Research progress and possible mechanisms of transplantation tolerance induced by mesenchymal stem cells*★

Zhang Ya-yong, Jiang Li-hong, Hou Zong-liu

Department of Cardiothoracic Surgery, Yan'an Affiliated Hospital of Kunming Medical University, Yan'an Hospital of Kunming, Kunming 650051, Yunnan Province, China

Zhang Ya-yong★, Studying for master's degree, Department of Cardiothoracic Surgery, Yan'an Affiliated Hospital of Kunming Medical University, Yan'an Hospital of Kunming, Kunming 650051, Yunnan Province, China
hyz_baoding@163.com

Correspondence to: Jiang Li-hong, Doctor, Master's supervisor, Department of Cardiothoracic Surgery, Yan'an Affiliated Hospital of Kunming Medical University, Yan'an Hospital of Kunming, Kunming 650051, Yunnan Province, China
jianglihong2@hotmail.com

Supported by: Yunnan Provincial Social Development Science and Technology Program, No. 2007CA005*

Received: 2009-11-19
Accepted: 2009-12-03
(20091119010/ZS)

Zhang YY, Jiang LH, Hou ZL.Research progress and possible mechanisms of transplantation tolerance induced by mesenchymal stem cells. Zhongguo Zuzhi Gongcheng Yanjiu yu Linchuang Kangfu. 2010;14(14): 2652-2656.

[http://www.crter.cn http://en.zglckf.com]

Abstract

BACKGROUND: Mesenchymal stem cells are capable of self-renew, a high degree of proliferation, with multi-differentiation potential, low immunogenicity and immunomodulatory properties. Both *in vivo* and *in vitro* it is able to regulate allogeneic immune response, to induce immune tolerance. In the solid organ transplantation it is playing an increasingly important role.

OBJECTIVE: To summarize the research progress on the immunomodulatory mechanism and application of mesenchymal stem cells in solid organ transplantation.

METHODS: An online search of Pubmed was undertaken by using the key words of "Mesenchymal Stem Cells, Mesenchymal Stem Cell Transplantation, Organ Transplantation, Transplantation Immunology, Immunologic Graft Enhancement, Graft *vs*. Host Disease" in Mesh to identify the relevant articles published in English from January 1994 to October 2009. At the same time, Wanfang database was screened to identify the relevant articles published between January 1994 and October 2009 with the key words of "Mesenchymal Stem Cells, Organ Transplantation, Transplantation Immunology" in Chinese. Inclusive criterion: The articles related to the immunomodulatory properties, transplantation immunology and application of mesenchymal stem cells in the solid organ transplantation were included. Exclusive criterion: The articles with repetitive research or Meta analysis were excluded.

RESULTS AND CONCLUSION: Totally 200 relevant articles were selected and 86 of them met the inclusive criterion. Mesenchymal stem cells exhibit low immunogenicity and immunomodulatory properties, have an indispensable advantage about inducing graft tolerance and repairing tissue in solid organ transplantation. The mechanism of inducting immune tolerance may be related to soluble factors, regulatory T cells, tolerant dendritic cells, bone marrow chimerism, anti-inflammatory and tissue repair, dose and time of injecting MSCs.

INTRODUCTION

Mesenchymal stem cells (MSCs) are one kind of pluripotent adult stem cells, with a wide variety of sources, easily separated and *in vitro* amplified, strong tissue repair capacity, as well as multi-differentiation potential to three germ layers[1], such as the endoderm cells (muscle cells, lung cells, liver cells, intestinal epithelial cells), mesodermal cells (bone cells, cartilage cells, fat cells, bone marrow stromal cells), ectodermal cells (neurons, epithelial cells); MSCs exhibit low immunogenicity and immune regulation effect, they are not damaged or killed by cytotoxic T lymphocytes and NK cells[2-3].

MSCs have been widely used in tissue damage repair, tissue regeneration, autoimmune disease and graft-*versus*-host disease, it could significantly prolong allogeneic skin graft survival time, exhibit a strong immune regulation, suggesting that it may play an important role in the induction of organ transplantation immune tolerance.

