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REVIEW

Mesenchymal stem cell transplantation in systemic lupus erythematous, a mesenchymal stem cell disorder

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Systemic lupus erythematosus (SLE) is a chronic autoimmune and inflammatory disorder with involvement of several organs and systems such as the kidney, lung, brain and the hematopoietic system. As the most prevailing organ manifestation, lupus nephritis is the major cause of mortality and morbidity in SLE patients. The most classically and widely administered immunosuppressive medications, namely corticosteroids and cyclophosphamide, have eventuated in a remarkable amelioration in disease complications over the last few years and reduced the progression to end-stage multiorgan failure. Mesenchymal stem cells (MSCs) are considered as non-hematopoietic and multipotential progenitor cells, which are able to differentiate into multiple cell lineages such as chondrocytes, osteoblasts, myoblasts, endothelial cells, adipocytes, neuron-like cells, hepatocytes and cardiomyocytes. MSCs from SLE patients have demonstrated defects such as aberrant cytokine production. Moreover, impaired phenotype, growth and immunomodulatory functions of MSCs from patients with SLE in comparison to healthy controls have been reported. Therefore, it is hypothesized that SLE is potentially an MSC-mediated disease and, as a result, allogeneic rather than autologous MSC transplantation can be argued to be a potentially advantageous therapy for patients with SLE. On the other hand, the MSC senescence phenomenon may meet the current therapeutic approaches with challenges and demand more attention. Here, we discuss MSC transplantations to date in animal models and humans and focus on the MSC senescence complications in SLE patients. *Lupus* (2018) **0,** 1–12.

Key words: Mesenchymal stem cell; systemic lupus erythematosus; senescence; treatment

Introduction

Systemic lupus erythematous (SLE) is a systemic autoimmune disease with skin rashes, which is seemingly mediated by autoantibodies. Impaired immune complex clearance is the suggested cause of autoantigen accumulation in various tissues including the kidneys, joints, vasculature and skin, and consequently the secretion of proinflammatory cytokines.[1–4] The incidence of SLE can be prone to diversity depending on the population of study. For example, its crude annual incidence per 100,000 ranges from low rates of 0.3 in Ukraine and 1.69 in Finland, 2.5–2.8 in South Korea and 3.32 in France, to an incidence of 5.5 in Michigan and 5.6 in Georgia in the US.[5–10] However, to a large extent, the incidence changes in association with the gender and ethnicity of the evaluated population. For example, in the Michigan and Georgia studies, the incidence was reported to be 10 and 5 times higher in women compared to men, respectively; these studies also reported that black women had 2.3 and 3 times higher incidence rates, respectively, compared to their white counterparts.[9,10] The prevalence of SLE in Iran has been reported to be 40 cases per 100,000 with a 9:1 female to male ratio. The most prevalent manifestations in SLE patients in Iran have been reported to be musculoskeletal, cutaneous, renal, neuropsychiatric, pulmonary, cardiac and hematologic symptoms;[11,12] however, the musculoskeletal manifestation has been reported to be more variable in juvenile SLE (JSLE) patients and is less frequent in children younger than 7 years old. Similar to other countries, the JSLE patients demonstrate poorer outcomes than adult SLE patients in Iran.[13]

