Lupus (2018) 0, 1–17
journals.sagepub.com/home/lup

REVIEW

Stem cells for lupus nephritis: a concise review of current knowledge

PD Sattwika[1], R Mustafa[2], A Paramaiswari[3] and EH Herningtyas[4]
[1]Department of Internal Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada/Dr Sardjito General Hospital, Indonesia; [2]Clinical Epidemiology and Biostatistics Unit, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada/Dr Sardjito General Hospital, Indonesia; [3]Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada/Dr Sardjito General Hospital, Indonesia; and [4]Department of Clinical Pathology and Laboratory Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Indonesia

Lupus nephritis (LN), a common manifestation of systemic lupus erythematosus (SLE), accounts for significant morbidity and mortality in SLE patients. Since the available standard therapies and biologic agents for LN are yet to achieve the desired response and have considerable secondary effects, stem cell therapy has now emerged as a new approach. This therapy involves the transplantation of hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs). Our current review will highlight the progress of stem cell therapy for LN, along with the challenges encountered and the future direction of this approach. *Lupus* (2018) **0,** 1–17.

Key words: Nephritis; stem cells; systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease with multi-organ manifestations due to the widespread deposition of immune complexes. It accounts for 81–129 cases per 100,000 people annually in the United States[1,2] and ranges from 30 to 50 cases per 100,000 people in Asia.[3] SLE predominantly affects women of childbearing age, with 6–10-fold higher prevalence in females than in males.[4]

Renal involvement in SLE, manifested as lupus nephritis (LN), occurs in 60% of cases and correlates with a higher mortality rate.[5] Despite low prevalence in pediatric patients, SLE commonly presents with a wider range of systemic manifestations, so such patients are at risk for a poor prognosis and worse survival rate.[6] Approximately 50–75% of pediatric SLE patients suffer from LN, with renal manifestations appearing within two years after the diagnosis in 90% of patients.[7] Therefore, pediatric patients may receive the most benefit from aggressive treatment for LN.

Corticosteroid and immunosuppressive regimens are the standard therapy for LN patients.[8] However, despite the aggressive regimen, 20% of patients do not respond to these medications.[9] A brief summary of current available pharmacologic therapies of LN is presented in Table 1. Since those studies did not use the same definition of complete response, the response and failure rates in Table 1 could not be compared directly. Long-term consumption of certain types of these immunosuppressive agents may lead to ovarian failure, serious infection, and secondary malignancy.[22,23]

Newer drugs have been developed to suppress B-cell activity, such as rituximab, a monoclonal antibody to human cluster of differentiation (CD)20 of B cells, and belimumab, a B-lymphocyte activating factor inhibitor.[24] Belimumab targets B-cell-activating factor (BAFF) and was approved as the first biologic agent for SLE treatment by the Food and Drug Administration (FDA) in 2011.[25] However, a phase III trial of belimumab revealed that fewer than 45% patients with SLE showed clinical response.[18] In clinical practice, the use of biologic agents is currently limited due to their high cost.[26]

Correspondence to: EH Herningtyas, Department of Clinical Pathology and Laboratory Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Jalan Farmako Sekip Utara, Yogyakarta, Indonesia 55281.
Email: ehennyh@ugm.ac.id; henny_herningtyas@yahoo.com
Received 25 June 2017; accepted 3 July 2018

10.1177/0961203318793206

Table 1 Current available therapeutic agents for LN

Agents	*Response rate*	*Survival rate*	*Failure rate*	*Common side effects*	*Phase*
Azathioprine (AZA)[10–12]	48.3%	99%	32.4%	Teratogenic, infection, gastro intestinal and hematological side effects	Maintenance
Cyclophosphamide (CYC)[13–15]	62%; in regard to the dose: 71% (low dose) vs. 54% (high dose) (not statistically significant)	90%	43%; in regard to the dose: 16% (low dose) vs. 20% (high dose) (not statistically significant)	Teratogenic, premature ovarian failure, severe infections, amenorrhea, infertility, cytopenias and opportunistic infections such as herpes zoster	Induction and maintenance
Mycophenolate mofetil (MMF) [10,16,17]	56.2%	95.1%	16.4%	Teratogenic, viral infection of the upper respiratory tract, gastrointestinal and hematological side effects, hepatotoxicity	Induction and maintenance
Belimumab[18,19]	41.5% (low dose) 51.5% (high dose)	99.3% (low dose) 99% (high dose)	NA	Infection, laboratory abnormalities, malignancies	Added to standard therapy
Rituximab[20]	56.9%	97.3%	NA	Infection, neutropenia, hypotension	Added to MMF and corticosteroids
Abatacept[21]	33% (complete response), 59% (complete or partial response)	NA	NA	Headache, upper respiratory tract infection, sore throat, and nausea	Added to regimen of low-dose CYC followed by AZA

The need for more effective therapy is becoming a big concern, as a considerable number of SLE patients will develop end-stage renal disease.[27] Interest has grown during the past few years in developing stem cell transplantation for LN. This review will highlight the pathogenesis of LN, followed by the application of stem cells in LN to date. The future prospects of stem cell transplantation for LN will also be discussed.

Pathogenesis of LN: the challenge to overcome

The production of autoantibodies

Recognition of self-antigen leads to the activation of naïve $CD4^+$ T cells, which, in turn, differentiate into T follicular helper (Tfh) cells, which later migrate into the germinal center[28] to assist in differentiation of B cells and production of autoantibodies.[29] Autoreactive B cells in SLE are able to pass through the tolerance checkpoint in the germinal center.[30] BAFF regulates the maturation of B cells and serves as an important factor that allows the survival of long-lived plasma cells in the bone marrow.[31] Upon B cells' differentiation, plasmoblasts migrate into the bone marrow or inflamed tissue to undergo further maturation into immunosuppressive therapy-resistant long-lived plasma cells.

Regulatory T (Treg) cells maintain immune homeostasis, and administration of thymic-derived Treg cells into lupus-prone mice was shown to suppress LN.[32] Treg cells express transcription factor FoxP3 to control their development and function following its release, so any functional defect in the FoxP3 gene may result in disturbance of Treg generation.[33,34]

The involvement of cytokines

The pathogenesis of LN involves imbalance between T helper (Th)1 and Th2 cell-related cytokines. Th1 predominance is associated with up-regulation of interleukin (IL)-18, which leads to disease acceleration.[35,36] $CD4^+$ T cells' differentiation in SLE with compensated renal function is skewed in the Th2 direction, whereas those with end-stage renal disease undergoing hemodialysis show a predominance of Th1 cell-related cytokines.[37] Th17 in LN produces IL-17, contributing to the inflammatory condition.[23] Tumor necrosis factor (TNF)-α up-regulates IL-6 and acts as a growth factor for B lymphocytes via an autocrine loop.[38] IL-6 promotes B and T cells' differentiation into immunoglobulin-producing and effector cells, respectively.

The progressive nature of LN is associated with increased expression of glomerular monocyte chemoattractant protein (MCP)-1,[39] which acts as a chemoattractant for monocytes, T cells, and natural killer (NK) cells in response to inflammatory cytokines. High-mobility group box 1 (HMGB1), a

non-histone protein with proinflammatory properties, mediates DNA-containing immune complex to stimulate toll-like receptor-9, which later contributes to the activation of dendritic and B cells.[40] HMGB1 antibodies in SLE are shown to be correlated with disease activity.[41]

The insult to renal tissues

Glomerular pathology remains a predominant feature of LN.[42] An animal model of lupus exhibits glomerular basal membrane disorder, proliferation of mesangial cells, complement C3 and IgG deposition, and $CD3^+$ cell infiltration.[43] The initiation of an inflammatory reaction, and subsequent glomerular injury, is facilitated by the activation and proliferation of mesangium that releases proinflammatory substances, such as prostaglandins, oxidants, and proteases.[44]

Potential sources of stem cells for LN

Hematopoietic stem cells

Hematopoietic stem cells (HSCs) can be harvested from bone marrow, umbilical cord blood, or peripheral blood. Some studies showed clinical advantages of HSC injection for lupus patients,[45,46] yet secondary autoimmune disorders may arise after the infusion of HSCs.[47]

Results from clinical studies

Starting from 1997, autologous HSC transplantation has become an alternative therapy for severe or refractory lupus.[48] The European Group for Blood and Marrow Transplantation considers severe and refractory SLE as one of indications for HSC transplantation.[49] Several parameters have been utilized to evaluate and monitor the effect of stem cell therapies for lupus patients, such as the SLE Disease Activity Index (SLEDAI) and the British Isles Lupus Assessment Group (BILAG) score.

Here, we discuss some clinical trials with LN patients as a subset of SLE subjects. The age of the patients recruited in the trials ranged between 6 and 53 years old. Different doses of peripheral blood-derived HSCs were introduced in the clinical trials (Table 2). Following mobilization using cyclophosphamide and granulocyte colony-stimulating factor, HSCs were harvested and then purified to select cells expressing $CD34^+$, a surface marker of undifferentiated HSCs. $CD34^+$ cells were injected with a range of 1.4–27 $\times$ 10^6 cells/kg

Table 2 Clinical studies of autologous peripheral blood-HSC transplantation to treat LN

Reference	*Study type*	*Cell dose (cells/kg body weight)*	*Administration route*	*Number of patients (LN/total SLE)*	*Age range (years)*	*Sex (female/total)*	*Race*	*WHO nephritis class*	*Disease duration (months)*	*Follow-up period (months)*
Traynor et al., 2000[50]	Clinical trial phase I	$CD34^+$ cells: 2.4×10^6 $CD3^+$ cells: 5.4×10^5 $CD19^+$ cells: 5.7×10^4 (median)	Intravenous	5/7	15–51	NA	NA	III–IV	<12-240 (range)	25 (12–40) (median)
Traynor et al., 2002[51]	Clinical trial phase I/II	$CD34^+$ cells: $>1.4 \times 10^6$	Intravenous	8/15	NA	NA	NA	II–III	NA	36 (12–66) (median)
Jayne et al., 2004[52]	Retrospective cohort	NA	Intravenous	33/53	29 (9–52) (median)	44/53	Caucasian/Arab/African/Asian 15/2/3/20	II–V	59 (2–155) (median)	26 (0–78) (mean)
Burt et al., 2006[53]	Clinical trial phase II	$CD34^+$ cells: $>1.4 \times 10^6$	Intravenous	25/50	30 (10.9) (mean (SD))	43/50	White/Black/Hispanic/Asian 35/6/6/3	III–IV	7.8 (5.3) (mean (SD))	(6–90) (mean)
Alexander et al., 2009[46]	Clinical trial phase I/II	$CD34^+$ cells: $2.0–6.1 \times 10^6$ $CD3^+$ cells: $0.4–1.6 \times 10^4$	Intravenous	7/7	19–48	5/7	NA	II–V	NA	54 (3–96) (median)
Alchi et al., 2013[54]	Retrospective cohort	$CD34^+$ cells: $4.2 (1.66–12) \times 10^6$ (median)	Intravenous	17/28	29 (16–48) (median)	25/28	NA	II–IV	52 (9–396) (median)	38 (1–110) (median)
Su et al., 2013[6]	Clinical trial phase I	NA	Intravenous	4/5	6–14	2/5	NA	II 3/5 IV 1/5	6 (5–90) (median)	40–83
Cao et al., 2017[55]	Clinical trial phase I/II	$CD34^+$ cells: $2.8–27 \times 10^6$	Intravenous	22/22	23 (11–37) (mean)	17/22	NA	II 8/22, III 3/22, IV 5/22, V 5/22	NA	112.82 (51–147) (median)

