International Journal of
Rheumatic Diseases

International Journal of Rheumatic Diseases 2015; **18:** 164–171

SPECIAL ISSUE ON LUPUS IN ASIA-PACIFIC REGION

Mesenchymal stem cells transplantation for systemic lupus erythematosus

Jun LIANG and Lingyun SUN

Department of Immunology and Rheumatology, the Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing, Jiangsu, China

Abstract

Mesenchymal stem cells are a rare subset of stem cells residing in the bone marrow where they closely interact with hematopoietic stem cells and support their growth and differentiation. They can suppress proliferation or functions of many immune cells such as T cells, B cells, natural killer cells and dendritic cells. Recently, a substantial progress has been made in the field of mesenchymal stem cell transplantation. Experimental and clinical data suggest that this therapy has been a promising strategy for severe and refractory systemic lupus erythematosus.

Key words: mesenchymal stem cells, systemic lupus erythematosus, transplantation.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease with diverse clinical symptoms due to multiple organ involvement, leading to a high mortality and mortality. Therapy with corticosteroids and cyclophosphamide (CTX) or mycophenolate mofetil achieved complete remission rates of approximately 80% in lupus nephritis[1] patients. Some refractory patients experienced progressive disease resulting in tissue damage, physical and psychosocial disability, or even death. In addition, significant concerns, including opportunistic infections and secondary malignancy remain regarding these immunosuppressive treatments. So, more effective and safer treatments for SLE are needed. In recent decades, stem cell transplantation has emerged as a new treatment modality for refractory and severe SLE, mainly hematopoietic stem cell transplantation (HSCT) and mesenchymal stem cell transplantation (MSCT). This review mainly will focus on the rationale and current status of MSCT in treatment of SLE.

Correspondence: Dr Lingyun Sun, Department of Rheumatology and Immunology, The Affiliated Drum Tower Hospital of Nanjing University Medical School, 321 Zhongshan Road, Nanjing, Jiangsu, CN 210008, China.
Email: lingyunsun@nju.edu.cn

HSCT IN SLE: EFFECTS AND PROBLEMS

HSCT for SLE should be discussed first, because it was used earlier than MSCT and inspired the development of the 'dream' of MSCT for lupus treatment.

More than two decades ago, there was significant evidence that autoimmune diseases originate from defects that reside within hematopoietic stem cells (HSCs). Isolated HSCs are sufficient to transfer autoimmune diseases from susceptible mice to normal mice.[2] Murine autoimmune disorders can be prevented and treated after transplantation with allogeneic T cell-depleted or whole bone marrow.[3] Another stimulating finding is that serendipitous remissions of autoimmune disease were observed in patients receiving HSCT for coexisting hematological disorders.[4] Following these observations, Ikehara *et al.* have proposed autoimmune diseases as HSC disorders.

SLE is a prototypical and systemic autoimmune disease and its exact etiopathogenesis remains unclear. It is believed that genetic predisposition and environmental factors such as UV exposure, infections and stress, or combination of both may contribute to the develop-

ment of SLE. Despite different involved factors, the basic and final pathway is the aberration of lots of immune cells, including T cells, B cells and monocytic lineage cells, resulting in T cell deficiencies, polyclonal B cell activation, autoantibody production and immune complex formation. To date, several more direct researches have revealed abnormal HSCs in SLE. $CD34^+$ cells in peripheral blood of SLE patients are markedly reduced with a limited capacity of granulocyte-macrophage colony-forming units, even when the disease is in clinical remission and despite patients receiving standard treatment.[5,6] Increased apoptosis of $CD34^+$ cells in patients with SLE, the possible underlying cause of the observed decreased progenitor cell levels, was confirmed by Westerweel.[7] Furthermore, sera obtained from SLE patients were found to reduce proliferation of autologous HSCs and induce apoptosis of allogeneic HSCs isolated from the peripheral blood or bone marrow of healthy controls.[8] Other studies have demonstrated that the expression of some surface markers, such as CD95, CD123 and CD166, were markedly increased in $CD34^+$ cells of SLE patients and correlated with overall lupus activity.[9] No doubt, defects in HSCs will change the fate of immune cells or exert an irreversible modification in the development of these cells. But up to now, no one can validate which is the most prominent factor, genetic or acquired, in the etiology of HSC abnormality in SLE. This issue is critical to know because it will ultimately determine the most appropriate source for HSCT, autologous or allogeneic. If HSC defects are from an acquired response, autologous HSCT would be a curative method after eradicating the risk cause, and reconstructing the immune system by deleting the auto-reactive lymphocyte clone of hematopoietic origin. However, if a genetic condition is dominant, allogeneic HSCT would be a more logical and more effective approach, substituting the genetic propensity to HSC autoimmunity. Further research is needed to elucidate this problem about the truth of HSC deficiency in SLE.