DATA AND METHODS

Literature source

An online search of Medline was undertaken by the first author using the key words of "Mesenchymal Stem Cells, Mesenchymal Stem Cell Transplantation, Organ Transplantation, Transplantation Immunology, Immunologic Graft Enhancement, Graft *vs*. Host Disease" to identify the relevant articles published in English from January 1994 to October 2009. At the same time, Wanfang database was screened to identify the relevant articles published between January 1994 and October 2009 with the key words of "Mesenchymal Stem Cells, Organ Transplantation, Transplantation Immunology" in Chinese.

Literature screening and evaluation

Inclusive criterion: The articles related to the immunomodulatory properties, transplantation immunology and application of mesenchymal stem cells in the solid organ transplantation were included.

Exclusive criterion: The articles with repetitive research or Meta analysis were excluded.

Data extraction and quality estimation: The inclusion criteria of the literature were evaluated according to the following aspects: ① random allocation; ② blind method; ③ intention to treat analysis; ④ animals loss or patients follow-off. Literature screening and quality assessment were carried out independently and cross-checked by the first author, once the differences occurred, it would be solved through discussion or by the second and third authors.

A total of 200 literatures were screened out by computer by reading the titles and abstracts, including 26 Chinese and 174 English. In total 62 literatures unrelated to this article for research purposes, 48 literatures with repetitive content, and 4 Meta analysis were excluded, finally 86 documents were reviewed.

COMPREHENSIVE ANALYSIS OF LITERATURES

MSCs definition

MSCs, known as multipotent mesenchymal stromal

cells, is firstly discovered in the bone marrow, with the study develops, this cell group has been proved to be not a single cell population, but a mixed group containing a number of stem/progenitor cells, so International Society for Cellular Therapy Association has termed this group of cells as multipotent mesenchymal stromal cells in 2005, and propose that not all MSCs are stem cells[4]. International Society for Cellular Therapy Association also specify three standards for identifying MSCs[5]: ① MSCs adhere and grow in plastic products under standard culture conditions. ② MSCs express CD105, CD73, CD90, don't express CD45, CD34, CD14 (or CD11b), CD79a (or CD19), don't express major histocompatibility antigen HLA-DR. ③ MSCs cultured *in vitro* must be able to differentiate into osteocyte, chondrocytes and adipocytes.

MSCs and organ transplantation

Inducing organ transplantation tolerance is a goal in the field of the transplantation, to date, the long-term survival of organ grafts can only rely on lifetime use of immunosuppressive agents, also is accompanied by significant cell toxicity, opportunistic infections, cancer and other side effects. A large number of studies have shown that MSCs can significantly prolong the survival time of organ transplant and induce donor specific immune tolerance, the mechanism may be associated with: ① Secreting a variety of soluble factors, transforming growth factor-β, hepatocyte growth factor, interleukin-10, indoleamine 2, 3-dioxy enzyme, prostaglandin E2, interferon-γ and other interactions. ② Inducing the production of $CD4^+$ $CD25^+$ regulatory T cells positive for FoxP3 gene expression. ③ Inducing apoptosis (programmed cell death). ④ Regulating antigen presenting cell function. ⑤ inducing bone marrow chimerism. ⑥ Anti-inflammatory and tissue repair functions. The tolerance effect is also affected by the input methods, dose and time effects of MSCs.