(continued)

Table 2 Continued

Reference	*Previous therapies*	*Conditioning regimens*	*Results*	Mortality
Traynor et al., 2000[50]	At least six cycles of intravenous CYC	200 mg/kg CYC, 1 g MP, 90 mg/kg equine ATG	No hematological toxic effects Clinical remission in all patients	No mortality reported
Traynor et al., 2002[51]	Intravenous CYC	200 mg/kg CYC, 90 mg/kg ATG, 1 mg/kg MP	Improvement of SLEDAI score, levels of complement and autoantibodies; discontinuation of immunosuppressive medications in 10 patients	No mortality reported
Jayne et al., 2004[52]	CYC 37/43	CYC 84%, ATG 76%, lymphoid irradiation 22%	Remission = 66% Relapse of those with remission = 32%	Treatment-related mortality = 12% Mortality was associated with a longer disease course before treatment procedure ($P = .036$)
Burt et al., 2006[53]	Corticosteroid 50/50, intravenous CYC 46/50, oral CYC 10/50, MTX 13/50	200 mg/kg CYC and 90 mg/kg equine ATG	Overall five-year survival = 84% Five-year disease-free survival = 50%	Treatment-related mortality = 2% (1/50) By intention to treat, treatment-related mortality = 4% (2/50)
Alexander et al., 2009[46]	CYC 7/7, AZA 7/7, HCQ 5/7, MTX 5/7, MMF 3/7, CsA 2/7	50 mg/kg/day CYC, 30 mg/kg/day rabbit ATG, 1 g MP	Long-term clinical remission in five patients	Two deaths due to (1) SLE-related pulmonary embolism 38 months after treatment procedure and (2) uncontrolled invasive central nervous system aspergillosis 3 months after the procedure
Alchi et al., 2013[54]	NA	Low-intensity regimens CYC or melphalan 10/28, intermediate-intensity regimen with the combination of CYC and ATG with or without MP, or with fludarabine, thiotepa, alemtuzumab, and melphalan 18/28	Five-year overall survival rate = 81 ± 8% Disease-free survival = 29 ± 9% Relapse incidence = 56 ± 11% Non-relapse mortality = 15 ± 7%	Five deaths within two years after treatment: three caused by infection, one by secondary autoimmune disease, and one by progressive SLE
Su et al., 2013[6]	Glucocorticoids, CYC, or human immunoglobulin for a period of 3 to 87 months	Patient 1: 300 mg/kg/day carmustine, 200 mg/kg/day etoposide, 300 mg/kg/day cytarabine (Ara-C), 120 mg/kg/day melphalan, 3.5 mg/kg/day rabbit ATG Patients 2 and 5: 50 mg/kg/day CTX and 3.5 mg/kg/day rabbit ATG Patient 3: 120 mg/kg/day melphalan added to the CTX and ATG regimens Patient 4: 300 mg/kg/day carmustine added to the CTX and ATG regimens	Non-lethal transplantation-related infection = 80% Long-term remission and improvement of quality of life	No mortality reported
Cao et al., 2017[55]	Pred 22/22, MP 5/22, CYC 12/22, MMF 2/22, MTX 2/22, *Tripterygium wilfordii* 9/22, AZA 2/222, thalidomide 1/22	100–200 mg/kg CTX, 2–10 mg/kg rabbit ATG, 60–500 mg/day MP	Three-year progression-free survival = 77.27% Five-year progression-free survival = 67.9% Overall survival rate = 95.2% Incidence of cytomegalovirus reactivation = 59.09%	One death due to serious pulmonary infection 57 months after transplantation

ATG: anti-thymocyte globulin; AZA: azathioprine; CD: cluster of differentiation; CsA: cyclosporin A; CYC: cyclophosphamide; HCQ: hydroxychloroquine; HSCs: hematopoietic stem cells; MMF: mycophenolate mofetil; MP: methylprednisolone; MTX: methotrexate; NA: not available; Pred: prednisone; SD: standard deviation; SLE: systemic lupus erythematosus; SLEDAI: systemic lupus erythematosus disease activity index.

body weight. The injection of autologous HSCs into lupus patients was able to decrease the titer of antinuclear antibodies (ANA), anti-dsDNA antibodies, and anti-Sm antibodies, reduce proteinuria, and normalize the serum level of C3 and C4.[55]

Although autologous HSCs could induce remission in patients with refractory SLE, the mortality rate related to the treatment should be taken into account.[52] Life-threatening events were reported, the majority of which were due to infection, thrombotic thrombocytopenic purpura, gastrointestinal bleeding, secondary leukemia, and post-transplant lymphoproliferative disorder associated with Epstein–Barr viremia. This study suggested that careful selection of SLE patients treated with HSCs might prevent the high mortality rate due to the treatment procedure.[54]

Another study involving 50 lupus patients reported one death after stem cell mobilization caused by disseminated mucomycosis before the start of HSC transplantation.[53] Other complications were reported, including infection during either HSC mobilization or transplantation or after hospital discharge, lung complication that required intubation or oxygen supplementation, or secondary autoimmune complications, including factor VIII deficiency and idiopathic thrombocytopenic purpura.

Injection of autologous HSCs into pediatric patients resulted in non-lethal infection, which occurred in four out of five patients with LN. Three of these infections were caused by cytomegalovirus infection and one by mixed infection with cytomegalovirus and Epstein–Barr virus.[6] Autologous HSC transplantation without in vitro graft manipulation was shown to be successful in resetting the impaired immune system, although a large number of T cells were included in the injection.[56]

As well as autologous HSCs, allogeneic HSCs were also investigated for treating lupus. Allogeneic HSC transplantation performed in 27 SLE patients demonstrated a disease-free period of 7.35 (range, 2.1–12.7) months.[57] Although the use of allogeneic HSCs provided 75% response rate among patients with autoimmune diseases, treatment-related mortality was still high (20%).[58] The reported mortality did not differ between hematological and non-hematological autoimmune diseases or among patients of different ages or those with different donor sources.

Possible mechanisms

The administration of HSCs is commonly preceded by a conditioning regimen, such as with cyclophosphamide or antithymocyte globulin.[49] These regimens are expected to immune-ablate the existing immune component in SLE patients; accordingly, injection of either autologous or allogeneic HSCs can restart the immune system. Autologous HSCs decreased the number of $CD4^+$ and $CD19^+$ cells.[6] Moreover, a marker of T-cell activation, CD69, was found to be decreased or normal.[50] Yet, disease flare might occur after autologous HSC infusion, related to the expression of interferon regulatory factor (IRF)-7, which regulates the response of type I interferon (IFN).[59]

Because autologous HSCs may be beneficial for selected patients with LN, but not for others, allogeneic HSCs then emerged as an alternative. Allogeneic HSCs are considered not only to reset but also to replace the defective immune system in LN.[49] Nonetheless, existing evidence shows high treatment-related mortality for allogeneic HSC transplantation (22.1% at two years).[58]

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) can be obtained from bone marrow (the non-hematopoietic component), umbilical cord, umbilical cord blood, adipose tissue, or embryonic tissue.

Results from preclinical studies

Table 3 presents several preclinical studies of MSC application in lupus-prone mice. Preclinical studies of MSCs commonly take cells from passage 4 of cell culture, which have undergone approximately 10 population doublings.[77] The cell number of MSCs injected in the lupus mice model shows variation among published preclinical studies, with the vast majority transplanting as many as 1×10^6 cells/animal. The search for the optimal dose is of pivotal importance, as increasing the dose, for instance to 1.25×10^6 cells/animal, did not show any greater effect.[63] Regarding the administration route, almost all MSCs were injected into mice intravenously via the tail vein; one study introduced MSCs retro-orbitally via the venous sinus, and one study administered them intraperitoneally.

While most studies elucidated MSCs' ability to ameliorate LN, two studies presented conflicting results. Schena et al. injected bone marrow-MSCs (BM-MSCs) via the tail vein in the lupus mice model and reported no improvement of proteinuria. A rationale for this result is due to the old passage (P20–25) used in the experiment.[63] Old MSCs lose their function sooner than young ones,[78] and extended in vitro culture impairs homing.[79] Therefore, limited in vitro expansion is