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Although JSLE is relatively a rare disease, its prevalence has been reported to be much higher in the Kurdistan and Azerbaijan provinces in northwest Iran comparing to the rest of the country.[14] The mortality rate in SLE patients is about 2–3 times greater than that of the normal population, and the death toll is in the range of 6–7% and 9–13% 5 and 10 years after incidence, respectively, which can be a little variable depending on the studied population.[15–17] What intensifies the issue is the significant premature death in SLE patients.[18] The leading causes of death for SLE patients include cardiovascular disease, respiratory disease, malignancies, infection, active SLE disease, cerebrovascular disease and renal failure.[15,16,19] However, some recent studies indicate that tumors cannot be considered as a cause of higher mortality rate in SLE patients; there may even be a lower rate of cancer-related deaths, possibly due to infection-related shorter life expectancy in more severely immunocompromised patients as a result of receiving therapeutics.[19,20] Although the mortality rate has diminished dramatically in recent decades compared to the 1950s because of the development of new therapeutics, it remains relatively striking.[17] Furthermore, the continuously decreasing slope pattern has dramatically reduced in recent decades,[17,21] indicating the lack of development of new therapeutics with higher efficiencies. Current protocols for the treatment of SLE have been used for a long time and include non-steroid anti-inflammatory drugs, corticosteroids, mycophenolate mofetil, azathioprine, cyclophosphamide, cyclosporine and, more recently, a class of biological drugs that includes the FDA-approved drug belimumab, which affects B cell maturation by targeting B Lymphocyte Stimulator (BLyS) and prevents immunoglobulin production by these cells.[4,22]

These treatments have several drawbacks, such as toxicity and adverse events (AEs), non-specific generalized immune suppression and the presence of drug refractory cases of the disease, e.g. the AEs, that are attributed to corticosteroids can be classified as chronic (such as hypertension, sleep disturbances and type II diabetes) and acute (such as pneumonias and herpes zoster and fungal infections). Corticosteroids have been reported to increase the possibility of chronic and acute AE incidence 1.5 and 2 times in SLE patients.[23] Furthermore, these treatments are not curative collectively,[4] leading to demand for the development of new therapeutics. Efforts are underway to find new therapeutics without the mentioned drawbacks, such as drugs specifically targeting innate and adaptive pathways engaged in the disease's pathology[4,24] and also mesenchymal stem cell (MSC)-based therapies. The latter is the topic of this review.

It appears that MSCs are of suitable potential to be exerted in the treatment of SLE. Greater understanding of the mechanobiology of these cells will further contribute to the design of much more sophisticated therapeutic tools. Nonetheless, the issue of MSC senescence in these patients requires further focus, as this phenomenon has been related to impaired function of MSCs. Here, we attempt to go through current understanding of MSC applications in SLE treatment, both in human cases and animal models of SLE. We also describe MSC senescence and the challenging issues that it causes regarding SLE therapy.

MSCs

MSCs are non-hematopoietic multipotent plastic-adherent fibroblastic cells that are found in adults and embryos and can differentiate into connective tissue cells, including adipocytes, osteoblasts, chondrocytes, myoblasts and early progenitors of neural cells.[25,26] MSCs are present in all organs containing connective tissue. In addition to bone marrow (BM), they can be isolated from adult and fetal tissues including amniotic fluid, skeletal muscle, synovial tissue, adipose tissue, the placenta, cord blood and circulating blood.[27–29] Due to their easy acquisition, fast ex vivo proliferation and the feasibility of autologous transplantation, MSCs have become the first choice for stem cells to be applied in clinical regenerative medicine.[30]

MSCs have immunosuppressive and anti-inflammatory effects, which can be mediated through cell-to-cell contact or be dependent on secretory soluble factors.[31] Owing to their potential in modifying the responses of immune cells, these stem cells are popular candidates for cell therapy of immune-related disorders, especially autoimmune disorders.[32,33] The immunomodulatory effects of MSCs have been evaluated in a variety of autoimmune and inflammatory disorders, including SLE, diabetes, multiple sclerosis, Crohn's disease, ulcerative colitis and osteoarthritis, both in preclinical and clinical studies.[34]

Therapeutic use of MSCs in SLE

Therapy in animal models of SLE

The primary and most important finding from MSC transplantation (MSCT) in SLE animal models is increased survival. Glomerulonephritis

is one of the most prevalent and complicated complications in active SLE disease. Therefore, a therapeutic with the potential to improve this complication would be greatly desirable. The effect of MSCT on SLE nephropathy was compared to other standard drugs in several studies. The results were mostly delightful and demonstrated improved kidney function following human xenograft [35–42] and mice auto- or allograft MSCT.[43,44] The improved kidney function was found out by renal pathology tests, proteinuria, Blood Urea Nitrogen (BUN) and serum creatinine (Table 1).

