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Immunomodulatory Properties and Therapeutic Application of Bone Marrow Derived-Mesenchymal Stem Cells

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Abstract

Mesenchymal stem cells (MSCs) are prototypical adult stem cells, identified as an adherent, fibroblast-like population positive for CD105, CD90 and CD73, and lacking hematopietic markers. MSCs can be isolated from different adult tissues including bone marrow (BM), umbilical cord, skeletal muscle and adipose tissue. MSCs have a potent immunomodulatory function via soluble factors, including PGE2, TGF-β, indoleamine 2,3-dioxygenase (IDO), IL-10, and HGF. Treatment with MSCs can improve type 1 diabetes, liver fibrosis and arthritis via their immunomodulatory function. Intra-bone marrow-bone marrow transplantation (IBM-BMT) can replace not only hemopoietic stem cells (HSCs) but also MSCs. IBM-BMT seems to be the best strategy for allogeneic BMT, and may improve aging-related diseases, including type 2 diabetes and osteoporosis. IBM-BMT has also been shown to be the most effective strategy to prevent the rejection of organ allografts. This review summarizes the immunomodulatory properties and therapeutic application of bone marrow derived-MSCs.

Keywords: Mesenchymal stem cells; Hemopoietic stem cells; Hematopietic markers; Allogeneic BMT; Organ allografts

Introduction

Mesenchymal stem cells (MSCs) are multi-potent progenitor cells isolated from bone marrow (BM) [1] and other adult tissue including skeletal muscle [2], adipose tissue [3], umbilical cord [4], synovium [5], the circulatory system [6], dental pulp [7], amniotic fluid [8], fetal blood [9] and lung [10]. Friedenstein and coworkers [11] first reported the existence of adherent, fibroblast-like cells isolated from BM [11], and that these cells could differentiate into mesodermal lineage cells such as osteoblasts, adipocytes and chondrocytes *in vitro* [12] and cadiomyocytes [13]. Also, MSCs have been reported to differentiate into types of cells of endodermal and ectodermal lineages, including lung [14], retinal pigment [15], skin [16], sebaceous duct cells [17], renal tubular cells [18], and neural cells [19,20], hepatocytes [21] and pancreatic islets [22]. MSCs are characterized by plastic adherence, colony forming capacity, and the expression of the surface molecules CD73, CD90, and CD105 and the absence of the expression of hematopoietic lineage markers [23].

Recently, there have been reports indicating that MSCs secrete a variety of factors that promote tissue repair, stimulate proliferation and differentiation of endogenous tissue progenitors, and decrease inflammatory and immune reactions [24-26]. MSCs have been shown to modulate immunological responses via T-cell suppression [24,26-28]. The therapeutic benefit of MSCs extends to T cell-mediated diseases such as graft-versus-host disease (GVHD) [29], Crohn's disease [30] and the prevention of organ transplantation rejection [31]. Moreover, MSCs have been observed to migrate to the site of injury in acute tissue injuries of kidney [32], liver [33], lung [34] and heart [35].

Adipose tissue and BM are the most readily available sources of MSCs because they are easy to harvest, and because of their relative abundance of progenitors and the lack of ethical concerns. Although adipose tissue-derived MSCs and bone marrow-derived MSCs (BMMSCs) show the same immunoregulatory functions and support of hematopoiesis [36], BMMSCs have a higher degree of commitment to differentiate into chondrogenic and osteogenic lineages than adipose tissue-derived MSCs [37]. Herein, we focus on immumodulation of BMMSCs and their benefits in a variety of therapies.

BMMSCs Soluble Factors

BMMSCs have the ability to modify and influence almost all the cells of the innate and adaptive immune systems, to interfere with and affect cellular proliferation, differentiation, maturation, and function to induce an anti-inflammatory phenotype and to modulate the immune response mediated by BMMSC soluble factors, including IL-6, M-CSF, IL-10, TGF-β, HGF and PGE2 [26,38,39].

PGE2 synthesized from arachidonic acid is a lipid intermediate that has been identified as one of the candidates responsible for T cell inhibition by MSCs [40]. PGE2 may have an immunostimulatory role by facilitating Th1 differentiation and expanding the Th17 T cell population [41]. Prostaglandins act as paracrine and autocrine factors in the local environment where they are produced. BMMSCs also express receptors for prostaglandins. Expression of PGE2 was upregulated by IFN-γ and TNF-α in the BMMSCs for immunomodulatory function [42]. Indoleamine 2,3 deoxygenase (IDO) is the rate-limiting enzyme involved in the catabolism of the essential amino acid tryptophan into its breakdown product kynurenine [43] and inhibition of T cell proliferation by dendritic cells (DCs) [44]. BMMSCs can be induced to express IDO when stimulated by IFN-γ [42].