Table 3 Examples of in vivo studies using MSCs to treat LN

Reference	*Species*	*MSC source*	*Number of cells injected/ animal*	*Administration route*	*Murine age when injected (weeks old)*	*Results*
Zhou et al., 2008[60]	MRL/lpr mice	Human bone marrow	1×10^6	Tail vein	16–20	• Decrease in proteinuria and level of autoantibodies • Improvement of histopathological structure
Sun et al., 2009[43]	Female MRL/lpr mice	Allogeneic bone marrow	0.1×10^6 cells/10 g of body weight	Tail vein	Group 1: 9 Group 1: 16	• In both groups: decrease in levels of autoantibodies, complement C3, and glomerular IgG deposition; improvement of renal function • Improvement of histopathological structure
Gu et al., 2010[61]	MRL/lpr mice	Human umbilical cord	1×10^6 Group 1: once Group 2: three times, weekly	Tail vein	18	• Decrease in proteinuria, serum creatinine, and level of autoantibodies; improvement of histopathological structure (related to crescent formation); with greater extent found in group 2
Youd et al., 2010[62]	NZB/WF1 mice	Allogeneic bone marrow	1×10^6 biweekly	Intraperitoneal injection	Group 1: 21 (before disease onset) Group 2: 32 (after disease onset)	• Worsening of proteinuria, glomerular immune complex deposition, and histopathological structure in both groups • Increase in level of serum autoantibodies and number of plasma cells in bone marrow
Schena et al., 2010[63]	NZB/WF1 mice	Allogeneic bone marrow	1.25×10^6 three times, weekly	Intravenous	27	• No improvement of levels of autoantibodies, proteinuria, or mortality rate • Decrease in glomerular immune complex deposition, lymphocytic infiltration, and glomerular proliferation
Chang et al., 2011[64]	NZB/WF1 mice	Human umbilical cord blood	1×10^6	Tail vein	Group 1: 8 Group 2: 24	• Delayed onset of proteinuria, decrease in level of autoantibodies, improvement of histopathological structure, and increase in survival; with greater extent found in group 1 • No long-term engraftment of MSCs in the kidney
Gu et al., 2012[65]	MRL/lpr and NZB/WF1 mice	Allogeneic or syngeneic (pre-lupus or lupus) bone marrow	1×10^6	Intravenous	MRL/lpr mice: 17–20 NZB/W F1 mice: 24–25	• In both species, allogeneic and pre-lupus syngeneic MSCs: decrease in proteinuria, level of autoantibodies, reduction of spleen size, and improvement of histopathological structure; with greater extent found in allogeneic MSCs injection
Choi et al., 2012[66]	NZB/WF1 mice	Human adipose tissue	Group 1: 5×10^5 28 times, biweekly Group 2: 2×10^6 5 times, biweekly	Intravenous	Group 1: 6 Group 2: 32	• Increase in survival, with greater extent in group 1 • Decrease in proteinuria, level of autoantibodies, and blood urea nitrogen • Improvement of histopathological structure and immunologic function
Ji et al., 2012[67]	MRL/lpr mice	Allogeneic bone marrow	Group 1: 0.05×10^6 Group 2: 0.2×10^6	Tail vein	14	• Improvement of histopathological structure • Decrease in proteinuria and level of autoantibodies in group 2
Ma et al., 2013[68]	MRL/lpr mice	Allogeneic bone marrow	1×10^6	Tail vein	18	• Increase in survival • Decrease in proteinuria and level of autoantibodies • Reduction of spleen size
Collins et al., 2014[69]	MRL/lpr mice	Group 1: human umbilical cord Group 2: healthy human bone marrow Group 3: lupus human bone marrow	1×10^6	Intravenous	15–17	• Groups 1 and 2: decrease in proteinuria and improvement of histopathological structure • Group 3: delayed onset of proteinuria and no improvement of histopathological structure
Thiel et al., 2015[70]	NZB/WF1 mice	Human embryonic	0.5 or 5×10^5 Group 1: 3 times, weekly	Tail vein	Group 1: 24–26 Group 2: 23–33	• Increase in survival • Decrease in proteinuria and level of serum creatinine

(continued)

Table 3 Continued

Reference	*Species*	*MSC source*	*Number of cells injected/ animal*	*Administration route*	*Murine age when injected (weeks old)*	*Results*
			Group 2: 6 times, biweekly			• Improvement of histopathological structure
Jang et al., 2016[71]	NZB/WF1 mice	Human bone marrow	1×10^6 Group 1: 3 times, biweekly Group 2: 5 times, weekly	Retro-orbital injection of the venous sinus	Group 1: 17 Group 2: 28	• Increase in survival, decrease in proteinuria, level of autoantibodies, and improvement of histopathological structure in group 1 • Decrease in level of autoantibodies but no improvement of proteinuria in group 2
Yuan et al., 2016[72]	MRL/lpr mice	Human embryonic	Group 1: 1×10^6 Group 2: saline Twice, 3 week interval	Tail vein	16	• Increase in survival, decrease in proteinuria, improvement of renal histopathological structure • Decrease in the proportion of Th7 cells and the concentration of IL-17
He et al., 2016[73]	MRL/lpr mice	Allogeneic adipose tissue	1×10^6 5 times, biweekly	Intravenous	30	• Decrease in proteinuria and anti-dsDNA antibodies • Decrease in IL-17 and IL-6 expression • Improvement of renal histopathological structure • Decrease in IL-17 and CD68 expression
Choi et al., 2016[74]	Groups C, Y, H: MRL/lpr mice Group N: control C3H/HeJ mice	Human adipose tissue	Group C: saline Group Y: CYC 20 mg/kg Group H: MSCs 1×10^6 Group N: saline 18 times, biweekly	Group C, H, N: intravenous Group Y: intraperitoneal	5	• Group Y: best improvement of disease parameters, damaged trabecular integrity • Group H: decrease in anti-dsDNA levels, glomerular C3 deposition, and CD138 proportion, preserved trabecular integrity • Group Y and H: decrease in Th1/Th2 ratio
Yang et al., 2017[75]	MRL/lpr mice	Allogeneic bone marrow	Group 1: 2×10^6 Group 2: saline Twice, 2 week interval	Tail vein	18	• Inhibition of T cell proliferation dose-dependently • Decrease in proteinuria and level of anti-dsDNA antibody • Increase in survival
Yang et al., 2018[76]	MRL/lpr mice	Human umbilical cord	Group 1: 5×10^5 Group 2: saline	Intravenous	18	• Decrease in proteinuria

anti-dsDNA: anti-double stranded DNA; AP-1: activator protein 1; CD: cluster of differentiation; CYC: cyclophosphamide; IgG: immunoglobulin G; IL: interleukin; MMP: matrix metalloproteinase; MSCs: mesenchymal stem cells; NF-kB: nuclear factor kappa B; SP-1: specificity protein 1; Th: T helper.

better to maintain MSC phenotype. The other study revealed that BM-MSCs even exacerbated lupus when given biweekly starting either before or after the onset of disease in lupus-prone mice. It is worth noting that this study used intraperitoneal injection for MSC administration, which might be one factor influencing the contrasting result.[62] Human MSCs intraperitoneally injected into mice are known to form aggregates with $B220^+$ lymphocytes and macrophages, which then become attached to the peritoneal wall, thus limiting the number of MSCs entering the systemic circulation.[80]

Allogeneic BM-MSCs are preferred to syngeneic ones, which have impaired immunomodulatory properties.[65] BM-MSCs from lupus patients only delayed the onset of proteinuria,[69] suggesting that lupus-derived MSCs are defective. The time of MSC administration into lupus-prone mice, whether prior to disease manifestation or after, can affect the degree to which MSCs ameliorate LN. Several studies comparing early and late administration of MSCs suggested that early administration of MSCs was better able to improve the histopathological structure and SLE clinical manifestation in lupus models.[66,71] In addition, multiple injections of umbilical cord-MSCs (UC-MSCs) into MRL/lpr mice, given three times at weekly intervals, showed better enhancement of LN compared with a single injection.[61]

While possessing properties that may improve nephritis, MSCs can also be utilized as a vehicle to introduce specific genes to alleviate LN. Kallikreins are associated with experimental anti-GBM antibody-induced nephritis and LN that acts through the kinin B2 receptor.[81] The human kallikrein (hKLK)1 gene was integrated into murine MSCs using a retroviral vector to produce

hKLK1-MSCs. Given to anti-GBM-induced nephritis 129/svj mice and lupus-prone B6.Sle1.Sle3 bicongenic mice, hKLK1-MSCs were able to improve nephritis by reducing the infiltration of macrophages and T-lymphocytes.[82] Another experiment utilized MSCs to suppress the oxidative stress involved in the pathogenesis of LN. Human oxidation resistance (hOXR)-1, expressed in various eukaryotes, is crucial for detoxification of reactive oxygen species and protects human cells against oxidative damage. hOXR-1 was inserted into genome MSCs via lentiviral vector to produce hOXR1-MSCs. Administration of these cells into nephritis mice model has been shown to ameliorate LN, prevent H_2O_2-induced oxidative stress, and inhibit tubular cell apoptosis.[83]

It is desirable to assess the effectiveness of MSC therapy in several animal models, given the fact that each model has its own limitations in mimicking SLE manifestations in humans. Another animal model that could be considered to investigate LN is the Chinese tree shrew (*Tupaia belangeri*). Intraperitoneal injection of pristane and lipopolysaccharide into that animal is one of the best ways to induce pathological changes as seen in lupus patients. Injection of UC-MSCs into these animals improved histopathological finding in the kidney.[84]

Results from clinical studies

A research group from Nanjing, China, which has been intensively reporting the clinical application of MSCs for SLE since 2009, standardized the injected dose of MSCs to 1×10^6 cells/kg body weight of patient intravenously.[43] In 2010, Liang et al. reported a pilot study of allogeneic MSC transplantation into 15 SLE patients, with the promising result that MSC therapy could improve SLEDAI score and 24-hour proteinuria.[85] A single-arm trial revealed the efficacy and safety of allogeneic UC-MSC infusion in patients with severe and treatment-refractory SLE.[86] In patients with LN, proteinuria decreased significantly at the three-month follow-up.

A case report revealed that combined therapy with infusion of autologous HSCs and allogeneic MSCs resulted in clinical remission in a 25-year-old female SLE patient with multiple life-threatening complications and refractory to standard conventional therapy. Remission in clinical symptoms was observed after infusion and remained after 36-month follow-up. LN and hematologic abnormalities in this patient were ameliorated, as evidenced by a decrease in 24-hour proteinuria and an increase in creatinine clearance, complement C3, leukocyte count, and platelet count.[87]

Single or double allogeneic BM-MSC infusion in a randomized trial showed no remarkable differences in disease remission and relapse, or improvement of serum index, after one-year follow-up.[88] Yet, the short interval of one week between the first and second injections, which may contribute to these comparable results, should be taken into consideration. This hypothesis is further supported by the result of a multicenter clinical study showing that repeated infusion after 6 months might be beneficial, as relapse occurred in 12.5% patients after 9 months and 16.7% patients after 12 months.[89]

Improvement after MSC transplantation was also observed for extra-renal manifestations of SLE, including the integumentum and hematopoietic systems, as assessed by BILAG score.[89] While some other trials reported improvement in both renal and extra-renal manifestations of SLE, the majority did not mention sufficient detail of the SLE subgroups that received the greatest benefit from the treatment.