The kidney is not the only organ involved during SLE. Other organs including liver, bone and spleen, which are also affected during SLE, have been evaluated in animals. MSCT improved the histological findings in the liver, including immune cell infiltration, fatty degeneration and glycogen degradation. In addition, the formation–resorption balance of bone, which is impaired in SLE animals, was restored. The transplantation of BM-MSCs also increased osteoblastic differentiation and improved osteoblastic niche reconstruction. Osteoblasts are necessary for hematopoietic stem cell (HSC) niche organization. These bone-related changes collectively contribute to enhancement of both bone and BM formation and can, in part, improve the hematopoiesis-related abnormalities in the animal.[36] Mouse spleen, the increased size of which is an indicator of adverse immune responses, was normal[38] or reduced[43] following MSCT therapy compared to the control groups.

The immunological profile following mice MSCT

Anti-ds-DNA (anti- double-stranded DNA) has been considered to be related to SLE and especially lupus nephritis, which is the most serious complication of active SLE disease. This autoantibody is included in the clinical classification criteria for the SLE.[45] The level of anti-ds-DNA in addition to diagnosis is also routinely measured to evaluate disease activity in clinical settings.[46] In MSCT studies in mice models of SLE, the level of anti-ds-DNA antibody was mostly decreased,[35–38,41,44] although some studies couldn't demonstrate any decrease in its level.[39,40,43] Consistent with this latter group of studies, it has been reported that anti-ds-DNA does not always follow clinical status and that there is a fraction of discordance between serologic and clinical status.[47] In some studies, in addition to anti-ds-DNA, reductions in ANAs, IgG1, IgG2a, IgG2b and IgM were observed.[36] However, in spite of the findings in old studies indicating the effect of high doses of corticosteroids in decreasing the ANA level,[48,49] ANA is not considered as a tool to monitor disease activity,[50] therefore its reduction cannot be interpreted as a clinically valuable finding (Table 1).

The anti-ds-DNA antibody, glomerular inflammatory cell infiltration, and antibody and C3 complement component deposition are immunological parameters, which are very precious due to their direct attribution to clinical outcomes and were almost uniformly decreased in the various studies following MSCT. However, there were significant changes in other immunological parameters such as decreasing $CD4^+$ cell number, especially T helper (Th)17 and Th1 lymphocytes,[35,36,40–44] a decreased number of precursors of B cells (namely, naïve mature B cells and plasma cells[42,43]), increased regulatory T (Treg) cells,[36–38,40,43,44] increased interleukin (IL)-4 and IL-10,[38] and decreased TNF-α, IL-6, IL-17,[40,44] MCP-1 and HMGB-1 cytokines.[37]

Regarding to the complex immune dysregulation in SLE, there is both hyperactivity and deficiency of the immune system at the same time in the disease. So, one of the drawbacks of the administration of immunosuppressive drugs can be a deepening of the immune deficiency present in the disease pathology. On the other hand, there is some evidence that MSCT not only modulates the immune hyperactivation but also immunodeficiency through restoring the production of cytokines including IL-2 and granulocyte-macrophage colony-stimulating factor. In fact, these findings can be interpreted as the potential of MSCT in restoring immune homeostasis.[38] There is although some evidence indicating that increased CD8 + cells and reduced tissue transforming growth factor (TGF)-β1 followed MSCT in a mouse model of lupus.[35]