MSCs and skin transplantation

In 2002, Bartholomew *et al*[6] confirmed that the donor source of MSCs input to receptor baboon could prolong skin graft survival time, the effect is equivalent to cyclosporine. Even MSCs from a third party (non-donor, non-receptor) baboon can also inhibit immune rejection. Likewise, MSCs can significantly prolong allogeneic skin graft survival in rats[7]. During *in vitro* mixed lymphocyte reaction, MSCs can inhibit the donor antigen-stimulated T lymphocyte proliferation, its inhibitory effect is enhanced with an increasing MSCs dose, but reduced with interleukin-2 level increases. In a later study, MSCs is found to play an immunosuppressive effect through the soluble factors and cell-cell contact, as well as inhibited by MSCs and co-cultured lymphocytes[8]. Aksu *et al* [9] found that MSCs could treat skin graft-versus-host disease in rats after transplantation, significantly prolong the survival of skin grafts. Similarly, hepatocyte growth factor-transfected MSCs also significantly prolonged allograft survival time of skin allografts in rats[3]. *In vitro* studies also found that MSCs and their supernatants can inhibit T-lymphocyte secret interferon-γ. *In vivo*, MSCs in combination with bone marrow transplanted in rats may enhance the production of mixed chimerism[9], which is possible one of the mechanisms underlying transplantation tolerance. However, Liu *et al* [10] have found that MSCs still have characteristics of immune privilege and immune regulation after differentiating into osteoblasts, but lost these characteristics after *in vivo* transplantation. In 2008, Sbano *et al*[11] gave intravenous injection of MSCs combined with cyclosporine A in rats following transplantation in the pre-clinical studies, as compared with the blank control group, the skin graft survival time was significantly prolonged in group of MSCs, MSCs combined cyclosporine A, and cyclosporine A group; but MSCs alone group produced earlier rejection. In MSCs combined with cyclosporine A group, the interferon-γ, interleukin-2 and TNF-α secretions were reduced; TNF-α was highly expressed in the MSCs group, indicating complex migration and transformation *in vivo* of MSCs, the specific molecular mechanisms need further study.

MSCs and heart transplantation

Chabannes *et al*[12] reported that, allograft rejection significantly delayed after MSCs treatment for heart transplantation in rats, while heme oxygenase and nitric oxide synthase were highly expressed in MSCs. Similarly, Popp *et al* [13] used MSCs combined with low doses of mycophenolate mofetil to induce cardiac allograft immune tolerance in rats, the mean survival was 100 days in the experimental group and 13 days in the control group, the cardiac allograft survival time was significantly extended. In the experimental group, indoleamine 2, 3-dioxy enzyme was highly expressed, after 1-methyl-L-tryptophan blocking, the tolerance effect is gone. Also, MSCs could lead to induce tolerogenic dendritic cells. Therefore, the interaction of a variety of soluble factors can achieve immune tolerance.

Zhou *et al*[14] reported that intravenous infusion of MSCs into allogeneic rat heart transplantation model in a specific period of time can significantly prolong cardiac allograft survival, the average survival time was 12.4 days in the experimental group and 6.4 days in the control group. Real-time quantitative PCR was applied to analyze the Th1/Th2 balance, results showed immune response was prone to Th2 type, which indicates that MSCs can induce transplantation tolerance by regulating the balance of Th1/Th2. In the heterotopic heart transplantation model, Casiraghi *et al*[2] found that the $CD4^+$ $CD25^+$ regulatory T cells were highly expressed in mice expressed $Foxp3^+$ gene, indicating that inducing the production of regulatory T cells may be the mechanism underlying MSCs inducing transplantation tolerance.

However, Inoue *et al*[15] have proved that, although MSCs exhibited immunosuppressive effects in the mixed lymphocyte reaction *in vitro*, they can inhibit alloreactive T-lymphocyte proliferation; however, MSCs cannot prolong the survival time of transplanted heart in allogeneic rat model, and even more prone to accelerate the rejection. Similarly, Wu *et al*[16] also shows that the intravenous injection of MSCs could shorten cardiac allograft survival time in rat heart transplantation model compared with injection of Ringer lactate solution, but they confirmed that intravenous injection of MSCs can migrate to allografts where acute rejection occurred, playing a restoration and protection role.

MSCs and liver transplantation

MSCs can significantly reduce the acute rejection of liver graft. Wan *et al* [17] recently reported that adipose tissue-derived

MSCs could significantly reduce acute rejection after transplantation in the rat orthotopic liver transplantation model. Compared with the control group, the ALT, AST, TBIL levels were significantly reduced in the MSCs group; interleukin-2 levels were significantly reduced, while interleukin-10 levels were significantly increased[18]. Likewise, MSCs can significantly reduce the acute rejection of liver allograft in rats. More significantly, they also found the migration of MSCs to the liver[19]. These outcomes indicate an important role of soluble cytokine in suppressing acute rejection after transplantation, possibly one of the mechanisms of MSCs inducing immune tolerance.