The combination of UC-MSCs and globulin component protein macrophage activating factor (GcMAF) therapy in a young adult female suffering from SLE and Sjogren's syndrome resulted in a complete reversal of both clinical and laboratory parameters without any side effects. This combination is considered to be a mild immunosuppressant regimen with robust anti-inflammatory effects and the ability to repair damaged cell lines.[90]

In contrast to the above results, the recent clinical trial of UC-MSCs conducted by Deng et al. showed no advantage of stem cell transfusion. There were four serious adverse events encountered, two from the UC-MSC group and two from the placebo group. In the UC-MSC arm, one death occurred due to severe pneumonia, and one patient suffered from leukopenia, pneumonia, and subcutaneous abscess. In the placebo group, there was one patient with stroke and one patient with ascites of unknown cause.[91] The adverse events encountered in the MSC group were related to the immunocompromised condition of the patients. The highly intensive immunosuppressive regimen for induction prior to MSC transplantation (pulse dose of intravenous methylprednisolone followed by low-dose intravenous cyclophosphamide) could explain the devastating side effects in this arm. Better selection of patients for clinical trial should also be considered, as a study conducted by Wang revealed that the higher level of IFN-γ prior to MSC transplantation could better predict the clinical response in lupus patients.[92]

Table 4 describes clinical trials of MSC transplantation to treat LN. MSC transplantation in LN cases resulted in remission in 60.5–75% of patients, with a relapse rate of 22.4–23% and a survival rate of 92.5–95%.[89,91,93,94] Currently available studies did not provide detailed results of stem cell transplantation based on the demographic and clinical characteristics of patients. Therefore, we could not identify specific populations who showed better response to stem cell transplantation. Available therapies for LN patients listed in Table 1 provide a response rate of 33–71%, a survival rate of 90–99%, and a failure rate of 16–43%. Although the study designs, populations, and operational definitions in those studies are not comparable, MSC application is expected to be a potential alternative therapy compared with current standard therapies.

Possible mechanisms

Allogeneic MSCs are increasingly regarded as a promising source for cell-based therapy of LN. Co-culture of umbilical cord blood-MSCs (UCB-MSCs) with mesangial cells promoted inhibition of lymphocytes and proliferation of splenocytes, but not mesangial cells.[64] Embryonic tissue-derived MSCs could limit protein cast deposition, $CD3^+$ lymphocyte infiltration, and interstitial inflammation in the kidney.[70] Furthermore, BM-MSCs decreased deposition of complement C3.[60] Several mechanisms are proposed regarding the potential of MSCs to ameliorate LN, including, but not limited to, homing, immunomodulatory properties, secretion of trophic factors, and differentiation ability (Figure 1).

Later studies on the roles of stem cells in SLE also focus on the epigenetic factors involved, such as microRNAs (miRNAs), in addition to biological factors that have been mentioned in the earlier part of this review. miRNAs regulate the homing of stem cells; for instance, miR-27b, miR-126, miR-146a-5p, and miR886-3p inhibit the translation of SDF-1α, a chemokine that is important for the homing of stem cells.[95] The role of miRNA in the proliferation and differentiation of muscle, hematopoietic, skin, and neural stem cells is also well described.[96] Furthermore, osteogenic and adipogenic differentiation of MSCs is determined by the expression of miRNAs.[97,98] However, further investigation is still needed to elucidate miRNA expression in the application of MSCs for lupus patients.

Seven miRNAs were found to be significantly downregulated in peripheral blood samples of 23 SLE patients: hsa_miR_196a, hsa_miR_17_5p, hsa_miR_409_3p, HMP_PREDICTED_MIR141,

Table 4 Clinical studies of MSC transplantation to treat LN

Cell source	*Reference*	*Study type*	*Cell dose (cells/kg body weight)*	*Administration route*	*Number of patients (LN/total SLE)*	*Age range (years)*	*Sex (female/total)*	*Race*	*WHO nephritis class*	*Disease duration (months)*	*Follow-up period (months)*
Allogeneic umbilical cord	Sun et al., 2010[86]	Clinical trial phase I/II	1×10^6	Intravenous	15/16	31.8 ± 11.3 (17–55) (mean)	14/16	NA	III–V (in 5 patients)	65.1 ± 53.9 (2–168) (mean)	8.25 (3–28) (median)
Allogeneic bone marrow or umbilical cord	Wang et al., 2012[88]	Clinical trial phase II	1×10^6 Group 1: once Group 2: twice, one week interval	Intravenous	Group 1: 26/30 Group 2: 24/28	Group 1: 30 (12–47) Group 2: 33 (16–54)	Group 1: 25/30 Group 2: 26/28	All Asian	NA	Group 1: 62 (7–232) Group 2: 92 (12–264) (median)	Group 1: 27 (12–48) Group 2: 26 (12–40) (median)
Allogeneic bone marrow or umbilical cord	Wang et al., 2013[93]	Clinical trial phase II	1×10^6	Intravenous	73/87	31.5 (12–56) (mean)	80/87	All Asian	NA	37.5 (2–264) (mean)	27 (12–48) (mean)
Allogeneic umbilical cord	Wang et al., 2014[89]	Clinical trial phase II	1×10^6 twice, one week interval	Intravenous	39/40	17–54	38/40	NA	NA	90.9 (15–264) (mean)	At 1, 3, 6, 9, and 12 months
Allogeneic bone marrow or umbilical cord	Gu et al., 2014[94]	Clinical trial phase II	1×10^6	Intravenous	81/81	31.6 (12–55) (mean)	74/81	All Asian	NA	83.1 (6–264) (mean)	At 1, 3, 6, and 12 months
Allogeneic umbilical cord	Deng et al., 2017[91]	Clinical trial phase I/II	1×10^8 twice, one week interval	Intravenous	18/18	Group 1 (MSCs): 29 (10) Group 2 (placebo): 29 (7) (mean (SD))	Group 1: 11/12 Group 2: 6/6	NA	IV	Group 1: 59 (44) Group 2: 94 (55) (mean (SD))	12 months

(continued)

Table 4 Continued

Reference	*Previous therapies*	*Conditioning regimens*	*Results*	*Mortality*
Sun et al., 2010[86]	Pred 16/16, DEX 1/16, CYC 15/16, HCQ 11/16, MMF 3/16, LEF 2/16, AZA 1/16, BM MSCT 1/16, intravenous albumin and plasma 1/16	11 patients: 0.8–1.8 g CYC, 5 patients without concomitant therapy	No severe adverse events Improvement of SLEDAI score, levels of autoantibodies, serum albumin, complement C3, and renal function	No mortality reported
Wang et al., 2012[88]	Most patients received CYC, no further details	10 mg/kg/day CYC	Improvement of SLEDAI scores, levels of autoantibodies, serum albumin, and complement C3 with no difference between the two groups	No treatment-related mortality One death in group 2 due to acute heart failure
Wang et al., 2013[93]	Corticosteroids 87/87, CYC 68/87, MMF 26/87, LEF 17/87, *Tripterygium* 11/87, thalidomide 7/87, AZA 5/87, vincristine 4/87, CsA 2/87, MTX 2/87, intravenous immunoglobulin 4/87, apharesis 3/87, rituximab 1/87, tacrolimus 1/87	10 mg/kg/day CYC	No transplantation-related adverse events Overall survival rate = 94% Overall relapse rate = 23% Improvement of SLEDAI score, proteinuria, renal function, GFR, levels of autoantibodies, serum albumin, and complement C3	No treatment-related mortality Five deaths due to (1) acute gastroenteritis and heart failure, (2) disseminated pulmonary infection and uncontrolled LN, (3) right sided heart failure, (4) pulmonary embolism, (5) uncontrolled progressive disease and acute heart failure
Wang et al., 2014[89]	Pred 40/40, CYC 26/40, HCQ 26/40, LEF 15/40, MMF 4/40, CsA 1/40	NA	No transplantation-related adverse events Overall survival rate = 92.5% Improvement of SLEDAI score, BILAG score, proteinuria, renal function, levels of autoantibodies, serum albumin, and complement C3	No treatment-related mortality Three deaths due to (1) uncontrolled progressive disease and acute heart failure, (2) right sided heart failure, (3) uncontrolled septicemia and respiratory failure
Gu et al., 2014[94]	Pred 81/81, CYC 66/81, HCQ 43/81, MMF 19/81	NA	No transplantation-related adverse events Overall survival rate = 95% Remission at 12 months = 60.5% Relapse of those with remission = 22.4% Improvement of SLEDAI score, BILAG score, proteinuria, renal function, and GFR	No treatment-related mortality Four deaths due to (1) acute gastroenteritis and heart failure, (2) disseminated pulmonary infection and uncontrolled LN, (3) disseminated pulmonary infection and uncontrolled LN, (4) right sided heart failure
Deng et al., 2017[91]	NA	Patients 1–11: MP plus low-dose CYC six pulses at a fixed dose of 500 mg every 2 weeks Patients 12–18: MP only	Remission at 12 months: 9/12 (75%) (group 1), 5/6 (83%) (group 2) Similar improvements in serum albumin, complement, renal function, SLEDAI and BILAG scores in both groups	One death in group 1 due to severe pneumonia

AZA: azathioprine; BILAG: British Isles Lupus Assessment Group; BM MSCT: bone marrow-derived MSC transplantation; CsA: cyclosporin A; CYC: cyclophosphamide; DEX: dexamethasone; GFR: glomerular filtration rate; HCQ: hydroxychloroquine; LEF: leflunomide; MMF: mycophenolate mofetil; MP: methylprednisolone; MSCs: mesenchymal stem cells; MTX: methotrexate; NA: not available; Pred: prednisone; SLE: systemic lupus erythematosus; SLEDAI: systemic lupus erythematosus disease activity index.