In contrast to the promising finding mentioned above, there are also some contradictory results. In a study performed by Youd et al. in 2010, prophylactic and therapeutic administration of MSCs from BALB/c mice for the treatment of an NZB/W mouse model of lupus resulted in converse findings as follows. First, MSC treatment increased anti-ds-DNA production and immune complex deposition in the glomeruli both in prophylactic and therapeutic administration, although only in the prophylactic administration was the anti-ds-DNA increase significant. Second, the proteinuria and kidney pathology were increased in MSC-treated groups. Third, the MSCs supported plasma cells through secreting chemokines and cytokines. Fourth, there was an increased plasma cell percentage in treated mice and increased antibody

Table 1 Summary of treatment trials of MSCs in SLE animal models

Cell source	*Recipient*	*Graft type*	*Route of injection*	*Results*	*Reference*
Human AD-MSCs	C3.MRL-*Fas*^{lpr}/J C3H/HeJ mice	Cross-species (xenograft)	Intravenous	Increased survival and decreased serum level of anti-ds-DNA antibody. Decreased CD138 cells; the ratio of Th1/Th2. Downregulation of miR-96-5p and miR-182-5p. Reduced infiltration of inflammatory cells to the kidney and reduced renal glomerulus C3 deposition.	42
Human AD-MSCs	Female (NZB × NZW) F1 mice	Xenograft	Intravenous	Increased survival rate, decreased serum level of anti-ds-DNA and BUN, delayed onset of proteinuria, increased serum level of IL-4 and IL-10, increased spleen Foxp3 CD4 + Treg cells.	38
C57BL/6J MRL/lpr (NZB/NZW) F1 mouse BM-MSCs	MRL/lpr (NZB/NZW) F1 mice	Allogeneic syngeneic		In vivo: increased survival, less proteinuria and decreased histopathologic lesions, no decrease in anti-ds-DNA, decreased spleen size and the absolute number of CD4 + T cells and CD19+CD21+B cells. In vitro: decreased T cell proliferation potential and increased iNOS mRNA.	43
Human UC-MSCs and BALB/c mice BM-MSCs	MRL/lpr mice	Allograft and xenograft	Infusion	Reduced levels of anti-ds-DNA, restored kidney function, decreased proinflammatory MCP-1 and HMGB-1 levels, increased Treg cells in MRL/*lpr*.	37
C57BL/6 mouse ADSCs	Female B6.MRL/lpr mice	Syngeneic (autologous)	Intravenous	Reduced proteinuria and serum levels of anti-ds-DNA, IL-17, IL-6, kidney inflammatory cell infiltration, kidney IL-17 expression, Foxp3 and ROR-γt mRNA. Upregulation of miR-23b. Decreased IL-17.	44
Human UC-MSCs	B6.MRL-Fas^{lpr} mice	cross-species (xenograft)	Infusion	No increase in therapeutic effects of human UC-MSCs following treatment with poly (I:C) in B6.MRL-Fas^{lpr} mouse model of SLE; all parameters were similar including reduced anti-ds-DNA antibodies.	53
C57BL/6J mouse BM-MSCs	Female (NZB × NZW) F_1 mice	Allogeneic	Intravenous	No decrease in anti-ds-DNA or proteinuria. Improved kidney histopathological findings.	39
C3H/HeJ BM-MSCs and human BM-MSCs	MRL/*lpr mice* *SLE patients*	Allogeneic	Intravenous infusion	Reduction in serum levels of anti-ds-DNA, ANA, IgG1, IgG2a, IgG2b and IgM. Kidney and liver function improvement, increased bone and BM generation, increased HSC niche creation and increased Treg/Th17 ratio.	36
hESC-MSCs	Female NZBxNZW F1 (BWF1) mice	cross-species (xenograft)	Intravenously by tail vein injection	No decrease in anti-ds-DNA. Delayed disease progression, increased the survival of the mice. Reduced proteinuria and histopathological scores, inflammatory cell infiltration and IgG deposition. Decreased serum level of creatinine, BUN, TNFα and IL-6. Decreased TNFα and IL-6 in co-culture with BWF1 mouse BM	40

(continued)