TGF-β1 and HGF represent MSC-derived molecules that have immunomodulatory activity on T cell responses [24]. Mouse BMMSCs deliver their inhibitory activity via inducible nitric oxide synthase while rat BMMSCs preferentially use heme-oxygenase-1 [45]. The production of nitric oxide by BMMSCs has also been suggested to suppress T cell proliferation via the phosphorylation of signal transducer and activator of transcription-5 (STAT5) [46,47].

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Immunomodulation of BMMSCs

The innate immune cells include neutrophils, dendritic cells (DC), natural killer (NK) cells, eosinophils, mast cells and macrophages. MSCs have been shown to suppress these inflammatory cells [48], and to alter NK cell phenotype and suppress proliferation, cytokine secretion and cytotoxicity against HLA class I-expressing targets [49]. The adaptive immune system which is composed of T and B lymphocytes, generates specific immune responses to pathogens with the production of memory cells. MSCs modulate DC function, indirectly regulate T and B cell activity, delay and prevent the development of acute graft versus host disease (GVHD) [50] and suppress DC function during allogeneic islet transplantation [51].

BMMSCs modulate different aspects of the rejection process, including the inhibition of DC differentiation [52], skewing of CD4+ T helper population phenotypes and modulation of CD8+ cytotoxic T lymphocyte and NK cell functions [53]. BMMSCs strongly inhibited the maturation and functioning of monocyte-derived DCs by interfering selectively with the generation of immature cells via inhibitory mediator of MSC-derived PGE2 [54]. However, one report has suggested that human adipose-derived MSCs are more potent in immunomodulating the differentiation of human DCs than BMMSCs [55]. BMMSCs can inhibit the cytotoxic effects of antigen-primed cytotoxic T cells by suppressing the proliferation than activity [56] via the inhibition of the nuclear translocation of nuclear factor-kappa B [57]. BMMSCs have been found to increase T reg cells when co-cultured with CD4+ cells *in vitro* [58], and to modulate immune response via inducing the generation of Treg *in vitro* [26]. BMMSCs have been shown to suppress NK cell proliferation and IFN-γ production via the secretion of TGF-β1and PGE2 [26,59].

BMMSCs have been showen to inhibit the proliferation of B cells when stimulated with anti-CD40L and IL-4 [60]. One report has suggested that allogeneic BMMSCs inhibit the activation, proliferation and IgG secretion of B cells in a BXSB mouse model of human systemic lupus erythematosus [61]. BMMSCs have been shown to attenuate sepsis via prostaglandin E(2)-dependent reprogramming of host macrophages to increase cytokine release [62] (Figure 1).

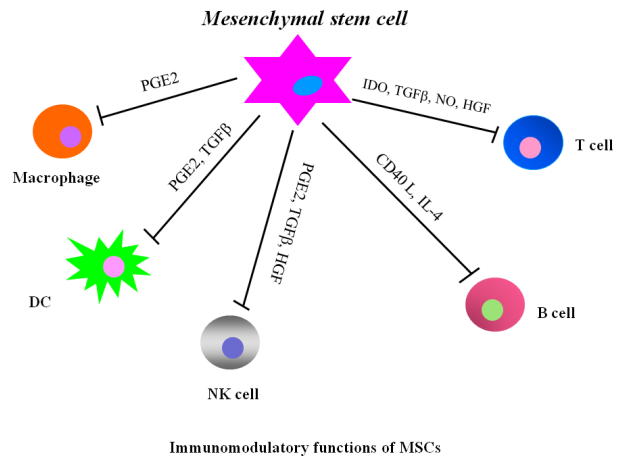

Figure 1: Immunomodulatory functions of MSCs.