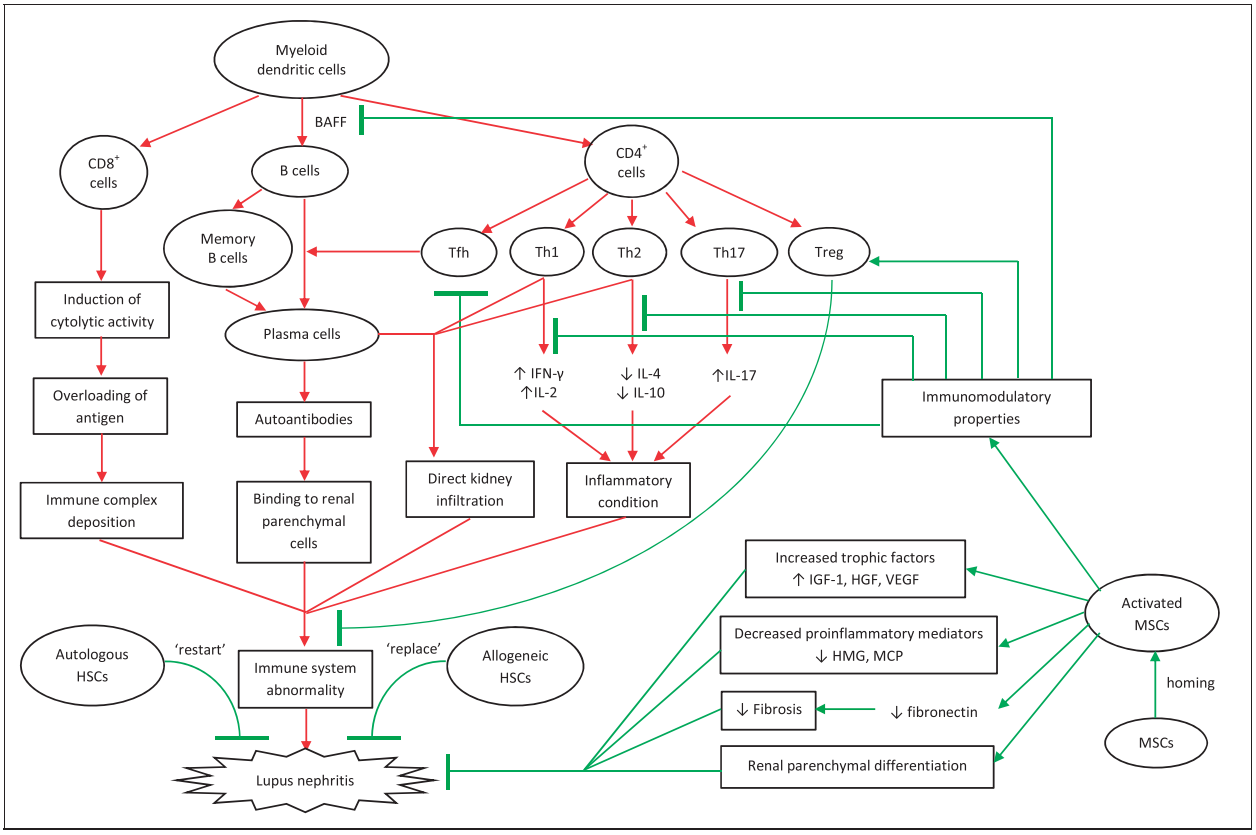

Figure 1 Schematic diagram depicts the possible mechanism of autologous HSCs, allogeneic HSCs, and MSCs in ameliorating LN. Myeloid dendritic cells facilitate B cells, $CD4^+$ cells, and $CD8^+$ cells to undergo subsequent events contributing to the impaired immune system in LN. Autologous HSCs are considered to restart the defective immune system, while allogeneic HSCs may replace the abnormal immune cells. MSCs exhibit immunomodulatory properties in LN by not only affecting Tfh, Th1, Th2, and T17 but also increasing Treg. Furthermore, they are expected to induce the secretion of trophic factors, suppress proinflammatory mediators and fibronectin, and differentiate into renal parenchyma.
BAFF: belimumab targets B-cell-activating factor; CD: cluster of differentiation; HGF: hepatocyte growth factor; HMG: high-mobility group; HSCs: hematopoietic stem cells; IFN: interferon; IGF: insulin-like growth factor; IL: interleukin; MCP: monocyte chemoattractant protein; MSCs: mesenchymal stem cells; Tfh: T follicular helper; Th: T helper; Treg: regulatory T; VEGF: vascular endothelial growth factor.

hsa_miR_383, HMP_PREDICTED_MIR112, and hsa_miR_184. On the other hand, nine were upregulated: HMP_PREDICTED_MIR189, HMP_PREDICTED_MIR61, HMP_PREDICTED_MIR78, hsa_miR_21, hsa_miR_142_3p, hsa_miR_342, hsa_miR_299_3p, hsa_miR_198, and mmu_miR_298.[99] miRNAs have been involved in the various stages of cell development, so their disregulation might also take part in the pathophysiology of autoimmune diseases. miRNAs play a pivotal role in both the activation of innate immunity and regulation of adaptive immunity. Microarray analysis of miRNAs in African American and European American populations has also demonstrated that a number of miRNAs are differentially expressed in LN patients of both races.[100] Treatment with MSCs was shown to reduce the expression of miR-96-5p and miR-182-5p, showing that miRNAs might also take part in mediating the therapeutic mechanism elicited by MSC treatment.[74] Thus, examining and regulating these miRNAs could also potentially be a future approach to the management of LN.

Homing

In an animal model of acute kidney injury, in vivo microscopic study has observed the ability of MSCs to reach the glomeruli and attach to the peritubular capillaries, suggesting an ability referred to as "homing".[101] Tubular localization of MSCs from transgenic mice expressing green fluorescent protein was observed in an animal model of acute tubular epithelial injury, with significant accumulation that persisted until 21 days after injection.[102] In experimental administration of carboxyfluorescein

diacetate succinimidyl ester (CFSE)-labeled human UC-MSCs to MRL/lpr mice, CFSE was found in the lungs and kidneys one week post injection. Human cells could then be found in the kidneys 11 weeks post injection.[61] Injection of human UCB-MSCs into BWF1 mice resulted in temporary detection of human specific b2-microglobulin in kidney tissue two weeks after transplantation. Despite this positive finding, no human DNA was found eight months after transplantation.[64] Moreover, BM-MSCs obtained from a lupus patient had impaired migration capacity, as no human indolamine 2,3 dioxygenase (IDO)1 or complement factor H (CFH) gene expression was found in the kidney post transplantation,[69] suggesting that a particular mechanism may contribute to the homing of MSCs.

Immunomodulatory properties

MSCs inhibit the development of proinflammatory Th1 cytokines, such as IFN-γ and IL-2, and other proinflammatory cytokines, namely TNF-α, IL-6, IL-1b, IL-12,[43,64,101] that are involved in SLE progression. A decrease in lymphocyte secretion of TNF-α and IL-6 as well as an increase in the number of T cells was observed in a co-culture experiment with human embryonic stem cells and lipopolysaccharide-stimulated BWF1 lymphocytes.[70] Besides, MSCs increase the secretion of IL-4 and IL-10, which belong to Th2 cytokines.[66,103] MSCs promote shifting from Th1 to Th2 polarization by direct interaction with immune cells or by altering the cytokine secretion profile.[104] Furthermore, MSCs modulate diverse lymphoid-lineage cells, including T and B lymphocytes and NK cells, through contact-dependent engagement involving programmed death (PD)-1 or contact-independent mechanisms by secretion of IDO, prostaglandin E2, IL-10, and tumor growth factor (TGF)-β.[105–107]

Stimulation of IFNγ towards human embryonic MSCs could increase the expression of IL-10, prostaglandin E2 (PGE2), and TGF-β, thus affecting the differentiation of Th17. Therapy with human embryonic MSCs could suppress T17 cells in spleen and decrease the concentration of IL-17.[72] The decrease in IL-17 expression was further supported by the work of He et al., showing that mouse adipose-derived MSCs could decrease IL-17 mRNA expression and increase Foxp3, retinoic acid receptor-related orphan receptor gamma (ROR-γt), and miR-23b mRNA expression. These MSCs were shown to be able to decrease infiltration of inflammatory cells to renal tissue and edema of renal interstitium.[73] The treatment effect of human UC-MSCs in alleviating LN might also be mediated by the suppression of the expression of matrix metalloproteinase (MMP-2), MMP-9, transcription factor AP-1, SP-1, NF-kB, and osteopontin, a cytokine related to inflammatory and autoimmune diseases.[76]

MSCs suppress B cells' proliferation and differentiation to plasma cells via an IFN-γ-dependent mechanism and PD ligand pathway.[63] Thereafter, MSCs decrease infiltration of plasma cells into kidney in a murine model of LN.[71] Though defective, MSCs from SLE patients are able to inhibit B cells' proliferation and terminal differentiation when the expression of the olfactory 1/early B cell factor-associated zinc-finger protein gene is down-regulated.[108] Improvement of proteinuria and level of anti-dsDNA autoantibodies in the MSC-treated lupus-prone murine model is associated with decrease in BAFF expression in the kidney. Secretion of BAFF by dendritic cells is also inhibited by MSCs.[68]

MSCs suppress lymphocyte reactivity by inhibiting the response of both naïve and memory T cells.[109] Likewise, MSCs decrease the proliferation of T lymphocytes; specifically, they decrease the number of $CD4^+$ T cells, thus enhancing their effect in ameliorating lupus progression.[60,65] Human UC-MSCs were able to inhibit Tfh cell expansion in lupus-prone mice related to the upregulation of inducible nitric oxide synthase production. This process is highly dependent on cell to cell contact.[110] BM-MSCs were shown to possess the ability to inhibit the differentiation of Tfh cells from naive $CD4^+$ cells and splenocytes, as well as to inhibit IL-21 gene expression and STAT3 phosphorylation.[75] In a lupus murine model experiment, MSCs suppressed abnormal activation of Akt/GSK3β cascade in T cells and disrupted the cell cycle of T lymphocytes in G1/S transition by upregulating the expression of $p21^{WAF1/CIP1}$ and $p27^{KIP1}$ as well as down-regulating the expression of cyclin-dependent kinase-2.[67]

T cells from SLE patients showed aberrant autophagic activity, which plays a pivotal role in the pathogenesis of SLE. UC-MSCs could inhibit autophagy by suppressing respiratory mitochondrial biogenesis and inhibit T-cell apoptosis through mitochondrial transfer.[111]

MSC transplantation into lupus-prone mice and lupus patients leads to an increase in the number of $CD4^+FoxP3^+$ Treg cells.[86] Moreover, the functional defect of lupus Treg cells is reversible,[112] suggesting that MSC transplantation may have the potential to improve both the quantity and the quality of Treg cells. An in vitro experiment using purified $CD4^+$ cells, incubated with or without UC-MSCs in a 1:1 ratio with the addition of IL-

10 and anti-TGF-β, showed a significant increase in the percentage of Treg cells in UC-MSC-treated cells. This implies that UC-MSCs increase the population of Treg cells with the presence of IL-10 or anti-TGF-β.[61] Despite the decline in number of Treg cells due to an increase in the secretion of TGF-β, TGF-β1 is required to maintain the suppressive function of Treg cells.[113]

Compared with BM and cord blood MSCs, adipose tissue MSCs (AT-MSCs) exhibited a more potent inhibitory effect in preventing the activation of $CD4^+$, $CD8^+$ T cells, and NK cells. On the other hand, UC-MSCs did not affect the activation of B cells and NK cells.[114] A review comparing AT-MSCs and BM-MSCs showed that at equal cell numbers, AT-MSCs exhibited stronger immunomodulatory effects and promoted higher secretion of cytokines involved in the immunomodulation process, such as IL-6 and TGF-b1.[115] With regard to LN, currently there is no evidence comparing the immunomodulatory effect of each MSC source, indicating a potential area to investigate further.