MSCs can significantly improve liver function after liver failure, and repair damaged liver. Gene-modified MSCs can highly express hepatocyte growth factor, significantly improve graft function and promote regeneration of liver transplant[20]. In the rat model of fulminant hepatic failure, MSCs can reverse liver failure efficiently, accelerate liver regeneration, significant improve liver function[21]. Through the treatment of inflammatory response, MSCs enhance the function of chemokines, change the migration of white blood cells, as well as play a role in repairing damaged tissue, but the molecular mechanism is not clear.

MSCs and renal transplantation

Acute and chronic injury after transplantation is a complex pathophysiological process, including ischemia, inflammation and immune mechanisms. *In vivo* and *in vivo* experimental studies have both demonstrated the regulatory effect of MSCs, which play a therapeutic effect through a variety of mechanisms. During *in vitro* experiments, the donor MSCs can significantly inhibit the allogeneic antigen receptor-stimulated T lymphocyte proliferation in renal transplant patients before and after transplantation[22]. The third party, human MSCs, can regulate humoral immunity, inhibit alloreactive-specific antibody production, in particular, significantly inhibit the production of interleukin-5 [23]. However, Zhang *et al* [24] reported that, although the intravenous infusion of MSCs can significantly prolong the survival time of renal graft in allogeneic rat kidney transplantation model, its efficacy is still inferior to cyclosporine A alone treatment, this may be related to MSCs injection approach and experimental conditions.

Morigi *et al* [25] found that MSCs transplanted into the damaged kidney could differentiate into renal tubular epithelial cells, thereby restoring renal structure and function in the cisplatin-induced renal injury model. Research has also confirmed that the MSCs improving the renal function is more prone to complex paracrine effect [26]. Therefore, intravenous and local injection of autologous and allogeneic MSCs can migrate and plant to the kidney, as well as improve renal function, but its mechanism is unclear.

Although in different pathological conditions, the mechanism of MSCs inducing immune tolerance and a new capacity of transforming into renal tissues need further study, but in renal transplantation, MSCs inherent immunoregulation ability and potential tissue repair capacity have broad application prospects for the prevention and treatment of acute and chronic rejection.

MSCs and pancreas transplantation

Syngeneic islet combined with MSCs transplantation, through temporal immunosuppressive effect, may make long-term survival of islet grafts, and achieve a normal serum insulin levels and normal blood glucose levels. Recipient serum interferon-γ and TNF-α levels decrease, while the $CD4^+$ T cells secreting interleukin-10 levels elevate[27]. Itakura *et al*[28] studies have shown that, MSCs can induce and produce hematopoietic chimerism, then induce immune tolerance in the allogeneic rat model of islet transplantation. Under the non-myeloid pretreatment conditions, the co-transplantation of MSCs is very easy to induce production of mixed chimerism; half of the rats exhibited a stable hematopoietic chimerism and donor-specific immune tolerance; the donor-derived skin grafts and islet re-transplantation are not rejected, but the skin grafts from a third party are rejected. Therefore, inducing the production of hematopoietic chimerism is one of the mechanisms of MSCs inducing organ transplantation immune tolerance.

Clinical application of MSCs

The present application of MSCs in the clinical field is mainly for the treatment of acute graft-versus-host disease. After the patients with steroid hormone-induced graft-versus-host disease were injected with MSCs, all of the symptoms disappeared in patients, with digestive tract to be repaired in 6 patients and liver to be repaired in 1 patient[29]. Among MSCs-treated 40 cases of acute and chronic graft-versus-host disease, more than 47% (47.5%) were completely effective, 22.5% improved, 10% stable, and only 17.5% invalid. From 6 weeks to 3.5 years after transplantation, more than half of patients are still alive[30].