Immunomodulatory Functions of BMMSCs in the Animal Models

Allogeneic BMMSCs are effective in the treatment of murine models of human disease [63-65]. BMMSCs could secrete regulatory cytokines that affect regulatory T cells, and modulate the immunological dysregulation observed in antibody producing B cells and cytotoxic NK cells in the NOD mouse, a type 1 diabetes model mouse [53]. BMMSCs promote the endogenous repair of pancreatic islets and renal glomeruli in a streptozotocin-induced diabetic mouse model [54]. Co-infusion of BMMSCs and BM cells inhibited the beta cells-specific T cell proliferation and restored insulin and glucose levels [52]. Administration of BMMSCs increased the recovery of renal function by inhibiting the production of proinflammatory cytokines, such as IL-1β,TNF, IFN-γ and through an anti-apoptotic effect on target cells [55].

BMMSCs secrete many cytokines and growth factors such as HGF [57], which shows anti-apoptotic activity in hepatocytes and plays an essential part in the regeneration of liver [27]. CCl4-induced liver fibrosis is a classical experimental fibrosis model, and treatment with BMMSCs can protect against experimental liver fibrosis in CCl4-induced rats [56]. BMMSCs potently inhibit *in vitro* T-cell proliferation in an IFN-γ-dependent mechanism that involves nitric oxide and PGE2. Moreover, anti-CD3-induced T-cell proliferation was suppressed by MSC treatment in the collagen-induced arthritis [66].

Intra Bone Marrow-BMT (IBM-BMT) for Metabolic Disorders and Organ Transplantation

BM transplantation (BMT) can be used to treat hematopoietic disorders, metabolic disorders and autoimmune diseases [23-26]. Allogeneic BMT can be used to treat autoimmune diseases [67-69]. Compared with intravenous BMT (IV-BMT), IBM-BMT [70] has been proven to be the most effective approach, since IBM-BMT can replace not only hemopoietic cells (including hemopoietic stem cells: HSCs) and BMMSCs to be recruited, thereby preventing the risk of graft rejection and allowing the use of a mild conditioning regimen. IBM-BMT thus seems to be the best strategy for allogeneic BMT, since 1) no GVHD develops even if whole BM cells are injected; 2) no graft failure occurs even if the radiation dose is reduced; 3) hemopoietic recovery is rapid and 4) the restoration of T cell functions is complete even in donor-recipient combinations across MHC barriers [71].

As donor MSCs can be effectively recruited by "IBM-BMT", we attempted to use the method to treat some disease in a mouse model. The SAMP6 mouse (a substrain of senescence-accelerated mice) spontaneously develops osteoporosis early in life and is therefore a useful model for examining the mechanisms underlying osteoporosis. After IBM-BMT, the hematolymphoid system was completely reconstituted with donor-type cells. Thus-treated SAMP6 mice (8 months after IBM-BMT) showed marked increases in trabecular bone even at 20 months of age, and the bone mineral density (BMD) remained similar to that of normal B6 mice. BMMSCs in "IBM-BMT"-treated SAMP6 mice were replaced with donor MSCs [72,73].

We previously reported that the transplantation of BMMSCs via IBM-BMT in conjunction with the induction of HO-1 could eradicate type 2 diabetes. The beneficial effect of HO-1 induction further suggests that the abnormality in endothelial progenitor cells is due to mesenchymal stem cell-stromal cell disorder exacerbated by oxidative stress and decreases in adiponectin. Thus, the transplantation of BMMSCs using the IBM-BMT strategy in conjunction with HO-1 induction offers a novel approach in the treatment of type 2 diabetes

[74]. Another report has suggested that IBM-BMT is a viable method of immunological manipulation that suppresses the severe joint destruction and bone absorption in SKG/Jcl mice and lends further credence to the use of this methodology in humans with intractable rheumatoid arthritis [75].

We previously found that the combination of organ allografts and IBM-BMT from the same donors was the most effective strategy to prevent the rejection of organ allografts, since the radiation dose could be reduced to 4Gy x 2 in skin allografts [76,77]. In addition, we have found that IBM-BMT is applicable to allografts of other organs and tissues in rats and mice, such as pancreas islets, legs, lungs, heart and ovary [78-83] .

Conclusion

The original use of BMMSCs was to accelerate hematopoiesis, but BMMSCs have been shown to establish connection and modulate the activity of many cells of the immune system. The immunosuppressive effect of BMMSCs is beneficial for organ transplantation. MSCs as immunosuppressants have been used in clinical trials, but the long-term safety of the infusion of MSCs needs to be proven prior to their clinical application.

Conflict of Interests

None of the authors have conflicts of interest to declare.

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