Secretion of other factors

MSCs play a crucial role in kidney regeneration through a paracrine mechanism by secreting several growth factors that exert antiapoptotic and anti-inflammatory properties, such as insulin-like growth factor (IGF)-1, hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF).[101,116,117] In addition, MSCs inhibited renal MCP-1 and HMGB-1,[61] thereby suppressing the inflammation process and activation of B cells, which may inhibit the progression of LN. Protection against oxidative stress is provided by MSCs, since they are able to up-regulate mRNA expression of inducible nitric oxide synthase.[65] By suppressing the production of fibronectin, MSCs may prevent the progression of fibrosis in the kidney.[60]

Differentiation potential

MSCs injected into a murine model of acute kidney injury were able to differentiate into functional tubular cells to replace damaged cells, maintain structural integrity, and further improve kidney function.[118] In contrast, another study did not show UCB-MSCs undergoing direct engraftment and differentiating into renal tissue. Rather, they suppressed the production of lymphocytes and proinflammatory cytokines and induced polarization of Th2 cytokines, leading to improvement of LN.[64]

The limitations of MSCs

The transplantation of MSCs has some limitations, such as the aging of MSCs, malignant transformation of MSCs, possibility of cross contamination, poor engraftment, and limited differentiation. For the purpose of treating LN, allogeneic MSCs are preferred to autologous ones, since acquiring MSCs from a diseased individual will raise concern over abnormalities of the cells related to their phenotype, proliferation, and differentiation. Normal BM-MSCs can be cultured until 10 passages while maintaining their basic characteristics. In contrast, BM-MSCs from SLE patients could only be cultured until five passages prior to showing senescence behavior.[119] BM-MSCs from individuals with SLE exhibited senescent activity due to the low proliferation rate, higher production of reactive oxygen species, increased DNA damage and repair, increased cell cycle blockage associated with higher expression of p53 and p16, and altered cytokine production. These senescence criteria are mediated by a mitochondrial antiviral signaling protein (MAVS) and IFN-β positive feedback loop.[120]

BM-MSCs from SLE patients showed early signs of senescence in that they demonstrated morphological changes starting from passage 3. In addition, BM-MSCs from SLE patients were unable to reach confluence at passage 4. These aging behaviors were suggested to be related to telomerase activity.[121] Autologous BM-MSCs express a lower level of Bcl-2 and a higher level of cytochrome C in cytoplasm, indicating the involvement of the mitochondrial death pathway related to apoptotic activity. The death receptor pathway also plays a role, as shown by the activation of caspase 8 in BM-MSCs from SLE patients.[122] Supported by their impaired migratory capacity[123] as well as altered gene expression profiles in pathways directing cell cycle and protein binding,[124] autologous BM-MSCs are confirmed to be defective. Hence, allogeneic MSC transplantation becomes a promising therapy for active and refractory LN. However, a preclinical study showed that intraperitoneally injected allogeneic BM-MSCs could increase the production of anti-dsDNA antibody and worsen lupus manifestations and kidney histopathology as well.[62]

Future direction

Stem cell transplantation has shown the ability to elicit therapeutic effects in SLE patients, even though the cells' in vivo mechanism needs to be studied further. Some remaining issues of stem cell therapy for SLE are the ideal source of stem cells, the exact dose to be administered, the

necessity for a preconditioning regimen, and the best time to introduce the cells.[125] Grading of LN prior to the application of stem cells, assessed by histopathological examination, plays an important role in determining the appropriate therapy and predicting the prognosis. A randomized controlled trial comparing the effects of stem cell injection with those of conventional therapy while considering the grade of nephritis may provide more insight related to the clinical benefit. Further investigation is needed to reveal specific populations (for instance, according to age, sex, race, disease duration, prior treatment protocol, and histopathological class) that may be potential candidates for stem cell transplantation.

Several procedures may be considered to achieve a better outcome of MSC transplantation in LN patients, such as optimizing preconditioning in vitro using pharmacological or chemical agents, growth factors, cytokines, chemokines, and hormones.[126] Homing can be optimized by modifying the MSCs' culture conditions, cell surface engineering, or genetic modifications,[127] as well as stimulating the target site to recruit MSC mobilization.[128]

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

References

1 Furst DE, Clarke AE, Fernandes AW, *et al*. Incidence and prevalence of adult systemic lupus erythematosus in a large US managed-care population. *Lupus* 2013; 22: 99–105.
2 Somers EC, Marder W, Cagnoli P, *et al*. Population-based incidence and prevalence of systemic lupus erythematosus: the Michigan Lupus Epidemiology and Surveillance program. *Arthritis Rheumatol* 2014; 66: 369–378.
3 Osio-Salido E, Manapat-Reyes H. Epidemiology of systemic lupus erythematosus in Asia. *Lupus* 2010; 19: 1365–1373.
4 Jiménez S, Cervera R, Font J, *et al*. The epidemiology of systemic lupus erythematosus. *Clin Rev Allergy Immunol* 2003; 25: 3–12.
5 Maroz N, Segal MS. Lupus nephritis and end-stage kidney disease. *Am J Med Sci* 2013; 346: 319–323.
6 Su G, Luan Z, Wu F, *et al*. Long-term follow-up of autologous stem cell transplantation for severe paediatric systemic lupus erythematosus. *Clin Rheumatol* 2013; 32: 1727–1734.
7 Hiraki LT, Benseler SM, Tyrrell PN, *et al*. Pediatric systemic lupus erythematosus: a longitudinal study. *J Pediatr* 2008; 152: 550–556.
8 Aringer M, Burkhardt H, Burmester GR, *et al*. Current state of evidence on "off-label" therapeutic options for systemic lupus erythematosus, including biological immunosuppressive agents, in Germany, Austria and Switzerland – a consensus report. *Lupus* 2012; 21: 386–401.
9 Mok CC. Therapeutic options for resistant lupus nephritis. *Semin Arthritis Rheum* 2006; 36: 71–81.
10 Dooley MA, Jayne D, Ginzler EM, *et al*. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. *N Engl J Med* 2011; 365: 1886–1895.
11 Nørgård B, Pedersen L, Jacobsen J, *et al*. The risk of congenital abnormalities in children fathered by men treated with azathioprine or mercaptopurine before conception. *Aliment Pharmacol Ther* 2004; 19: 679–685.
12 Ordi-Ros J, Sáez-Comet L, Pérez-Conesa M, *et al*. Enteric-coated mycophenolate sodium versus azathioprine in patients with active systemic lupus erythematosus: a randomised clinical trial. *Ann Rheum Dis* 2017; 76: 1575–1582.
13 Wang CL, Wang F, Bosco JJ. Ovarian failure in oral cyclophosphamide treatment for systemic lupus erythematosus. *Lupus* 1995; 4: 11–14.
14 Gourley MF, Austin HA, Scott D, *et al*. Methylprednisolone and cyclophosphamide, alone or in combination, in patients with lupus nephritis. *Ann Intern Med* 1996; 125: 549–557.
15 Houssiau F, Vasconcelos C, D'Cruz D, *et al*. Immunosuppressive therapy in lupus nephritis: the Euro-Lupus Nephritis trial, a randomized trial of low-dose versus high-dose intravenous cyclophosphamide. *Arthritis Rheum* 2002; 46: 2121–2131.
16 Balal M, Demir E, Paydas S, *et al*. Uncommon side effect of MMF in renal transplant recipients. *Ren Fail* 2005; 27: 591–594.
17 Appel GB, Contreras G, Dooley MA, *et al*. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. *J Am Soc Nephrol* 2009; 20: 1103–1112.
18 Furie R, Petri M, Zamani O, *et al*. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. *Arthritis Rheum* 2011; 63: 3918–3930.
19 van Vollenhoven RF, Petri MA, Cervera R, *et al*. Belimumab in the treatment of systemic lupus erythematosus: high disease activity predictors of response. *Ann Rheum Dis* 2012; 71: 1343–1349.
20 Rovin BH, Furie R, Latinis K, *et al*. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. *Arthritis Rheum* 2012; 64: 1215–1226.
21 Askanase A, Byron M, Keyes-Elstein L, *et al*. (ACCESS Trial Group). Treatment of lupus nephritis with abatacept: the Abatacept and Cyclophosphamide Combination Efficacy and Safety Study. *Arthritis Rheumatol* 2015; 66: 3096–3104.
22 Rovin BH, Parikh SV. Lupus nephritis: the evolving role of novel therapeutics. *Am J Kidney Dis* 2014; 63: 677–690.
23 Saxena R, Mahajan T, Mohan C. Lupus nephritis: current update. *Arthritis Res Ther* 2011; 13: 240–251.
24 Xiong W, Lahita RG. Pragmatic approaches to therapy for systemic lupus erythematosus. *Nat Rev Rheumatol* 2014; 10: 97–107.
25 Stohl W. Future prospects in biologic therapy for systemic lupus erythematosus. *Nat Rev Rheumatol* 2013; 9: 705–720.
26 Borba HHL, Wiens A, De Souza TT, *et al*. Efficacy and safety of biologic therapies for systemic lupus erythematosus treatment: systematic review and meta-analysis. *BioDrugs* 2014; 28: 211–228.
27 Lateef A, Petri M. Unmet medical needs in systemic lupus erythematosus. *Arthritis Res Ther* 2012; 14: S4.
28 Vinuesa CG, Sanz I, Cook MC. Dysregulation of germinal centres in autoimmune disease. *Nat Rev Immunol* 2009; 9: 845–857.
29 Kim CH, Rott LS, Clark-Lewis I, *et al*. Subspecialization of CXCR5+ T cells: B helper activity is focused in a germinal center-localized subset of CXCR5+ T cells. *J Exp Med* 2001; 193: 1373–1381.
30 Gatto M, Zen M, Ghirardello A, *et al*. Emerging and critical issues in the pathogenesis of lupus. *Autoimmun Rev* 2013; 12: 523–536.
31 Aggarwal BB. Signalling pathways of the TNF superfamily: a double-edged sword. *Nat Rev Immunol* 2003; 3: 745–756.

