Medical Hypotheses 76 (2011) 322–324

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

Mesenchymal stem cell transplantation: A potential therapy for oral lichen planus

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ARTICLE INFO

Article history:
Received 8 May 2010
Accepted 19 September 2010

ABSTRACT

Oral lichen planus is a type of T cell-mediated autoimmune disease. Satisfactory therapy results are not usually achieved with conventional treatment; however, a new therapy employing T cell immune modulation may treat this disease. Mesenchymal stem cells are multipotent nonhematopoietic progenitor cells that are capable of self-renewal and differentiation into various cell types, including osteocytes and adipocytes. Thus, mesenchymal stem cells are regarded as a promising cell population for tissue regeneration in the clinic. In the past several years, there has been a dramatic improvement in the understanding of immunosuppressive properties of mesenchymal stem cells on various immune cell types. We propose that mesenchymal stem cells can be utilized to treat oral lichen planus patients via systemic infusion or local application.

Background

Oral lichen planus (OLP) is a common and chronic oral mucosa disease that potentially leads to cancer. It is generally accepted that the onset of OLP is a T cell-mediated immune damage course, and is associated with autoimmunity [1]. T cells are the main cell type infiltrating the diseased region of OLP, and the amount, distribution, subpopulation ratios, and T cell products change regularly according to local pathogenesis development [2]. In the epithelium of oral mucosa of OLP patients, CD8+ T cells account for the largest proportion of local lymphocytes. CD8+ T cells are close to the apoptotic keratinocytes, whereas CD4+ T cells are primarily located in the lamina propria of the mucosa [3].

Gándara Rey et al. [4] observed immune alterations in 52 OLP patients and found that CD4+ T cells, the ratios of CD4+/CD8+ T cells, and CD8+ CD45RO+/CD8+ CD45RA+ T cells were higher than those of undiseased individuals. In addition, the alteration of cellular immunity was associated with not only the numbers of lymphocytes, but also with the reactional capability of lymphocytes [4]. Although the symptoms of OLP are similar to those of oral mucosa graft-versus-host diseases (GVHD), the levels of CD1a, CD4, CD8, CD25, and CD86 in OLP epithelium were higher than in epithelium of GVHD oral mucosa, suggesting a stronger immune reaction in OLP [5]. CD8+ T cells in OLP highly expressed CCR5H and CXCR3, which can carry the respective ligands of chemotactic factors for cellular degranulation, indicating that activation of cytotoxic T cells is a potential mechanism of OLP [6]. Furthermore, antigen-presenting cells (including dendrites and Langerhan's cells), cytokines (IL-2, IL-6, IL-8, INF-γ, and TNF-α), and cell adhesion molecules (ELAM-1, ICAM-1, VCAM-1, PECAM-1, VLA4, P-selectin, and L-selectin) also play important roles in OLP [7–11]. Collectively, these data indicate that OLP pathogenesis is a T cell-mediated autoimmune reaction. To date, the primary therapy for OLP is the application of immunosuppressive drugs, such as glucocorticoid, *Tripterygium wilfrodii*, and artrichin. Although these drugs have some effect on symptoms, such treatment often causes severe side effects, and satisfactory outcomes cannot be reliably predicted. Thus, it is urgent to develop a novel method to treat OLP.

The hypothesis

We hypothesize that mesenchymal stem cells (MSCs) can be utilized to treat OLP patients via systemic infusion or local application. This hypothesis is based on the following four points: (1) MSCs can be easily isolated and expanded *in vitro*; (2) MSCs possess immunosuppressive properties *in vitro* and *in vivo*; (3) OLP is a type of T cell-mediated autoimmune disease; (4) immunosuppressive drugs including glucocorticoids, *T. wilfrodii*, and artrichin affect OLP.