Following the first case report of autologous HSCT for SLE in 1997, SLE is rapidly becoming a major target for autologous transplants. Over the past 15 years, more than 200 SLE patients worldwide have received HSCT as a salvage therapy, mostly autologous, according to one of the latest review articles. The two largest and convincing datasets were published by Northwestern University in 2004 ($n = 50$, mean follow-up, 29 months)[10] and by the European Group for Bone Marrow Transplantation (EBMT) in 2005 ($n = 62$, mean follow-up, 20 months).[11] There is remarkable clinical benefit after autologous HSCT for SLE as reflected by improvement of SLE disease activity index (SLEDAI) scores, autoantibody and complement levels, renal and pulmonary dysfunction, but at a high price.[12] In the former study, overall 5-year survival was 84%, and probability of disease-free survival at 5 years following HSCT was 50%. In the latter study, the 3-year probabilites of survival was 78%.

It seems that allogeneic HSCT, known to be curable in the murine models, has developed much more slowly than autologous HSCT, because of fears of graft versus host disease (GVHD). For the time being, only a few case reports and small series have been published on the effect of allogeneic HSCT in treatment of SLE. Mostly, patients received an allogeneic HSCT for SLE and concomitant hematological diseases, and obtained complete remission from both conditions. However, despite these encouraging results, there remain some problems in the field of HSCT treatment in SLE. A major one would be the high rate of transplantation-related mortality (TRM), which was reported as 14% in the EBMT registry and 4% in North American cases,[10,11] the different rates between two studies could be attributed to the difference of disease activity, patient selection, the conditioning regimen, and supportive care during and after transplantation.[12] Toxicity from the conditioning regimen may be the most important cause of TRM. The conditioning regimen intensity was reported to be correlated directly to the rate of TRM, from 3% in patients with low-intensity conditioning to 14% in patients with high-intensity conditioning. No-responders and relapse after the transplantation are the second issue. In the EBMT registry data, about one-third (17/50) of SLE patients receiving HSCT did not respond by 6 months, one-third (10/31) of whom later relapsed to some degree after a median 6 (3–40) months.[13] The relapse was associated with negative anti-double-stranded DNA (anti-dsDNA) antibodies before HSCT and intensity of the conditioning. It was found that disease relapse was 31% at 3 years for patients with high-intensity conditioning and almost 70% in patients with low-intensity conditioning. In addition, the third problem arises from GVHD. Allogeneic HSCT appears to offer curative potential, but the high risk of GVHD which has high occurance and is directly responsible for the worse outcome of allogeneic transplantation in hematologic disease, has greatly limited its broader application in autoimmune disease. GVHD are known to be associated with acute organ toxicity, an increase in TRM,

delayed reconstitution of the immune system, persistence of autoreactive lymphocytes, and an increase in the rate of opportunistic infection.

So, neither autologous nor allogeneic HSCT has been the best supposed stem cell therapy for SLE, unless ongoing and future clinical investigations will bring about overwhelmingly solid data. Recently, MSCT has emerging as another promising new stem cell therapy for lupus.

BIOLOGIC CHARACTERISTICS OF MSCS

Mesenchymal stem cells (MSCs), originally described in the 1960s as bone-forming cells in bone marrow (BM), have attracted major interest over the last decade. A variety of names have been used to describe the plastic-adherent and colony-forming cell population isolated from bone marrow, such as mesenchymal stromal cells, marrow stromal cells, multipotent stromal cells and stromal stem cells. Recently, the term mesenchymal stem cells has been most often employed. They show pluripotent activities and behaviors similar to other adult stem cells, differentiating into many different cell types of mesodermal origin, as well as ectodermal and endodermal origin. Besides bone marrow, MSCs can be isolated from almost all adult tissues, including adipose tissue, synovium, placenta, skeletal muscle, lung, liver and a variety of fetal tissues, such as amniotic fluid, cord blood and umbilical cord (UC). Many authors have found that UC-derived MSCs (UC-MSCs) can be cultured much more efficiently and have higher proliferative potential than BM-derived MSCs (BM-MSCs).[14]