32 Scalapino KJ, Tang Q, Bluestone JA, *et al*. Suppression of disease in New Zealand Black/New Zealand White lupus-prone mice by adoptive transfer of ex vivo expanded regulatory T cells. *J Immunol* 2006; 177: 1451–1459.
33 Sakaguchi S. Naturally arising CD4+ regulatory T cells for immunologic self-tolerance and negative control of immune responses. *Annu Rev Immunol* 2004; 22: 531–562.
34 Hsu WT, Suen JL, Chiang BL. The role of CD4+CD25+ T cells in autoantibody production in murine lupus. *Clin Exp Immunol* 2006; 145: 513–519.
35 Calvani N, Tucci M, Richards HB, *et al*. Th1 cytokines in the pathogenesis of lupus nephritis: the role of IL-18. *Autoimmun Rev* 2005; 4: 542–548.
36 Chan RW-Y, Lai FM-M, Li EK-M, *et al*. Imbalance of Th1/Th2 transcription factors in patients with lupus nephritis. *Rheumatology* 2006; 45: 951–957.
37 Heine G, Sester U, Sester M, *et al*. A shift in the Th(1)/Th(2) ratio accompanies the clinical remission of systemic lupus erythematosus in patients with end-stage renal disease. *Nephrol Dial Transplant* 2002; 17: 1790–1794.
38 Aringer M, Smolen JS. SLE - Complex cytokine effects in a complex autoimmune disease: tumor necrosis factor in systemic lupus erythematosus. *Arthritis Res Ther* 2003; 5: 172–177.
39 Marks SD, Williams SJ, Tullus K, *et al*. Glomerular expression of monocyte chemoattractant protein-1 is predictive of poor renal prognosis in paediatric lupus nephritis. *Nephrol Dial Transplant* 2008; 23: 3521–3526.
40 Tian J, Avalos AM, Mao S-Y, *et al*. Toll-like receptor 9-dependent activation by DNA-containing immune complexes is mediated by HMGB1 and RAGE. *Nat Immunol* 2007; 8: 487–496.
41 Hayashi A, Nagafuchi H, Ito I, *et al*. Lupus antibodies to the HMGB1 chromosomal protein: epitope mapping and association with disease activity. *Mod Rheumatol* 2009; 19: 283–292.
42 Schwartz MM. The pathology of lupus nephritis. *Semin Nephrol* 2007; 27: 22–34.
43 Sun L, Akiyama K, Zhang H, *et al*. Mesenchymal stem cell transplantation reverses multi-organ dysfunction in systemic lupus erythematosus mice and humans. *Rheumatology* 2009; 27: 1421–1432.
44 Gómez-Guerrero C, Hernández-Vargas P, López-Franco O, *et al*. Mesangial cells and glomerular inflammation: from the pathogenesis to novel therapeutic approaches. *Curr Drug Targets Inflamm Allergy* 2005; 4: 341–351.
45 Burt RK, Traynor AE. SLE – hematopoietic stem cell transplantation for systemic lupus erythematosus. *Arthritis Res Ther* 2003; 5: 207–209.
46 Alexander T, Thiel A, Rosen O, *et al*. Depletion of autoreactive immunologic memory followed by autologous hematopoietic stem cell transplantation in patients with refractory SLE induces long-term remission through de novo generation of a juvenile and tolerant immune system. *Blood* 2009; 113: 214–223.
47 Loh Y, Oyama Y, Statkute L, *et al*. Development of a secondary autoimmune disorder after hematopoietic stem cell transplantation for autoimmune diseases: Role of conditioning regimen used. *Blood* 2007; 109: 2643–2648.
48 Marmont A, van Lint M, Gualandi F, *et al*. Autologous marrow stem cell transplantation for severe systemic lupus erythematosus of long duration. *Lupus* 1997; 6: 545–548.
49 Snowden JA, Saccardi R, Allez M, *et al*. Haematopoietic SCT in severe autoimmune diseases: updated guidelines of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant* 2012; 47: 770–790.
50 Traynor AE, Schroeder J, Rosa RM, *et al*. Treatment of severe systemic lupus erythematosus with high-dose chemotherapy and haemopoietic stem-cell transplantation: a phase I study. *Lancet* 2000; 356: 701–707.
51 Traynor AE, Barr WG, Rosa RM, *et al*. Hematopoietic stem cell transplantation for severe and refractory lupus: analysis after five years and fifteen patients. *Arthritis Rheum* 2002; 46: 2917–2923.
52 Jayne D, Passweg J, Marmont A, *et al*. Autologous stem cell transplantation for systemic lupus erythematosus. *Lupus* 2004; 13: 168–176.
53 Burt RK, Traynor A, Statkute L, *et al*. Nonmyeloablative hematopoietic stem cell transplantation for systemic lupus erythematosus. *JAMA* 2006; 295: 527–535.
54 Alchi B, Jayne D, Labopin M, *et al*. Autologous haematopoietic stem cell transplantation for systemic lupus erythematosus: data from the European Group for Blood and Marrow Transplantation registry. *Lupus* 2013; 22: 245–253.
55 Cao C, Wang M, Sun J, *et al*. Autologous peripheral blood haematopoietic stem cell transplantation for systemic lupus erythematosus: the observation of long-term outcomes in a Chinese centre. *Clin Exp Rheumatol* 2017; 35: 500–507.
56 Wada H, Terasako K, Kamiya Y, *et al*. Immune recovery after autologous PBSC transplantation without in vitro graft manipulation for refractory systemic lupus erythematosus. *Bone Marrow Transplant* 2011; 46: 1450–1454.
57 Vanikar AV, Modi PR, Patel RD, *et al*. Hematopoietic stem cell transplantation in autoimmune diseases: the Ahmedabad experience. *Transplant Proc* 2007; 39: 703–708.
58 Daikeler T, Hügle T, Farge D, *et al*. Allogeneic hematopoietic SCT for patients with autoimmune diseases. *Bone Marrow Transplant* 2009; 44: 27–33.
59 Sweeney SE. Hematopoietic stem cell transplant for systemic lupus erythematosus: Interferon Regulatory Factor 7 activation correlates with the IFN signature and recurrent disease. *Lupus* 2011; 20: 975–980.
60 Zhou K, Zhang H, Jin O, *et al*. Transplantation of human bone marrow mesenchymal stem cell ameliorates the autoimmune pathogenesis in MRL/lpr mice. *Cell Mol Immunol* 2008; 5: 417–424.
61 Gu Z, Akiyama K, Ma X, *et al*. Transplantation of umbilical cord mesenchymal stem cells alleviates lupus nephritis in MRL/lpr mice. *Lupus* 2010; 19: 1502–1514.
62 Youd M, Blickarz C, Woodworth L, *et al*. Allogeneic mesenchymal stem cells do not protect NZBxNZW F1 mice from developing lupus disease. *Clin Exp Immunol* 2010; 161: 176–186.
63 Schena F, Gambini C, Gregorio A, *et al*. Interferon-γ-dependent inhibition of B cell activation by bone marrow-derived mesenchymal stem cells in a murine model of systemic lupus erythematosus. *Arthritis Rheum* 2010; 62: 2776–2786.
64 Chang J-W, Hung S-P, Wu H-H, *et al*. Therapeutic effects of umbilical cord blood-derived mesenchymal stem cell transplantation in experimental lupus nephritis. *Cell Transplant* 2011; 20: 245–257.
65 Gu F, Molano I, Ruiz P, *et al*. Differential effect of allogeneic versus syngeneic mesenchymal stem cell transplantation in MRL/lpr and (NZB/NZW)F1 mice. *Clin Immunol* 2012; 145: 142–152.
66 Choi EW, Shin IS, Park SY, *et al*. Reversal of serologic, immunologic, and histologic dysfunction in mice with systemic lupus erythematosus by long-term serial adipose tissue-derived mesenchymal stem cell transplantation. *Arthritis Rheum* 2012; 64: 243–253.
67 Ji S, Guo Q, Han Y, *et al*. Mesenchymal stem cell transplantation inhibits abnormal activation of Akt/GSK3β signaling pathway in T cells from systemic lupus erythematosus mice. *Cell Physiol Biochem* 2012; 29: 705–712.
68 Ma X, Che N, Gu Z, *et al*. Allogenic mesenchymal stem cell transplantation ameliorates nephritis in lupus mice via inhibition of B-cell activation. *Cell Transplant* 2013; 22: 2279–2290.
69 Collins E, Gu F, Qi M, *et al*. Differential efficacy of human mesenchymal stem cells based on source of origin. *J Immunol* 2014; 193: 4381–4390.
70 Thiel A, Yavanian G, Nastke M-D, *et al*. Human embryonic stem cell-derived mesenchymal cells preserve kidney function and extend lifespan in NZB/W F1 mouse model of lupus nephritis. *Sci Rep* 2015; 5: 17685.
71 Jang E, Jeong M, Kim S, *et al*. Infusion of human bone marrow-derived mesenchymal stem cells alleviates autoimmune nephritis in a lupus model by suppressing follicular helper T-cell development. *Cell Transplant* 2016; 25: 1–15.
72 Yuan L, Xiao Z, Huang X, *et al*. Human embryonic mesenchymal stem cells alleviate pathologic changes of MRL/Lpr mice by regulating Th7 cell differentiation. *Ren Fail* 2016; 38: 1432–1440.