MSCs have a positive effect on hematopoietic function and rapidly recover hematopoietic function, which may be attributed to its induced immune tolerance. When hematopoietic stem cell transplantation is used for treating advanced acute leukemia, hematopoietic stem cells of the grafts may be quickly accepted after the injection of the HLA-mismatched MSCs[31]. In a European clinical I–II phase study, allogeneic hematopoietic stem cells were given in combination with MSCs, results showed an accelerated recovery of leukocyte[32]. In a multi-center clinical trial, the combined treatment of HLA-matched hematopoietic stem cells and MSCs from the same cell, can restore hematopoietic system (including peripheral mononuclear cells and platelets) in the myeloma patients after chemotherapy, rapidly improve the absolute count of neutrophils and induce a 100% donor chimerism[28]. MSCs transplantation into immune-suppressed patients, neither generate allogeneic antibodies for MSCs, nor exclude the fetal calf serum in culture medium[33]. These results indicated a significant therapeutic effect of MSCs, however, the scheme of using MSCs to treat graft-*versus*-host disease, that is an appropriate dose and frequency, requires further analysis. Although the mechanisms underlying MSCs *in vivo* immune suppression remain unclear, considerable results have been achieved in the treatment of autoimmune diseases, GVHD, and prolonging the survival time of organ transplantation.

MSCs *in vivo* migration and transformation

Because MSCs have been widely used in tissue repair, treatment of graft-versus-host disease and inducing transplantation tolerance, MSCs *in vivo* migration, transformation and plating in specific organs become the focus

of study. MSCs express homing receptors, tend to plant in the target organs and inflammatory tissue [15, 34], but whether these receptors are able to make mesenchymal stem cells migrate to the target organ is unclear. Sackstein *et al*[35] have proved that *in vitro* cultured MSCs surface molecule CD44 can affect its *in vivo* migration. By intravenous injection, MSCs are easier to migrate to lung and liver. In order to increase the MSCs number in the target organ, intra-arterial infusion has also been applied[36], local injection also achieved the desired effect[37], thus the duplicated multi-lesion injection of MSCs can obtain effective dose in organ transplantation.

In short, MSCs can colonization in most organs in healthy experimental animals, with the ability to migrate to inflammation or injury sites, can stimulate primitive progenitor cells proliferation and exhibit directional differentiation, re-construct and promote the injured tissue by secreting growth factors and matrix. However, it's unclear that which locations *in vivo* are prone to be effectively treated, the advantages and disadvantages between systemic and local injections.

MSCs safety

Intravenous infusion of *in vitro* amplified MSCs is considered to be relatively safe, which is based on that MSCs have no immunogenicity and can produce inhibitory effect on allogeneic immune response, also inhibit tumor cell growth. Clinical studies have confirmed that intravenous infusion of MSCs has no side effects[30]. Studies have shown that MSCs exhibit APCs-like functions and can activate the immune response under appropriate conditions[38]; when human MSCs are transplanted into the animals of intact immune system, the MSCs do not have the characteristics of immune privilege[39]; the long-term *in vitro* cultured MSCs may transform into tumor cells[40]; MSCs can promote the acceptance of transplanted tumor cells and accelerate the transfer of cancer cells[41].

Although the security of MSCs infusion is controversial in clinical reports, in theory, MSCs may promote tumor growth through direct contact or suppress anti-tumor effects of the immune system. MSCs immune suppression effect and anti-inflammatory effects may temporally suppress the immune system before disappearring *in vivo.* Therefore, the future focus is MSCs suppression on the immune system, ectopic tissue formation capabilities, potential malignant transformation and immunogenicity.

DISCUSSION

MSCs have a variety of advantages such as wide sources, easily separated and amplified *in vitro*, stable biological characteristics and immunological characteristics after subculture, can migrate *in vivo* and plant in the target organ, repair damaged tissue; possess low immunogenicity, escape cytotoxic T lymphocytes and natural killer, as well as immune regulation, these are the basis for the induction of immune tolerance. MSCs immunological characteristics may be cross-species, which provides a wider space for the study of its immunological characteristics.

The MSCs used in pre-clinical trials should be faced the following issues: ① The mechanisms of MSCs *in vivo* immune regulation and inducing transplantation tolerance remain unclear. ② MSCs *in vivo* migration, transformation, and planting in the target organ remain unclear. ③ The security of MSCs applied *in vivo* (for the immune system suppression, directional differentiation and potential malignant transformation) remains controversial. ④ The present achievements obtained in rodents studies lack of large animal model.