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doi:10.1016/j.mehy.2010.09.025

Immunological properties of MSCs

MSCs were first described by Fridenstein et al., as the clonal, plastic, adherent cells serving as a source of osteoblastic, adipogenic, and chondrogenic cell lines [12]. Although the main source of MSCs is the bone marrow, these cells constitute only a small percentage of the total number of bone marrow-populating cells. Indeed, only 0.01–0.001% of mononuclear cells isolated on density gradients gave rise to plastic adherent fibroblast-like colonies [13].

In the absence of a standardized marker, MSCs are typically defined by a combination of phenotypic and functional characteristics. Phenotypically, *ex vivo*-expanded MSCs express a number of nonspecific markers, including CD105 (SH2 or endoglin), CD73, CD90, CD166, CD44, and CD29 [13,14]. MSCs are negative for hematopoietic and endothelial markers, such as CD11b, CD14, CD31, and CD45 [13]. The functional criterion of MSCs is trilineage potential *in vitro*: the ability to differentiate into bone, cartilage, and fat upon proper induction [15].

In addition to their regenerative capacities, culture-expanded MSCs also possess the unique ability to modulate immune responses, both *in vitro* and *in vivo*, and may function as immunomodulators in the maintenance of peripheral tolerance, transplantation tolerance, and autoimmunity. Making use of multiple pathways, MSCs suppress the function of a broad range of immune cells, including T cells and B cells.

MSCs express low levels of major histocompatibility complex (MHC) class I molecules. As MSCs express neither MHC class II molecules nor costimulatory molecules (such as CD40, CD80, and CD86) on their surfaces, they therefore do not exhibit antigen-presenting cell activities [16,17]. When differentiating into adipose, bone, and cartilage cells, MSCs exhibit MHC class I molecules, but the expression of MHC class II molecules can no longer be induced. The addition of IFN-γ to the MSC cultures increases the expression of MHC class I molecules and triggers the expression of MHC class II molecules, but not of the costimulatory molecules. In coculture experiments, MSCs failed to induce proliferation of allogenic lymphocytes *in vitro*, even after provision of a costimulatory signal by addition of CD28-stimulating antibodies or transfection of CD80 or CD86 costimulatory molecules, thus confirming their low immunogenicity [18–20].

MSCs are able to suppress T cell activation and proliferation *in vitro*, irrespective of the identity of the MSC source: human, baboon, or rodent. This suppression affects the proliferation of T cells induced by alloantigens, mitogens, and in mixed lymphocyte reactions (MLRs), as well as activation of T cells by CD3 and CD28 antibodies [21–23]. Suppression is MHC-independent and mostly significant if MSCs are added on the first day of the 3- or 5-day culture [22].

In the presence of signals that favor T-helper cell 1 (Th1) development, naïve T cells mature into IFN-γ-secreting cells. If MSCs are present in the culture, IFN-γ secretion is reduced. Thus, MSCs induce a bias toward Th2 differentiation [24]. MSCs also suppress CD8+ T cell-mediated lysis if added at the beginning of the MLR; lysis was partially abrogated by the addition of IL-2. MSCs may inhibit the afferent phase of alloreactivity and prevent the development of cytotoxic T cells. MSCs have been reported to induce formation of CD8+ regulatory T cells that were responsible for inhibition of allogeneic lymphocyte proliferation. Furthermore, an increase in the population of CD4+CD25+ T cells displaying a regulatory phenotype was demonstrated in mitogen-stimulated T cell cultures in the presence of MSCs [24,25].

