; 1.6×10^6; 5.0×10^6	Allogeneic bone marrow-derived MSCs (Prochymal)	[39]
GvHD	46	Systemic infusion (peripheral vein)	Reduced grades of GvHD; well tolerated without adverse event	Phase I	$1.0–5.0 \times 10^6$	Allogeneic bone marrow-derived MSCs	[107]
Multiple system atrophy	29	Systemic or local infusion (peripheral or portal vein)	Glucose metabolism increased significantly in brain area; no serious adverse effects related to MSC therapy	Phase II	4.0×10^7 (total hMSCs per time injection)	Autologous bone marrow-derived MSCs	[44]
Liver failure	105	Local infusion (proper hepatic artery)	TBIL, PT, and MELD score were improved; no serious side effects or complications	Phase I–II	Unknown	Autologous bone marrow-derived MSCs	[49]
Liver cirrhosis	8	Systemic infusion (peripheral vein) or local infusion (portal vein)	MELD score, prothrombin complex, and serum creatinine decreased; serum albumin increased; no adverse effects	Phase I–II	4.0×10^7 (total hMSCs per time injection)	Autologous bone marrow-derived MSCs	[50]
Diabetic critical limb ischemia and foot ulcer	N/A	Local infusion (intramuscular injection)	Improved painless waking time, ABI, TcO_2 (transcutaneous oxygen pressure); no serious adverse events	Phase I	Unknown	Autologous bone marrow-derived MSCs	[51]
Periodontal tissue defect	1	Local infusion (root surface and adjacent defect space)	Reduced probing depths and clinical attachment gain; bleeding and tooth mobility disappeared; no adverse effects	Phase I	Unknown	Autologous iliac crest marrow-derived MSCs	[52]
Chronic spinal cord injury	64	Local infusion (intrathecal injection)	No significant improvements in clinical measures; may have side defects	Phase I–II	Unknown	Autologous bone marrow-derived MSCs	[55]

Abbreviations: ABI, ankle-brachial index; GvHD, graft-versus-host disease; hMSC, human mesenchymal stem cell; MELD, end-stage liver disease; MSC, mesenchymal stem cell; N/A, not applicable; PT, prothrombin time; TBIL, total bilirubin; TcO_2, transcutaneous oxygen pressure.

defects, and spinal cord injury were using local injections instead of systemic administration of MSCs [53]. Nevertheless, extensive investigations are still needed to determine which cell sources are the best for the specific diseases.

Therapeutic Mechanisms of MSCs

As mentioned above, MSCs have displayed a great potential in treating a large number of immune and nonimmune diseases. However, there are still major questions concerning the optimal dosage of MSCs, routes of administration, and the fate of the cells after infusion [58]. Thus, it is critical to explore the mechanisms governing MSC-based therapies. Although a uniform mechanism may have never been discovered, the available data have revealed several working models for the beneficial effects of MSCs. On the basis of the current understanding, we sum up some key mechanisms that are significant to MSC-mediated therapies. It is noteworthy that for a given disease, multiple coordinated mechanisms likely contribute to the therapeutic effect of MSCs.

Homing Efficiency

MSCs have a tendency to home to damaged tissue sites. When MSCs are delivered exogenously and systemically administered into humans and animals, they are always found to migrate specifically to damaged tissue sites with inflammation [59, 60], although many of the intravenously administered MSCs are trapped in the lung [20, 61]. The inflammation-directed MSC homing has been demonstrated to involve several important cell trafficking-related molecules: chemokines, adhesion molecules, and matrix metalloproteinases (MMPs). Among the chemokines, the chemokine (C-X-C motif) ligand 12 (CCL-12)-chemokine (C-X-C motif) receptor 4 (CXCR4) and chemokine (C-C motif) ligand-2 (CCL-2)-chemokine (C-C motif) receptor 2 (CCR2) axes are most studied [62, 63]. Accordingly, CXCR4 has been transduced into MSCs to improve their in vivo engraftment and therapeutic efficacy in a rat myocardial infarction model [64]. Adhesion molecule P-selectin and vascular cell adhesion protein 1 (VCAM-1)-very late antigen-4 interaction have been shown as key mediators in MSC rolling and firm adherence to endothelial cells in vitro and in vivo [65]. Interestingly, in a recent report, VCAM-1 antibody-coated MSCs exhibited a higher efficiency in their engraftment into inflamed mesenteric lymph nodes and colon than uncoated MSCs in a mouse IBD model [66], suggesting that the modulations on the homing property of MSCs could be a viable approach in enhancing their therapeutic effectiveness. In

addition to chemokines and adhesion molecules, several MMPs, such as MMP-2 and membrane type 1 MMP, have been shown to be essential in the invasiveness of MSCs [67, 68]. It is worth mentioning that all the homing-related molecules are able to be upregulated by inflammatory cytokines such as tumor necrosis factor-α (TNFα) and IL-1 [69, 70]. Therefore, different inflammation status (i.e., different levels of inflammatory cytokines) might lead to distinct MSC engraftment and therapeutic efficiency.

Tumors can be regarded as wounds that never heal and continuously generate various inflammatory cytokines [71]. Indeed, MSCs, either de novo mobilized or exogenously administered, have been found to migrate to the tumor and adjacent tissue sites [72]. In view of this property, approaches have been developed to engineer several tumor-killing agents, such as IFNα, IFNβ, IL-12, and TNF-related apoptosis-inducing ligand, in MSCs for tumor targeted therapy in animal models [73–77]. More recently, MSCs have also undergone development into vehicles for delivery of nanoparticles to enhance their tumoricidal effects [78, 79]. Further investigation in this direction may lead to novel therapeutic strategies for cancer.