REFERENCES

[1] Pittenger MF, Mackay AM, Beck SC, et al. Multilineage potential of adult human mesenchymal stem cells. Science. 1999; 284(5411): 143-147.
[2] Casiraghi F, Azzollini N, Cassis P, et al. Pretransplant infusion of mesenchymal stem cells prolongs the survival of a semiallogeneic heart transplant through the generation of regulatory T cells. J Immunol. 2008;181(6):3933-3946.
[3] Bian L, Guo ZK, Wang HX, et al. In vitro and in vivo immunosuppressive characteristics of hepatocyte growth factor-modified murine mesenchymal stem cells. In Vivo. 2009; 23(1):21-27.
[4] Horwitz EM, Le BK, Dominici M, et al. Clarification of the nomenclature for MSC: The International Society for Cellular Therapy position statement. Cytotherapy. 2005;7(5):393-395.
[5] Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. Cytotherapy. 2006;8(4):315-317.
[6] 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(1): 42-48.
[7] Guo Z, Li H, Li X, et al. In vitro characteristics and in vivo immunosuppressive activity of compact bone-derived murine mesenchymal progenitor cells. Stem Cells. 2006;24(4): 992-1000.
[8] Xu G, Zhang L, Ren G, et al. Immunosuppressive properties of cloned bone marrow mesenchymal stem cells. Cell Res. 2007; 17(3):240-248.
[9] Aksu AE, Horibe E, Sacks J, et al. Co-infusion of donor bone marrow with host mesenchymal stem cells treats GVHD and promotes vascularized skin allograft survival in rats. Clin Immunol. 2008;127(3):348-358.
[10] Liu H, Kemeny DM, Heng BC, et al. The immunogenicity and immunomodulatory function of osteogenic cells differentiated from mesenchymal stem cells. J Immunol. 2006;176(5): 2864-2871.
[11] Sbano P, Cuccia A, Mazzanti B, et al. Use of donor bone marrow mesenchymal stem cells for treatment of skin allograft rejection in a preclinical rat model. Arch Dermatol Res. 2008; 300(3):115-124.
[12] Chabannes D, Hill M, Merieau E, et al. A role for heme oxygenase-1 in the immunosuppressive effect of adult rat and human mesenchymal stem cells. Blood. 2007;110(10): 3691-3694.
[13] Popp FC, Eggenhofer E, Renner P, et al. Mesenchymal stem cells can induce long-term acceptance of solid organ allografts in synergy with low-dose mycophenolate. Transpl Immunol. 2008;20(1-2):55-60.
[14] Zhou HP, Yi DH, Yu SQ, et al. Administration of donor-derived mesenchymal stem cells can prolong the survival of rat cardiac allograft. Transplant Proc. 2006;38(9):3046-3051.
[15] Inoue S, Popp FC, Koehl GE, et al. Immunomodulatory effects of mesenchymal stem cells in a rat organ transplant model. Transplantation. 2006;81(11):1589-1595.
[16] Wu GD, Bowdish ME, Jin YS, et al. Contribution of mesenchymal progenitor cells to tissue repair in rat cardiac allografts undergoing chronic rejection. J Heart Lung Transplant. 2005; 24(12): 2160-2169.
[17] Wan CD, Cheng R, Wang HB, et al. Immunomodulatory effects of mesenchymal stem cells derived from adipose tissues in a rat orthotopic liver transplantation model. Hepatobiliary Pancreat Dis Int. 2008;7(1):29-33.
[18] Niu J, Liu B, Zhang YW, et al. Perfusion of MSCs transfected by human IL-10 gene prolonging survival of rat liver xenografts. Zhonghua Qiguan Yizhi Zazhi. 2009;30(7):398-402.
[19] Hong ZF, Huang XJ, Yin ZY, et al. Immunosuppressive function of bone marrow mesenchymal stem cells on acute rejection of liver allografts in rats. Transplant Proc. 2009;41(1):403-409.
[20] Yu Y, Yao AH, Chen N, et al. Mesenchymal stem cells over-expressing hepatocyte growth factor improve small-for-size liver grafts regeneration. Mol Ther. 2007;15(7): 1382-1389.
[21] Parekkadan B, van Poll D, Suganuma K, et al. Mesenchymal stem cell-derived molecules reverse fulminant hepatic failure. PLoS One. 2007;2(9):e941.