A large body of evidence has demonstrated that human MSCs can suppress, in a dose-dependent manner, the proliferative response of many allogeneic immune cells, such as T cells, B cells, natural killer cells, and dendritic cells.[15–17] MSCs also can alter the cytokine secretion profiles of these cells to induce a more anti-inflammatory or tolerant phenotype.[18] MSCs have also been found to release a number of soluble factors involved in MSC-mediated immunoregulation: indoleamine 2, 3-dioxygenase, interleukin-6 (IL-6) and human leukocyte antigen-G5.[19,20] Several adhesion molecules expressed by MSCs, such as vascular cell adhesion molecule-1, intercellular adhesion molecule-2 and lymphocyte function-associated antigen-3, are involved in the interaction between MSCs and immune cells.[21,22] Other studies have suggested that human MSCs, not just as third-party cells, can also act as non-professional antigen-presenting cells and suppress the cytotoxic effects of Ag-primed T effector cells in a short time.[23]

MSCs express low levels of major histocompatibility (MHC) class I molecules and do not express MHC class II or co-stimulatory molecules such as CD40, CD40L, CD80 or CD86. These properties make MSCs immune-privileged cells, able to escape immune recognition and clearance, then are unable to activate alloreactive T cells. *In vitro* results have confirmed that using MHC-mismatched MSCs does not trigger proliferative T-cell response in the allogeneic mixed lymphocyte reaction.[24]

The anti-proliferative and immunomodulatory properties of MSCs combined with their immunological privilege will offer a new strategy in treatment of numerous autoimmune inflammatory diseases. So far, MSCs have been applied successfully in patients with multiple sclerosis, neuromyelitis optica, chronic and acute GVHD.

MSC DEFICIENCY IN SLE

The story of MSC deficiency in SLE initially began with some experimental findings. Transplantation of allogeneic HSCs with bones to recruit MSCs was indeed found to prevent the recurrence of autoimmune diseases in MRL/lpr mice, a murine model of lupus, whereas relapse easily happened if HSCs alone were infused.[25] Soon after, Kushida *et al.*[26] also confirmed the transplantation with allogeneic HSCs and MSCs increased the survival rate in MRL/lpr mice, but not conventional bone marrow transplantation. Another interesting finding was that MSCs in SLE patients failed to support the growth of allogeneic CD34+ blood cells.[5] These findings have made some researchers try to clarify if there are some MSC defects existing in lupus patients.

Up to now, many researchers have shown that BM-MSCs, from SLE patients and lupus mouse models, were structurally and functionally abnormal compared with respective control groups. MSCs from SLE patients grew slower than those of normal controls, aged more quickly and lost vitality sooner during passage. The cells from lupus patients, compared to controls, were defective in secreting transforming growth factor β, IL-6 and IL-7.[27] Nie and El-Badri also confirmed structural and functional defects in MSC populations from SLE patients and lupus-prone BXSB mice with bigger appearance, slow growth rate, increased telomerase activity, reduced level of proliferation and gap junction protein.[28,29] Moreover, our team studies have showed that BM-MSCs from MRL/lpr mice displayed impair-

ment of osteogenic differentiation verified by decreased mineralization and osteogenic gene expression, and impairment of adipogenic differentiation proven by reduced lipid-specific Oil red O-positive cells and adipocyte-specific gene expression.[30] Other results also demonstrated that BM-MSCs from SLE patients have impaired osteoblastic differentiation which was reduced compared with that from healthy controls. The activated nuclear factor (NF)-κB signaling in SLE BM-MSCs inhibits bone morphogenic protein-2 induced osteoblastic differentiation through the BMP/Smad signaling pathway, while addition of pyrollidine dithiocarbamate, an NF-κB inhibitor, to lupus BM-MSCs could partially reverse these effects.[31]

Besides impaired proliferation and differentiation capacities, BM-MSCs from SLE patients have been found to have abnormal apoptosis and senescence, with upregulated expression of Fas and tumor necrosis factor-α receptors via their activation.[32,33] In addition, MSCs from SLE patients display abnormal F-actin cytoskeleton, which leads to impairment of migration capacity of MSCs. The authors suggest that the abnormality may result from the high oxidation status via downregulation of RhoA.[34]

While all these results have stressed deficiency in lupus MSC populations and give a strong impetus for MSCT in lupus treatment, it is difficult to claim such abnormality is from genetic or acquired factors, for now at least. This issue is equally important as that in HSCT, because it will ultimately determine the most suitable source for MSCT, autologous or allogeneic.