Differentiation Potential and Tissue Engineering

As typical multipotent stem cells, MSCs have been shown to possess the capability to differentiate into a variety of cell types, including adipocytes, osteoblasts, chondrocytes, myoblasts, and neuron-like cells. Although it is currently believed that the therapeutic benefits of MSCs are due to more complicated mechanisms, they have been shown to be able to differentiate into osteoblasts, cardiomyocytes, and other tissue-specific cells after their in vivo systemic infusion in the treatment of osteogenesis imperfecta and myocardial infarction in both animals and humans [59, 80, 81].

Instead of the systemic delivery, MSCs can be delivered together with various natural and synthetic biomaterial scaffolds. Either undifferentiated or differentiated MSCs can be loaded onto the scaffolds before their implantation into the damaged tissue sites [82, 83]. Such technologies have been successfully applied in cartilage repair and long-bone repair with generation of well-integrated and functional hard tissues [84, 85]. The advantage of the tissue-engineered MSC delivery system lies in the ease of controlling and manipulating the implanted cells and tissues, with reduced side effects on other organs and tissues. The current improvement in delivery vehicles and compatibility between the scaffolds and MSCs will help develop a mature technology for clinical applications.

Production of Trophic Factors

Accumulating evidence has revealed that the therapeutic benefits from MSCs are largely dependent on their capacity to act as a trophic factor pool. After MSCs home to the damaged tissue sites for repair, they will closely interact with the local stimuli, such as inflammatory cytokines, ligands of Toll-like receptors, and the hypoxia condition, which would stimulate MSCs to produce a large amount of growth factors performing multiple functions for tissue regeneration [86, 87]. Many of these factors are critical mediators in angiogenesis and prevention of cell apoptosis, such as vascular endothelial growth factor, insulin-like growth factor 1, basic fibroblast growth factors, hepatocyte growth factor, IL-6, and CCL-2 [87, 88]. Interestingly, a recent study found that the therapeutic effect of neuronal progenitors on EAE was solely dependent on leukemia inhibitory factor, revealing a similar trophic function of other tissue progenitors/stem cells [89]. Moreover, many reports have demonstrated that pretreatment with growth factors or gene modification of MSCs enhances the therapeutic efficacy for myocardial infarction and other wound healing processes [90, 91]. Further understanding of the molecular pathways involved in growth factor production will be very helpful to develop better strategies for MSC-based therapies.

Immunomodulation

In the last few years, MSCs have been manifested to be very effective in treating various immune disorders in human and animal models. In both in vitro and in vivo studies, MSCs suppress the excessive immune responses from T cells, B cells, dendritic cells, macrophages, and natural killer cells [29]. It is believed that the underlying mechanisms are a combinational effect from many immunosuppressive mediators. Among the mediators, a majority of them are inducible by inflammatory stimuli, such as nitric oxide, indoleamine 2,3-dioxygenase, prostaglandin E2, TSG-6, CCL-2, and programmed death ligand 1 [14, 17, 62, 92–95]. These factors are minimally expressed in the inactivated MSCs unless they are stimulated by several inflammatory cytokines, IFNγ, TNFα, and IL-1 [14, 96]. Neutralization of either immunosuppressive effectors or inflammatory cytokines reverses MSC-mediated immunosuppression. The concept of inflammation-licensed immunosuppression will be in favor of a more rational design for clinical use of MSCs. First, an optimal administration time point should be carefully selected according to the levels and ratios of different cytokines in the body during the disease progression. Previous reports have demonstrated that administration of MSCs after disease onset should be better than at the same time of disease induction in a mouse GvHD model [13, 14]. Second, cytokine priming should be an attemptable maneuver to improve the therapeutic effect of MSCs. Polchert et al. reported that IFNγ-pretreated MSCs protect 100% of mice from GvHD-induced death [13]. Third, the therapeutic efficacy of MSCs probably depends on the nature of different diseases because of the distinct inflammatory environments existed. Even for one specific disease, the diversity of microenvironments in different tissues may also produce curative effects different from those of MSCs. Therefore, the precise in vivo mechanism of MSCs should be more complex than what we observed in vitro. Further defining such mechanisms will help us develop more trustworthy strategies for clinical use of MSCs.

Conclusion

Although MSCs have been widely applied in preclinical studies and clinical trials, with many of them displaying effective outcomes in prevention and control of a diversity of diseases, the underlying mechanisms, especially in the in vivo models, still remain largely undefined. Available data have suggested that MSCs have a close interaction with the inflammatory milieu in the tissue damage sites. The therapeutic effects of MSCs should not be simple actions from themselves but a coordinated process with the local microenvironment. Understanding such interactions will be helpful in choosing an optimal dose and time points for MSC administration and in predicting the range of diseases for which MSCs should be effective. Another major question is how to translate the in vitro readouts into clinical applications; this translation will probably also require a deep understanding of the intricate link between MSCs and the

inflammatory conditions. Moreover, the above studies on MSC-based therapies will also have important implications for recognizing the physiological roles of stromal cells.

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Author Contributions

G.R., X.C., F.D., W.L., X.R., and Y.Z.: conception and design, manuscript writing; Y.S.: conception and design, manuscript writing, financial support, final approval of manuscript.

Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

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