[22] Crop MJ, Baan CC, Korevaar SS, et al. Donor-derived mesenchymal stem cells suppress alloreactivity of kidney transplant patients. Transplantation. 2009;87(6):896-906.
[23] Comoli P, Ginevri F, Maccario R, et al. Human mesenchymal stem cells inhibit antibody production induced in vitro by allostimulation. Nephrol Dial Transplant. 2008;23(4):1196-1202.
[24] Zhang W, Qin C, Zhou ZM. Mesenchymal stem cells modulate immune responses combined with cyclosporine in a rat renal transplantation model. Transplant Proc. 2007;39(10):3404-3408.
[25] Morigi M, Imberti B, Zoja C. Mesenchymal stem cells are renotropic, helping to repair the kidney and improve function in acute renal failure. J Am Soc Nephrol. 2004;(15):1794-1804.
[26] Kunter U, Rong S, Djuric Z. Transplanted mesenchymal stem cells accelerate glomerular healing in experimental glomerulonephritis. J Am Soc Nephrol. 2006;(17):2202-2212.
[27] Solari MG, Srinivasan S, Boumaza I, et al. Marginal mass islet transplantation with autologous mesenchymal stem cells promotes long-term islet allograft survival and sustained normoglycemia. J Autoimmun. 2009;32(2):116-124.
[28] Itakura S, Asari S, Rawson J, et al. Mesenchymal stem cells facilitate the induction of mixed hematopoietic chimerism and islet allograft tolerance without GVHD in the rat. Am J Transplant. 2007; 7(2):336-346.
[29] Ringden O, Uzunel M, Rasmusson I, et al. Mesenchymal stem cells for treatment of therapy-resistant graft-versus-host disease. Transplantation. 2006;81(10):1390-1397.
[30] Le Blanc K, Frassoni F, Ball L, et al. Mesenchymal stem cells for treatment of steroid-resistant, severe, acute graft-versus-host disease: a phase II study. Lancet. 2008;371(9624):1579-1586.
[31] von Bonin M, Stolzel F, Goedecke A, et al. Treatment of refractory acute GVHD with third-party MSC expanded in platelet lysate-containing medium. Bone Marrow Transplant. 2009; 43(3):245-251.
[32] Ball LM, Bernardo ME, Roelofs H, et al. Cotransplantation of ex vivo expanded mesenchymal stem cells accelerates lymphocyte recovery and may reduce the risk of graft failure in haploidentical hematopoietic stem-cell transplantation. Blood. 2007;110(7): 2764-2767.
[33] Sundin M, Ringden O, Sundberg B, et al. No alloantibodies against mesenchymal stromal cells, but presence of anti-fetal calf serum antibodies, after transplantation in allogeneic hematopoietic stem cell recipients. Haematologica. 2007; 92(9):1208-1215.
[34] Herrera MB, Bussolati B, Bruno S, et al. Exogenous mesenchymal stem cells localize to the kidney by means of CD44 following acute tubular injury. Kidney Int. 2007; 72(4): 430-441.
[35] Sackstein R, Merzaban J S, Cain D W, et al. Ex vivo glycan engineering of CD44 programs human multipotent mesenchymal stromal cell trafficking to bone. Nat Med. 2008; 14(2):181-187.
[36] Behr L, Hekmati M, Fromont G, et al. Intra renal arterial injection of autologous mesenchymal stem cells in an ovine model in the postischemic kidney. Nephron Physiol. 2007;107(3):p65-p76.
[37] Poh KK, Sperry E, Young RG, et al. Repeated direct endomyocardial transplantation of allogeneic mesenchymal stem cells: safety of a high dose, "off-the-shelf", cellular cardiomyoplasty strategy. Int J Cardiol. 2007;117(3):360-364.
[38] Chan JL, Tang KC, Patel AP, et al. Antigen-presenting property of mesenchymal stem cells occurs during a narrow window at low levels of interferon-gamma. Blood. 2006;107(12): 4817-4824.
[39] Grinnemo KH, Mansson A, Dellgren G, et al. Xenoreactivity and engraftment of human mesenchymal stem cells transplanted into infarcted rat myocardium. J Thorac Cardiovasc Surg. 2004;127(5):1293-1300.
[40] Tolar J, Nauta AJ, Osborn MJ, et al. Sarcoma derived from cultured mesenchymal stem cells. Stem Cells. 2007; 25(2): 371-379.
[41] Karnoub AE, Dash AB, Vo AP, et al. Mesenchymal stem cells within tumour stroma promote breast cancer metastasis. Nature. 2007;449(7162):557-563.