Indeed, one study demonstrate that BM-MSCs from 11 SLE patients all have a normal karyotype despite abnormal functions,[27] indicating that the genetic event may not be a main source for the defective MSCs. Yet, some animal experiment results are more convincing. Zhou *et al.* and Sun *et al.*[30,35] have reported the successful transplantation of human BM-MSCs to MRL/lpr mice, resulting in significantly reduced serum levels of anti-ds DNA antibodies and 24-h proteinuria, as well as complement C3 in renal tissue. Other data have further verified that only allogeneic sources of MSC infusion, but not autologous lupus-derived sources of MSCs, improved survival, stabilized proteinuria and decreased glomerular immunoglobulin G (IgG) deposition, in both MRL/lpr and (NZB × NZW)F1 mice.[36] Recently, Carrion and coworkers[37] have showed that autologous BM-MSC treatment did not modify initial disease activity in two SLE patients during 14 weeks of follow-up in spite of increasing $CD4^+CD25^+FoxP3^+$cell counts. All these evidences have directly or indirectly illustrated an acquired deficiency of lupus MSCs and favored allogeneic rather than autologous MSCT as an effective treatment for patients with lupus.

ALLOGENEIC MSCT IN SLE PATIENTS

The first report of MSC infusions in humans was published in 1995, demonstrating the safety of *ex vivo* expansion and subsequent infusion of autologous MSCs in 15 patient volunteers. From then on, MSCT has been steadily reported as a promising tool in the promotion of engraftment, management graft failure, prevention or treatment of GVHD after HSCT, and treatment of several autoimmune diseases.[38–40] Perhaps the most remarkable results of human MSC therapy are emerging now from clinical trials aimed at severe and refractory SLE patients,[41] although the mechanisms by which MSCs exert their immunomodulatory functions are still incompletely understood, but most likely involve multiple pathways (Fig. 1).

At the time of this review, three clinical trials, registered using MSCT to treat SLE patients, are found at the National Institutes of Health (NIH) website (http://clinicaltrials.gov/), in which two are in recruiting status. Several studies have reported the outcome of MSCT in the treatment of SLE.

Maybe the Affiliated Drum Tower Hospital (ADTH) of Nanjing University Medical School is the first unit engaged in MSCT for treatment of autoimmune disease. From March 2007 through December 2013, more than 300 patients with persistently active SLE, who were refractory to standard treatment, underwent allogeneic MSCT. The pilot and preliminary findings about the first 15 patients was published in 2010.[42] All the patients were followed for more than 12 months, showing remarkable reductions of 24-h proteinuria and improvement of SLEDAI scores. Four subjects experienced significant improvement in their serum creatinine levels. Anti-dsDNA titers decreased at 1 month post-MSCT in all patients. They were all able to taper the doses of steroids and CTX, with two patients completely off CTX at 6-month follow-up. No GVHD and TRM were observed after the allogeneic MSCT.

In April 2007, UC-MSCs have been selected as another source of allogeneic transplantation, because they share most of the characteristics with BM-MSCs and have distinct advantages of higher proliferation, accessibility and lower risk of viral contamination.[43,44] Up to the present, more than 250 SLE patients have received allogeneic UC-MSCT in ADTH. The prelimin-