MSCs cocultured with purified CD19+ B cells in the presence of a cocktail of stimuli significantly inhibited B cell proliferation [26]. Maximum inhibition was observed at 1:1 B cells:MSCs, and disappeared at ratios of 1:5 and 1:10, in marked contrast with the inhibition of T cell proliferation induced by MSCs [26]. MSCs cocultured with B cells in transwell plates similarly inhibited B cell proliferation, suggesting that at least one soluble factor was implicated. The same study also showed that B cells cocultured with MSCs downregulated their expression of CXCR4, CXCR5, and CXCR7 chemokine receptors, and exhibited significant defects in chemotaxis. In another study, MSCs did not inhibit TNF-α, IFN-γ, IL-4, or IL-10 production. However, MSCs downregulated the expression of the chemokine receptors CXCR4, CXCR5, and CCR7B, and chemotaxis toward CXCL12 (the CXCR4 ligand) and CXCL13 (the CXCR5 ligand), suggesting that high numbers of MSCs affect the chemotactic properties of B cells [27]. In a murine study, allogeneic MSCs were shown to inhibit the proliferation, activation, and IgG secretion of B cells from BXSB mice, which was usually used as an experimental model for human systemic lupus erythematosus [28].

Clinical applications of MSCs

Significant clinical results were obtained by Le Blanc et al., whose work led to the successful treatment of severe, treatment-resistant GVHD [29–31]. Haploidentical MSCs were used in a 9-year-old boy with severe, treatment-resistant GVHD of the gut, skin, and liver after allogeneic hematopoietic stem cell (HSC) transplantation for acute lymphocytic leukemia. His symptoms of GVHD and related clinical and pathological findings improved following transplantation of haploidentical MSCs derived from his mother. Other patients with acute and chronic GVHD have been treated with MSCs, and no side effects were observed following MSC infusions. Among the 40 patients treated with MSCs for severe acute GVHD, 19 experienced complete responses, nine patients showed improvements, seven patients did not respond, and four maintained stable diseases. Twenty-one patients lived between 6 weeks and up to 3.5 years after transplantation.

The marrow stroma is damaged after high-dose chemoradiotherapy prior to autologous or allogeneic HSC transplantation, and is slow to reconstitute. Due to their immunosuppressive properties and particular function in marrow microenvironment, MSCs have been regarded as a promising means to prevent graft rejection and to enhance HSC engraftment. An elderly woman with end-stage severe aplastic anemia received MSCs derived from her human leukocyte antigen (HLA)-haploidentical son on two occasions [32]. Engraftment of donor MSCs was detected by PCR in the endostium of a bone marrow biopsy, but not in the marrow aspirates, suggesting that transplanted MSCs are primarily located in the bone tissue and can be transplanted across HLA barriers. A 20-year-old woman with acute myeloid leukemia received peripheral blood stem cells combined with MSCs from her HLA-haploidentical father [33]. The patient engrafted rapidly with no acute or chronic GVHD, despite the fact that using haploidentical grafts that are not T cells depleted by conventional immunosuppression lead to a significant risk of GVHD and rejection. Lazarus et al. [34] reported 46 patients who received HSCs and culture-expanded MSCs from their HLA-identical siblings. MSCs were infused 4 h prior to HSC-graft infusion without any infusion-related adverse events. Moderate to severe GVHD was observed in 28% of the patients, and 2-year progression-free survival was observed in 53% of the patients.

Clinical significance of MSC-mediated treatment for OLP

An original therapeutic strategy for the treatment of OLP will result from the effective use of MSCs to treat OLP. If the new

cell-based therapeutic approach appears more effective than conventional therapy, the application of immunosuppressive drugs, which have serious drug-related cytotoxicities, will be decreased.

Evaluation of the hypothesis

The biological and immunological characteristics of bone marrow MSCs of OLP patients should first be investigated, including colony-forming capacity, cell proliferation, *in vitro* multi-lineage differentiation, stem cell marker expression, *in vivo* tissue formation capability, immunogenicity, and immunosuppressive function. Upon observation of differential biological and immunological characteristics of bone marrow MSCs, we next should establish animal models of OLP, transplant autologous or allogeneic MSCs into the animals, and evaluate the results and the side effects of this method. Evaluation methods include the clinical assessments, histological examinations, and hematological and immunological evaluations that comprise routine blood and biochemical tests, immunoglobulin tests in whole blood, analysis of T cell-related immunological markers, including determination of the expression profiles of CD3, CD4, CD8, and CD40L, and the quantitation of the percentages of CD4+CD25^{high}Foxp3+ regulatory T cells should also be carried out. After demonstration of therapy effectiveness in the animal model, well-designed, double-blind, randomized and controlled clinical trials with large sample size should be set in motion to test the feasibility of MSC transplantation before its clinical application.