间充质干细胞诱导移植耐受的研究进展及可能机制*★

张雅永，蒋立虹，侯宗柳(昆明医学院附属延安医院，昆明市延安医院心胸外科，云南省昆明市 650051)

张雅永★，男，1981 年生，河北省定兴县人，汉族，昆明医学院在读硕士，主要从事心胸外科及移植免疫学方面的研究。

通讯作者：蒋立虹，博士，硕士生导师，昆明医学院附属延安医院，昆明市延安医院心胸外科，云南省昆明市 650051

摘要

背景：间充质干细胞能自我更新、高度增殖，具有多向分化潜能、低免疫原性及免疫调节特性。在体内和体外均能调节同种异体免疫反应，在实体器官移植中发挥着重要作用，有望成为诱导移植耐受的新途径。

目的：综述间充质干细胞在实体器官移植中的应用及其免疫调节机制的最新进展。

方法：应用计算机检索 Pubmed 1994-01/2009-10 期间相关文章，运用 MeSH 主题词检索，检索词为“Mesenchymal Stem Cells，Mesenchymal Stem Cell Transplantation，Organ Transplantation，Transplantation Immunology，Immunologic Graft Enhancement，Graft vs Host Disease”，并限定文章语言种类为“English”。同时计算机检索万方数据库 1994-01/2009-10 期间相关文章，检索词为“间充质干细胞、器官移植、移植免疫”。纳入标准：文章所述内容应与间充质干细胞免疫学特性、器官移植中的应用及移植免疫进展研究相关。排除标准：重复研究或 Meta 分析类文章。

结果与结论：共收集到 200 篇相关文献，86 篇文献符合纳入标准。间充质干细胞具有低免疫原性及调节免疫调节特性，在诱导移植耐受和器官移植后组织修复中有着不可或缺的优势，其诱导免疫耐受的机制可能与可溶性因子、调节性 T 细胞、耐受性树突细胞、骨髓嵌合状态、抗炎和组织修复功能有关，并受间充质干细胞输入方式、剂量与时间的影响。

关键词：移植免疫；移植耐受；移植；间充质干细胞；干细胞

doi:10.3969/j.issn.1673-8225.2010.14.039

中图分类号: R394.2 文献标识码: A

文章编号: 1673-8225(2010)14-02652-05

张雅永，蒋立虹，侯宗柳.间充质干细胞诱导移植耐受的研究进展及可能机制[J].中国组织工程研究与临床康复，2010,14(14): 2652-2656.

[http://www.crter.org http://cn.zglckf.com]

(Edited by Yang Y/Wang L)

*基金资助：云南省社会发展科技计划项目(2007CA005)。

*利益冲突：无其他利益冲突。

***此问题的已知信息：**间充质干细胞能自我更新、高度增殖，具有多向分化潜能及免疫调节特性，在体内外均能调节同种异体免疫反应，诱导免疫耐受。其诱导免疫耐受的机制可能与可溶性因子、调节性 T 细胞、耐受性树突细胞、骨髓嵌合状态、抗炎和组织修复功能有关，并受到间充质干细胞输入方式、剂量与时间的影响。

***本综述增加的新信息：**随着对间充质干细胞认识的深入和存在问题的进一步阐明，间充质干细胞在器官移植领域将有着广阔的临床应用前景。