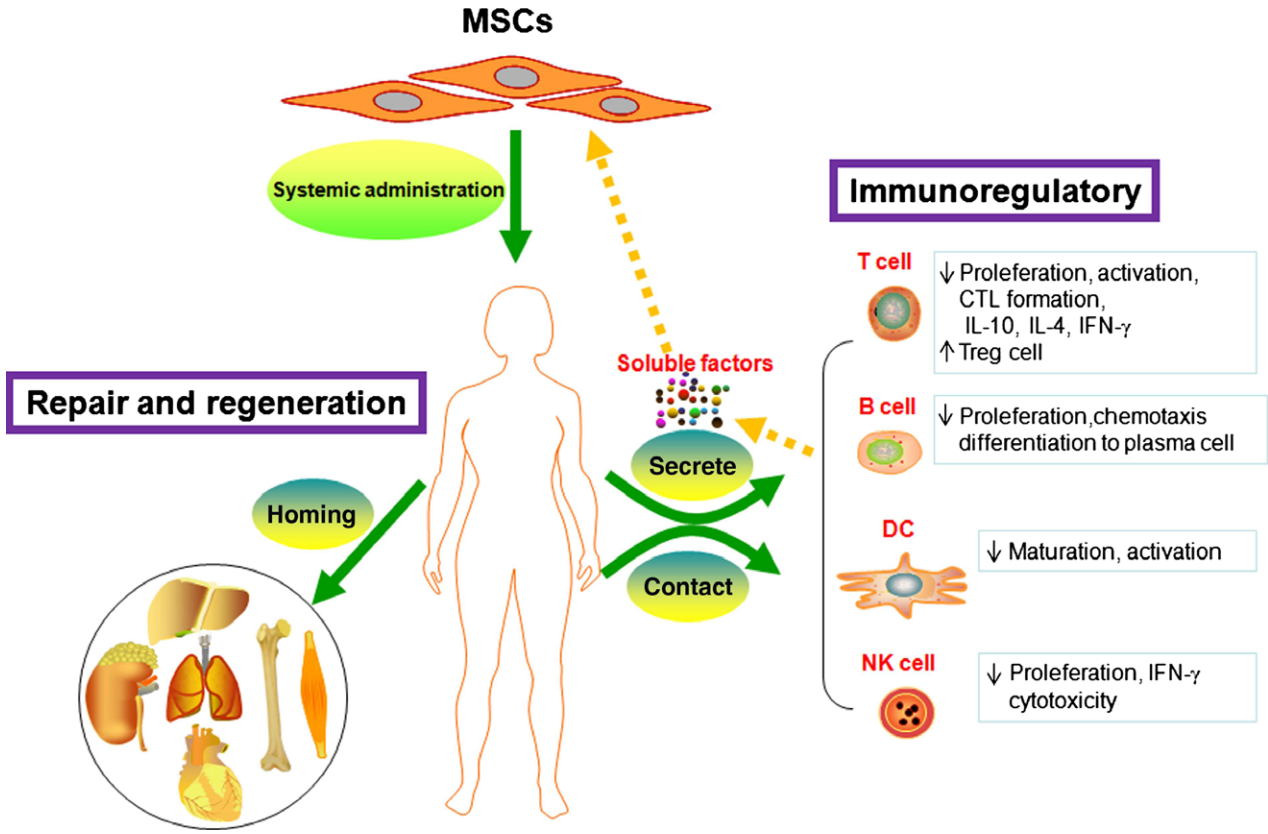

Figure 1 Mechanistic aspects of mesenchymal stem cell transplantation (MSCT) in treatment of systemic lupus erythematosus (SLE): the bidirectional interaction between MSCs and immune cells such as T cells, B cells, natural killer (NK) cells and dendritic cells; promotion of repair and regeneration after homing to the target organs.

ary data about 16 patients was published in 2010.[45] Significant improvements were observed, regarding the SLEDAI score, renal function and levels of serum antinuclear antibodies (ANA), anti-dsDNA antibody, serum albumin and complement component 3. No TRMs were found in allogeneic UC-MSCT, indicating a similar safe and effective therapy as allogeneic BM-MSCT. Moreover, the data collected from a multicenter clinical study about UC-MSCT in treatment of lupus patients have been published in 2014.[46]

Recently, a prospective, 4-year follow-up study was published, aiming to evaluate the long-term safety and efficacy of allogeneic MSCT in 87 treatment-resistant SLE patients.[47] Primary outcomes were rates of survival, disease remission and relapse, as well as transplantation-related adverse events. Secondary outcomes included changes of SLEDAI score and serologic features. The authors showed that the overall rate of survival was 94% (82/87). Complete clinical remission rate (CR) at 1 year was 28% (23/83), and rates of relapse at 1 year were 12% (10/83), confirmed by a multicenter clinical study of 40 refractory lupus patients being treated by UC-MSCT with 32.5% CR (13/40), 27.5% (11/40) partial remission (PR) and 16.7% relapse during 12 months follow-up, respectively. The overall rate of relapse during 4-year follow-up was 23% (20/87). Disease activity declined as revealed by significant changes in the SLEDAI score, levels of serum autoantibodies, albumin and complements. A total of five patients (6%) died after MSCT from non-treatment-related events in the 4-year follow-up, and no transplantation-related adverse event was observed.

These uncontrolled studies showed efficacy and safety of allogeneic MSCT in refractory SLE patients, albeit the length of follow-up is short. Further long-term follow-up results are needed to confirm this. Furthermore, randomized clinical trials are needed to compare allogeneic MSCT with HSCT and conventional treatments.

ISSUES RELATED TO MSCT

It is clear that MSCs have tremendous therapeutic potential. We may hear more about MSCT for the treatment of SLE or other autoimmune diseases, but further small phase I/II studies will not shed further light on the clinical benefit of MSCT. The future of this cell therapy will depend on more knowledge about biological capacities of MSCs, more information gained in larger prospective controlled trials and the end-points of such trials should concentrate not only on survival but also on relapse-free survival and quality of life.