Conflicts of interest statement

None declared.

Acknowledgements

This work was supported by Grants from the National Basic Research Program of China (2007CB947304 and 2010CB944801), the National Natural Science Foundation of China (81070799) and the Funding Project for Academic Human Resources Development in the Institutions of Higher Learning under the Jurisdiction of Beijing Municipality (PHR20090510).

References

[1] Sugerman PB, Savage NW, Walsh LJ, Seymour GJ. Disease mechanisms in oral lichen planus: a possible role for autoimmunity. Aust J Dermatol 1993;34:63–9.
[2] Sugerman PB, Savage NW, Walsh LJ, et al. The pathogenesis of oral lichen planus. Crit Rev Oral Biol Med 2002;13:350–65.
[3] Khan A, Farah CS, Savage NW, Walsh LJ, Harbrow DJ, Sugerman PB. Th1 cytokines in oral lichen planus. J Oral Pathol Med 2003;32:77–83.
[4] Gándara Rey J, García García A, Blanco Carrión A, Gándara Vila P, Rodríguez Nuñez I. Cellular immune alterations in fifty-two patients with oral lichen planus. Med Oral 2001;6:246–62.
[5] Hasséus B, Jontell M, Brune M, Johansson P, Dahlgren UI. Langerhans cells and T cells in oral graft versus host disease and oral lichen planus. Scand J Immunol 2001;54:516–24.
[6] Iijima W, Ohtani H, Nakayama T, et al. Infiltrating CD8+ T cells in oral lichen planus predominantly express CCR5 and CXCR3 and carry respective chemokine ligands RANTES/CCL5 and IP – 10/CXCL10 in their cytolytic granules: a potential self-recruiting mechanism. Am J Pathol 2003;163:261–8.
[7] Chou MJ, Daniels TE. Langerhans cells expressing HLA-DQ, HLA-DR and T6 antigens in normal oral mucosa and lichen planus. J Oral Pathol Med 1989;18:573–6.
[8] Villarroel Dorrego M, Correnti M, Delgado R, Tapia FJ. Oral lichen planus: immunohistology of mucosal lesions. J Oral Pathol Med 2002;31:410–4.
[9] Simark-Mattsson C, Bergenholtz G, Jontell M, et al. Distribution of interleukin-2, -4, -10, tumour necrosis factor-alpha and transforming growth factor-beta mRNAs in oral lichen planus. Arch Oral Biol 1999;44:499–507.
[10] Hiroki A, Nakamura S, Shinohara M, Oka M. Significance of oral examination in chronic graft-versus-host disease. J Oral Pathol Med 1994;23:209–15.
[11] Zhao ZZ, Sugerman PB, Zhou XJ, Walsh LJ, Savage NW. Mast cell degranulation and the role of T cell RANTES in oral lichen planus. Oral Dis 2001;7:246–51.
[12] Friedenstein AJ, Gorskaja U, Kalugina NN. Fibroblast precursors in normal and irradiated mouse hematopoietic organs. Exp Hematol 1976;4:267–74.
[13] Pittenger MF, Mackay AM, Beck SC, et al. Multilineage potential of adult human mesenchymal stem cells. Science 1999;284:143–7.
[14] Deans RJ, Moseley AB. Mesenchymal stem cells: biology and potential clinical uses. Exp Hematol 2000;28:875–84.
[15] Prockop DJ. Marrow stromal cells as stem cells for nonhematopoietic tissues. Science 1997;276:71–4.
[16] Angoulvant D, Clerc A, Benchalal S, et al. Human mesenchymal stem cells suppress induction of cytotoxic response to alloantigens. Biorheology 2004;41:469–76.
[17] Fibbe WE, Noort WA. Mesenchymal stem cells and hematopoietic stem cells transplantation. Ann NY Acad Sci 2003;996:235–44.