73 He X, Zhang Y, Zhu A, *et al*. Suppression of interleukin 17 contributes to the immunomodulatory effects of adipose-derived stem cells in a murine model of systemic lupus erythematosus. *Immunol Res* 2016; 64: 1157–1167.
74 Choi EW, Lee M, Song JW, *et al*. Mesenchymal stem cell transplantation can restore lupus disease-associated miRNA expression and Th1/Th2 ratios in a murine model of SLE. *Sci Rep* 2016; 6: 38237.
75 Yang X, Yang J, Li X, *et al*. Bone marrow-derived mesenchymal stem cells inhibit T follicular helper cell in lupus-prone mice. *Lupus* 2018; 27: 49–59.
76 Yang J, Qin R, Zhang P, *et al*. Transplantation of human umbilical cord mesenchymal stem cell relieves the symptoms of lupus nephritis by inhibiting osteopontin expression. *Int J Clin Exp Med* 2017; 10: 6586–6594.
77 Kimbrel EA, Kouris NA, Yavanian GJ, *et al*. Mesenchymal stem cell population derived from human pluripotent stem cells displays potent immunomodulatory and therapeutic properties. *Stem Cells Dev* 2014; 23: 1611–1624.
78 Wu LW, Wang YL, Christensen JM, *et al*. Donor age negatively affects the immunoregulatory properties of both adipose and bone marrow derived mesenchymal stem cells. *Transpl Immunol* 2014; 30: 122–127.
79 Rombouts WJC, Ploemacher RE. Primary murine MSC show highly efficient homing to the bone marrow but lose homing ability following culture. *Leukemia* 2003; 17: 160–170.
80 Bazhanov N, Ylostalo JH, Bartosh TJ, *et al*. Intraperitoneally infused human mesenchymal stem cells form aggregates with mouse immune cells and attach to peritoneal organs. *Stem Cell Res Ther* 2016; 7: 27.
81 Li Q-Z, Zhou J, Yang R, *et al*. The lupus-susceptibility gene kallikrein downmodulates antibody-mediated glomerulonephritis. *Genes Immun* 2009; 10: 503–508.
82 Li Y, Raman I, Du Y, *et al*. Kallikrein transduced mesenchymal stem cells protect against anti-GBM disease and lupus nephritis by ameliorating inflammation and oxidative stress. *PLoS One* 2013; 8: e67790–e67801.
83 Li Y, Li W, Liu C, *et al*. Delivering oxidation resistance-1 (OXR1) to mouse kidney by genetic modified mesenchymal stem cells exhibited enhanced protection against nephrotoxic serum induced renal injury and lupus nephritis. *J Stem Cell Res Ther* 2014; 4: 231–255.
84 Ruan G, Yao X, Liu J, *et al*. Establishing a tree shrew model of systemic lupus erythematosus and cell transplantation treatment. *Stem Cell Res Ther* 2016; 7: 1–14.
85 Liang J, Zhang H, Hua B, *et al*. Allogenic mesenchymal stem cells transplantation in refractory systemic lupus erythematosus: a pilot clinical study. *Ann Rheum Dis* 2010; 69: 1423–1429.
86 Sun L, Wang D, Liang J, *et al*. Umbilical cord mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus. *Arthritis Rheum* 2010; 62: 2467–2475.
87 Wang Q, Qian S, Li J, *et al*. Case report: combined transplantation of autologous hematopoietic stem cells and allogenic mesenchymal stem cells increases T regulatory cells in systemic lupus erythematosus with refractory lupus nephritis and leukopenia. *Lupus* 2015; 24: 1221–1226.
88 Wang D, Akiyama K, Zhang H, *et al*. Double allogenic mesenchymal stem cells transplantations could not enhance therapeutic effect compared with single transplantation in systemic lupus erythematosus. *Clin Dev Immunol* 2012; 2012: 273291.
89 Wang D, Li J, Zhang Y, *et al*. Umbilical cord mesenchymal stem cell transplantation in active and refractory systemic lupus erythematosus: a multicenter clinical study. *Arthritis Res Ther* 2014; 16: R79–92.
90 Phillips CD, Wongsaisri P, Htut T, *et al*. Purified umbilical cord derived mesenchymal stem cell treatment in a case of systemic lupus erythematosus. *Clin Transl Med* 2017; 6: 31.
91 Deng D, Zhang P, Guo Y, *et al*. A randomised double-blind, placebo-controlled trial of allogeneic umbilical cord-derived mesenchymal stem cell for lupus nephritis. *Ann Rheum Dis* 2017; 76: 1436–1439.
92 Wang D, Wang S, Huang S, *et al*. Serum IFN-γ predicts the therapeutic effect of mesenchymal stem cells transplantation in systemic lupus erythematosus patients. *Stem Cells Transl Med* 2017; 6: 1777–1785.
93 Wang D, Zhang H, Liang J, *et al*. Allogeneic mesenchymal stem cell transplantation in severe and refractory systemic lupus erythematosus: 4 years of experience. *Cell Transpl* 2013; 22: 2267–2277.
94 Gu F, Wang D, Zhang H, *et al*. Allogeneic mesenchymal stem cell transplantation for lupus nephritis patients refractory to conventional therapy. *Clin Rheumatol* 2014; 33: 1611–1619.
95 Clark EA, Kalomoiris S, Nolta JA, *et al*. Concise review: microRNA function in multipotent mesenchymal stromal cells. *Stem Cells* 2014; 32: 1074–1082.
96 Shenoy A, Blelloch RH. Regulation of microRNA function in somatic stem cell proliferation and differentiation. *Nat Rev Mol Cell Biol* 2015; 15: 565–576.
97 Yao S. MicroRNA biogenesis and their functions in regulating stem cell potency and differentiation. *Biol Proced Online* 2016; 18: 1–10.
98 Kang H, Hata A. The role of microRNAs in cell fate determination of mesenchymal stem cells: balancing adipogenesis and osteogenesis. *Biochem Mol Biol* 2015; 48: 319–323.
99 Dai Y, Huang Y-S, Tang M, *et al*. Microarray analysis of microRNA expression in peripheral blood cells of systemic lupus erythematosus patients. *Lupus* 2007; 16: 939–946.
100 Te JL, Dozmorov IM, Guthridge JM, *et al*. Identification of unique microRNA signature associated with lupus nephritis. *PLoS One* 2010; 5: 1–7.
101 Tögel F, Hu Z, Weiss K. Administered mesenchymal stem cells protect against ischemic acute renal failure through differentiation-independent mechanisms. *Am J Physiol Ren Physiol* 2005; 289: 31–42.
102 Herrera MB, Bussolati B, Bruno S, *et al*. Mesenchymal stem cells contribute to the renal repair of acute tubular epithelial injury. *Int J Mol Med* 2004; 14: 1035–1041.
103 Bai L, Lennon D, Eaton V, *et al*. Human bone marrow-derived mesenchymal stem cells induce th2-polarized immune response and promote endogenous repair in animal models of multiple sclerosis. *Glia* 2009; 57: 1192–1203.
104 Aggarwal S, Pittenger MF. Human mesenchymal stem cells modulate allogeneic immune cell responses. *Transplantation* 2005; 105: 1815–1822.
105 Augello A, Tasso R, Negrini SM, *et al*. Bone marrow mesenchymal progenitor cells inhibit lymphocyte proliferation by activation of the programmed death 1 pathway. *Eur J Immunol* 2005; 35: 1482–1490.
106 Ren G, Chen X, Dong F, *et al*. Concise review: mesenchymal stem cells and translational medicine: emerging issues. *Stem Cells Transl Med* 2012; 1: 51–58.
107 Wang D, Feng X, Lu L, *et al*. A CD8 T cell/indoleamine 2,3-dioxygenase axis is required for mesenchymal stem cell suppression of human systemic lupus erythematosus. *Arthritis Rheumatol* 2014; 66: 2234–2245.
108 Feng X, Che N, Liu Y, *et al*. Restored immunosuppressive effect of mesenchymal stem cells on B cells after olfactory 1/early B cell factor-associated zinc-finger protein down-regulation in patients with systemic lupus erythematosus. *Arthritis Rheumatol* 2014; 66: 3413–3423.
109 Krampera M, Glennie S, Dyson J, *et al*. Bone marrow mesenchymal stem cells inhibit the response of naive and memory antigen-specific T cells to their cognate peptide. *Stem Cells* 2003; 101: 3722–3729.
110 Zhang J, Huang X, Wang H, *et al*. The challenges and promises of allogeneic mesenchymal stem cells for use as a cell-based therapy. *Stem Cell Res Ther* 2015; 6: 234–240.
111 Chen J, Wang Q, Feng X, *et al*. Umbilical cord-derived mesenchymal stem cells suppress autophagy of T cells in patients with systemic lupus erythematosus via transfer of mitochondria. *Stem Cells Int* 2016; 2016: 4062789.
112 Valencia X, Yarboro C, Illei G, *et al*. Deficient CD4+CD25high T regulatory cell function in patients with active systemic lupus erythematosus. *J Immunol* 2007; 178: 2579–2588.

113 Marie JC, Letterio JJ, Gavin M, *et al*. TGF-β1 maintains suppressor function and Foxp3 expression in CD4+CD25+ regulatory T cells. *J Exp Med* 2005; 201: 1061–1067.
114 Ribeiro A, Laranjeira P, Mendes S, *et al*. Mesenchymal stem cells from umbilical cord matrix, adipose tissue and bone marrow exhibit different capability to suppress peripheral blood B, natural killer and T cells. *Stem Cell Res Ther* 2013; 4: 125–140.
115 Melief SM, Zwaginga JJ, Fibbe WE, *et al*. Adipose tissue-derived multipotent stromal cells have a higher immunomodulatory capacity than their bone marrow-derived counterparts. *Stem Cells Transl Med* 2013; 2: 455–463.
116 Chen Y, Qian H, Zhu W, *et al*. Hepatocyte growth factor modification promotes the amelioration effects of human umbilical cord mesenchymal stem cells on rat acute kidney injury. *Stem Cells Dev* 2011; 20: 103–113.
117 Villanueva S, Ewertz E, Carrión F, *et al*. Mesenchymal stem cell injection ameliorates chronic renal failure in a rat model. *Clin Sci* 2011; 121: 489–499.
118 Li K, Han Q, Yan X, *et al*. Not a process of simple vicariousness, the differentiation of human adipose-derived mesenchymal stem cells to renal tubular epithelial cells plays an important role in acute kidney injury repairing. *Stem Cells Dev* 2010; 19: 1267–1275.
119 Sun LY, Zhang HY, Feng XB, *et al*. Abnormality of bone marrow-derived mesenchymal stem cells in patients with systemic lupus erythematosus. *Lupus* 2007; 16: 121–128.
120 Gao L, Bird AK, Meednu N, *et al*. Bone marrow-derived mesenchymal stem cells from patients with systemic lupus erythematosus have a senescence-associated secretory phenotype mediated by a mitochondrial antiviral signaling protein-interferon-β feedback loop. *Arthritis Rheumatol* 2017; 69: 1623–1635.
121 Nie Y, Lau C, Lie A, *et al*. Defective phenotype of mesenchymal stem cells in patients with systemic lupus erythematosus. *Lupus* 2010; 19: 850–859.
122 Li X, Liu L, Meng D, *et al*. Enhanced apoptosis and senescence of bone-marrow-derived mesenchymal stem cells in patients with systemic lupus erythematosus. *Stem Cells Dev* 2012; 21: 2387–2394.
123 Geng L, Li X, Feng X, *et al*. Association of TNF-α with impaired migration capacity of mesenchymal stem cells in patients with systemic lupus erythematosus. *J Immunol Res* 2014; 2014: 169082.
124 Tang Y, Ma X, Zhang H, *et al*. Gene expression profile reveals abnormalities of multiple signaling pathways in mesenchymal stem cell derived from patients with systemic lupus erythematosus. *Clin Dev Immunol* 2012; 2012: 826182.
125 Wang D, Sun L. Stem cell therapies for systemic lupus erythematosus: current progress and established evidence. *Expert Rev Clin Rheumatol* 2015; 11: 763–769.
126 Schäfer R. Mesenchymal stem/stromal cells in regenerative medicine: can preconditioning strategies improve therapeutic efficacy? *Transfus Med Hemother* 2016; 43: 256–267.
127 De Becker A, Riet IV. Homing and migration of mesenchymal stromal cells: how to improve the efficacy of cell therapy? *World J Stem Cells* 2016; 8: 73–87.
128 Kang SK, Shin IS, Ko MS, *et al*. Journey of mesenchymal stem cells for homing: strategies to enhance efficacy and safety of stem cell therapy. *Stem Cells Int* 2012; 2012: 342968.