There are still many issues remaining to be resolved in order to pave the way for MSCT in the treatment of lupus. One is how to get a standardization of cell products regarding heterogeneity, potency, impact of expansion media on phenotype, and suitability of the source. Factors such as the donor's age and growth conditions are likely to change expansion capability, potency and phenotype, even the surface markers of MSCs.[48] Recently, fibroblast growth factor and platelet-derived growth factor, often used to supplement the expansion media of human BM-MSCs, have been shown to induce the expression of MHC II molecules.[49] These MHC II molecules can functionally bind superantigens and induce the stimulation of responder lymphocytes, which may make MSC inflammatory cells but not immunosuppressive cells.

Long-term safety concerns remain another important issue. Although MSCs may exert therapeutic function through their immunosuppressive potential and immunogenicity, high immunosuppressive potential permits MSCs to suppress host immune response and develop infectious agents or tumor cells to escape. Recently, Liu and his colleagues reported the potential impact of allogeneic MSCT as an adjunctive therapy in 20 patients with poor graft function after allo-HSCT. However, their data show that within the first 100 days after MSCT, 13 patients developed 20 episodes of infection and six died from infections within the first 100 days of MSC transplantation. Moreover, five patients experienced cytomegalovirus-DNA viremia, and seven experienced Epstein–Barr virus (EBV)-DNA viremia within the first 100 days after MSC treatment; three of the latter developed EBV-associated post-transplant lymphoproliferative disorders within the follow-up period. Such a high incidence of infections should urge a greater understanding of MSC biology before their wide use in patients. Next, although transformation of MSCs has not been noted to date in the clinical trials using human MSCs, *in vitro* experiments demonstrate that murine BM-MSCs, after numerous passages, can confer risk of chromosomal instability and lead to malignant transformation.[50]

CONCLUSIONS

Lupus is not only hematopoietic but also a mesenchymal stem cell disease, in view of the defects in both HSCs and MSCs from SLE patients. Genetic and acquired factors may both contribute to cell deficiency, but the latter will be more predominant considering the curative efficacy of the allogeneic transplantation with its ability to provide a new system. The hazards of GVHD have limited greatly the clinical use of allogeneic HSCT. But, allogeneic MSCT will be superior and more attractive than allogeneic HSCT in lupus treatment, with its efficacy and safety in the preliminary experience. It will give a new platform in the treatment of refractory and severe SLE patients. Further advances are needed to establish safe criteria for the use of MSCT.

CONFLICT OF INTEREST

The authors declare that they have no competing interests. Jun Liang, drafted the manuscript and obtained funding; Lingyun Sun, drafted the manuscript, supported material and obtained funding.

ACKNOWLEDGMENT

Some studies reported in this review article were supported by grants from the National Natural Science Foundation of China (No. 81273304, No. 81120108021 and No. 812 02333).

REFERENCES

1 Chan TM, Li FK, Tang CS, *et al.* (2000) Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. *N Engl J Med* **343**, 1156–62.
2 Ikehara S, Kawamura M, Takao F *et al.* (1990) Organ -specific and systemic autoimmune diseases originate from defects in hematopoietic stem cells. *Proc Natl Acad Sci USA* **87**, 8341–4.
3 Ikehara S, Yasumizu R, Inaba M *et al.* (1989) Long-term observations of autoimmune-prone mice treated for autoimmune disease by allogeneic bone marrow transplantation. *Proc Natl Acad Sci USA* **86**, 3306–10.
4 Yin JA, Jowitt SN (1992) Resolution of immune-mediated diseases following allogeneic bone marrow transplantation for leukemia. *Bone Marrow Transplant* **9** (1), 31–3.

5 Papadaki HA, Boumpas DT, Gibson FM *et al.* (2001) Increased apoptosis of bone marrow CD34(+) cells and impaired function of bone marrow stromal cells in patients with systemic lupus erythematosus. *Br J Haematol* **115**, 167–74.

6 Moonen JR, de Leeuw K, van Seijen XJ *et al.* (2007) Reduced number and impaired function of circulating progenitor cells in patients with systemic lupus erythematosus. *Arthritis Res Ther* **9** (4), R84.

7 Westerweel PE, Luijten RK, Hoefer IE *et al.* (2007) Haematopoietic and endothelial progenitor cells are deficient in quiescent systemic lupus erythematosus. *Ann Rheum Dis* **66** (7), 865–70.

8 Tiefenthaler M, Bacher N, Linert H *et al.* (2003) Apoptosis of CD34+ cells after incubation with sera of leukopenic patients with systemic lupus erythematosus. *Lupus* **12** (6), 471–8.

9 Sun LY, Zhou KX, Feng XB *et al.* (2007) Abnormal surface markers expression on bone marrow CD34+ cells and correlation with disease activity in patients with systemic lupus erythematosus. *Clin Rheumatol* **26** (12), 2073–9.