[18] Tse WT, Pendleton JD, Beyer WM, Egalka MC, Guinan EC. Suppression of allogeneic T-cell proliferation by human marrow stromal cells: implications in transplantation. Transplantation 2003;75:389–97.
[19] Bartholomew A, Sturgeon C, Siatskas M, et al. Mesenchymal stem cells suppress lymphocyte proliferation in vitro and prolong skin graft survival in vivo. Exp Hematol 2002;30:42–8.
[20] Le Blanc K, Tammik L, Sundberg B, Haynesworth SE, Ringdén O. Mesenchymal stem cells inhibit and stimulate mixed lymphocyte cultures and mitogenic responses independently of the major histocompatibility complex. Scand J Immunol 2003;57:11–20.
[21] Djouad F, Plence P, Bony C, et al. Immunosuppressive effect of mesenchymal stem cells favors tumor growth in allogeneic animals. Blood 2003;102:3837–44.
[22] Krampera M, Glennie S, Dyson J, et al. Bone marrow mesenchymal stem cells inhibit the response of naïve and memory antigen-specific T cells to their cognate peptide. Blood 2003;101:3722–9.
[23] Maitra B, Szekely E, Gjini K, et al. Human mesenchymal stem cells support unrelated donor hematopoietic stem cells and suppress T-cell activation. Bone Marrow Transplant 2004;33:597–604.
[24] Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. Blood 2005;105:1815–22.
[25] Maccario R, Podestà M, Moretta A, et al. Interaction of human mesenchymal stem cells with cells involved in alloantigen-specific immune responses favors the differentiation of CD4+ T-cell subsets expressing a regulatory/suppressive phenotype. Haematologica 2005;90:516–25.
[26] Corcione A, Benvenuto F, Ferretti E, et al. Human mesenchymal stem cells modulate B-cell functions. Blood 2006;107:367–72.
[27] Rasmusson I, Le Blanc K, Sundberg B, Ringdén O. Mesenchymal stem cells stimulate antibody secretion in human B cells. Scand J Immunol 2007;65:336–43.
[28] Deng W, Han Q, Liao L, You S, Deng H, Zhao RC. Effects of allogeneic bone marrow-derived mesenchymal stem cells on T and B lymphocytes from BXSB mice. DNA Cell Biol 2005;24:458–63.
[29] Le Blanc K, Rasmusson I, Sundberg B, et al. Treatment of severe acute graft-versus-host disease with third party haploidentical mesenchymal stem cell. Lancet 2004;363:1439–41.
[30] Ringdén O, Uzunel M, Rasmusson I, et al. Mesenchymal stem cells for treatment of therapy-resistant graft-versus-host disease. Transplantation 2006;81:1390–7.
[31] Le Blanc K, Frassoni F, Ball LM. Mesenchymal stem cells for treatment of severe acute graft-versus-host disease [abstract]. Blood 2006;108:753.
[32] Fouillard L, Bensidhoum M, Bories D, et al. Engraftment of allogeneic mesenchymal stem cells in the bone marrow of a patient with severe idiopathic aplastic anemia improves stroma. Leukemia 2003;17:474–6.
[33] Lee ST, Jang JH, Cheong JW, et al. Treatment of high-risk acute myelogenous leukaemia by myeloablative chemoradiotherapy followed by co-infusion of T cell-depleted haematopoietic stem cells and culture-expanded marrow mesenchymal stem cells from a related donor with one fully mismatched human leucocyte antigen haplotype. Br J Haematol 2002;118:1128–31.
[34] Lazarus HM, Koc ON, Devine SM, et al. Cotransplantation of HLA-identical sibling culture-expanded mesenchymal stem cells and hematopoietic stem cells in hematologic malignancy patients. Biol Blood Marrow Transplant 2005;11:389–98.