10 Gratwohl A, Passweg J, Bocelli-Tyndall C *et al.* (2005) Autologous hematopoietic stem cell transplantation for autoimmune diseases. *Bone Marrow Transplant* **35**, 869–79.

11 Burt RK, Traynor A, Statkute L *et al.* (2006) Nonmyeloablative hematopoietic stem cell transplantation for systemic lupus erythematosus. *JAMA* **295** (5), 527–35.

12 Tyndall A (2011) Successes and failures of stem cell transplantation in autoimmune diseases. *Hematology Am Soc Hematol Educ Program* **2011**, 280–4.

13 Jayne D, Passweg J, Marmont A *et al.* (2004) Autologous stem cell transplantation for systemic lupus erythematosus. *Lupus* **13** (3), 168–76.

14 Chen MY, Lie PC, Li ZL, Wei X (2009) Endothelial differentiation of Wharton's jelly-derived mesenchymal stem cells in comparison with bone marrow-derived mesenchymal stem cells. *Exp Hematol* **37** (5), 629–40.

15 Nauta AJ, Fibbe WE (2007) Immunomodulatory properties of mesenchymal stromal cells. *Blood* **110**, 3499–506.

16 Jiang XX, Zhang Y, Liu B *et al.* (2005) Human mesenchymal stem cells inhibit differentiation and function of monocyte-derived dendritic cells. *Blood* **105**, 4120–6.

17 Sotiropoulou PA, Perez SA, Gritzapis AD *et al.* (2006) Interactions between human mesenchymal stem cells and natural killer cells. *Stem Cells* **24**, 74–85.

18 Aggarwal S, Pittenger MF (2005) Human mesenchymal stem cells modulate allogeneic immune cell responses. *Blood* **105** (4), 1815–22.

19 Uccelli A, Moretta L, Pistoia V (2008) Mesenchymal stem cells in health and disease. *Nat Rev Immunol* **8** (9), 726–36.

20 Carrion FA, Figueroa FE (2011) Mesenchymal stem cells for the treatment of systemic lupus erythematosus: is the cure for connective tissue diseases within connective tissue? *Stem Cell Res Ther* **2** (3), 23.

21 Tse WT, Pendleton JD, Beyer WM, Egalka MC, Guinan EC (2003) Suppression of allogeneic T-cell proliferation by human marrow stromal cells: implications in transplantation. *Transplantation* **75**, 389–97.

22 Majumdar MK, Keane-Moore M, Buyaner D *et al.* (2003) Characterization and functionality of cell surface molecules on human mesenchymal stem cells. *J Biomed Sci* **10**, 228–41.

23 Potian JA, Aviv H, Ponzio NM *et al.* (2003) Veto-like activity of mesenchymal stem cells: functional discrimination between cellular responses to alloantigens and recall antigens. *J Immunol* **171**, 3426–34.

24 Le Blanc K, Tammik C, Sundberg B *et al.* (2003) Mesenchymal stem cells inhibit and stimulate mixed lymphocyte cultures and mitogenic responses independently of the major histocompability complex. *Scand J Immunol* **57**, 11–20.

25 Ishida T, Inaba M, Hisha H *et al.* (1994) Requirement of donor-derived stromal cells in the bone marrow for successful allogeneic bone marrow transplantation. Complete prevention of recurrence of autoimmune diseases in MRL/MP-Ipr/Ipr mice by transplantation of bone marrow plus bones (stromal cells) from the same donor. *J Immunol* **152** (6), 3119–27.

26 Kushida T, Inaba M, Hisha H *et al.* (2001) Crucial role of donor-derived stromal cells in successful treatment for intractable autoimmune diseases in MRL/lpr mice by BMT via portal vein. *Stem Cells* **19**, 226–35.

27 Sun LY, Zhang HY, Feng XB *et al.* (2007) Abnormality of bone marrow-derived stem cell in patients with systemic lupus erythematosus. *Lupus* **16**, 121–8.

28 Nie Y, Lau C, Lie A, Chan G, Mok M (2010) Defective phenotype of mesenchymal stem cells in patients with systemic lupus erythematosus. *Lupus* **19**, 850–9.

29 El-Badri NS, Hakki A, Ferrari A, Shamekh R, Good RA (2008) Autoimmune disease: is it a disorder of the microenvironment? *Immunol Res* **41** (1), 79–86.

30 Sun L, Akiyama K, Zhang H *et al.* (2009) Mesenchymal stem cell transplantation reverses multi-organ dysfunction in systemic lupus erythematosus mice and humans. *Stem Cells* **27**, 1421–32.

31 Tang Y, Xie H, Chen J *et al.* (2012) Activated NF-kB in bone marrow mesenchymal stem cells from SLE patients inhibits osteogenic differentiation through down-regulating Smad signaling. *Stem Cells Dev* **22** (4), 668–78.

32 Gu Z, Cao X, Jiang J *et al.* (2012) Upregulation of p16INK4A promotes cellular senescence of bone marrow-derived mesenchymal stem cells from systemic lupus erythematosus patients. *Cell Signal* **24** (12), 2307–14.

33 Li X, Liu L, Meng D *et al.* (2012) Enhanced apoptosis and senescence of bone-marrow-derived mesenchymal stem cells in patients with systemic lupus erythematosus. *Stem Cells Dev* **21** (13), 2387–94.

34 Shi D, Li X, Sun L (2012) High oxidation status induced the rearrangement of F-actin cytoskeleton of bone marrow-derived mesenchymal stem cells in patients with systemic lupus erythematosus via downregulation of RhoA signaling pathway. *Int J Rheum Dis* **15** (Suppl 1), 26–8.
35 Zhou K, Zhang H, Jin O *et al.* (2008) Transplantation of human bone marrow mesenchymal stem cell ameliorates the autoimmune pathogenesis in MRL/lpr mice. *Cell Mol Immunol* **5** (6), 417–24.
36 Gu F, Molano I, Ruiz P, Sun L, Gilkeson GS (2012) Differential effect of allogeneic versus syngeneic mesenchymal stem cell transplantation in MRL/lpr and (NZB/NZW)F1 mice. *Clin Immunol* **145**, 142–52.
37 Carrion F, Nova E, Ruiz C *et al.* (2010) Autologous mesenchymal stem cell treatment increased T regulatory cells with no effect on disease activity in two systemic lupus erythematosus patients. *Lupus* **19** (3), 317–22.
38 Newell LF, Deans RJ, Maziarz RT (2014) Adult adherent stromal cells in the management of graft-versus-host disease. *Expert Opin Biol Ther* **14** (2), 231–46.
39 Connick P, Kolappan M, Crawley C *et al.* (2012) Autologous mesenchymal stem cells for the treatment of secondary progressive multiple sclerosis: an open-labelphase 2a proof-of-concept study. *Lancet Neurol* **11**, 150–6.
40 Guiducci S, Porta F, Saccardi R *et al.* (2010) Autologous mesenchymal stem cell foster revascularization of ischemic limbs in systemic sclerosis: a case report. *Ann Intern Med* **153** (10), 650–4.
41 Figueroa FE, Carrión F, Villanueva S, Khoury M (2012) Mesenchymal stem cell treatment for autoimmune diseases: a critical review. *Biol Res* **45**, 269–77.
42 Liang J, Zhang H, Hua B *et al.* (2010) Allogenic mesenchymal stem cells transplantation in refractory systemic lupus erythematosus: a pilot clinical study. *Ann Rheum Dis* **69** (8), 1423–9.
43 Weiss ML, Troyer DL (2006) Stem cells in the umbilical cord. *Stem Cell Rev* **2**, 155–62.
44 Lu LL, Liu YJ, Yang SG *et al.* (2006) Isolation and characterization of human umbilical cord mesenchymal stem cells with hematopoiesis-supportive function and other potentials. *Haematologica* **91**, 1017–26.
45 Sun L, Wang D, Liang J *et al.* (2010) Umbilical cord mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus. *Arthritis Rheum* **62** (8), 2467–75.
46 Wang D, Chen J, Li J *et al.* (2014) Umbilical cord mesenchymal stem cells transplantation in active and refractory systemic lupus erythematosus-a multicenter clinical study. *Arthritis Res Ther* **16** (2), R79.
47 Wang D, Zhang H, Liang J *et al.* (2013) Allogeneic mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus: 4 years of experience. *Cell Transplant* **22** (12), 2267–77.
48 Troyer DL, Weiss ML (2008) Wharton's jelly-derived cells are a primitive stromal cell population. *Stem Cells* **26** (3), 591–9.
49 Bocelli-Tyndall C, Zajac P, Di Maggio N *et al.* (2010) Fibroblast growth factor 2 and platelet-derived growth factor, but not platelet lysate, induce proliferation-dependent, functional class II major histocompatibility complex antigen in human mesenchymal stem cells. *Arthritis Rheum* **62** (12), 3815–25.
50 Miura M, Miura Y, Padilla-Nash HM *et al.* (2006) Accumulated chromosomal instability in murine bone marrow mesenchymal stem cells leads to malignant transformation. *Stem Cells* **24** (4), 1095–103.