Table 1 Continued

Cell source	*Recipient*	*Graft type*	*Route of injection*	*Results*	*Reference*
				mononuclear cells. Decreased T cell percentage and increased Treg cells.	
Balb/c mouse BM-MSCs	NZB/W mice	Allogeneic Balb/c MSCs	Intraperitoneal injection	Reverse results: increased anti-ds-DNA production and immune complex deposition, increased proteinuria and kidney pathology, increased plasma cell percentage and increased antibody production by plasma cells in co-culture conditions.	51
hESC-MSCs	MRL/Lpr mice	Cross-species (xenograft)	Tail vein injection	Increased survival and reduced anti-ds-DNA antibodies, decreased proteinuria and increased serum albumin. Improved kidney pathology. Reduced spleen Th17/lymphocyte ratio and serum IL-17 level. Upregulation of IL-10, PGE2 and TGF-β.	41
Human BM-MSCs	MRL/lpr mice	Xenograft		In vitro: inhibited T cell proliferation. In vivo: increased the survival, reduced anti-ds-DNA, decreased 24-hour proteinuria and serum creatinine level, decreased CD4 + T cells and increased CD8 + T cells Histopathologic amelioration and reduced expression of VEGF, TGF-β1 and fibronectin in glomeruli.	35
Kallikreins-modified (B6) mouse BM-MSCs	*B6.Sle1.Sle3* mice	Not mentioned clearly, probably syngeneic (B6 mice)	Tail vein injection	Amelioration of lupus nephritis, shown by reduced proteinuria, BUN and renal histopathological changes; anti-ds-DNA not evaluated. Reduced macrophages and T cell infiltration to the glomeruli and renal interstitium. Decreased proinflammatory and apoptosis-related cytokines in the SLE nephritis. Reduced apoptosis in renal histologic sections.	52

BM: bone marrow; BUN: blood urea nitrogen; ds: double-stranded; iNOS: inducible nitric oxide synthase; hESC: human embryonic stem cell; miR: microRNA; MSC: mesenchymal stem cell; SLE: systemic lupus erythematosus; Th: T helper; UC: umbilical cord.

production by plasma cells in co-cultured conditions (Table 1).[51]

Pretreated MSC for the treatment of a mouse model of lupus

There are some studies in which MSCs were modified ex vivo before administration in MSCT. In one study, mouse BM-MSCs were genetically modified to express Human kallikrein (hKLK) to synergize both kalikrin's renoprotective effect and the alleviating potential of MSCs on lupus nephritis. Treatment of mouse models of lupus by human kallikrein-1 (hKLK1) MSCs resulted in lupus nephritis amelioration, shown by reduced proteinuria, BUN, renal histopathological changes, reduced macrophages and T cell infiltration to the glomeruli and renal interstitium, and reduced proinflammatory and apoptosis related cytokines.[52]

In another study, human umbilical cord (hUC)-MSCs were treated by poly (I:C) prior to transfusion to a mouse model of SLE. Poly (I:C) is a toll-like receptor 3 ligand, and was used to enhance the anti-inflammatory effects of MSCs and consequently improve its therapeutic effects on SLE. Nonetheless, poly (I:C) had no effect on the therapeutic potential of the hUC-MSCs.[53]

Therapy in human SLE patients

Some evidence implies a decreased curative potential of MSCs derived from SLE disease. One noteworthy finding is that both bone and BM formation were impaired following transplantation of MSCs from human SLE patients to immunocompromised mice in contrast to healthy human cells. This MSC-related impairment can be correlated to a decreased BM CD34 + subset and consequent hematopoietic abnormalities in the SLE patients.[36] In addition, it was demonstrated that the efficacies of healthy and prelupus mouse MSCs were significantly higher than autografted MSCs derived from SLE mice with active disease (Table 2).[43]

Clinical effects of MSCT to humans

MSCT has been reported to improve the SLE disease activity index (SLEDAI), renal function-related parameters including proteinuria, BUN and creatinine, hematopoietic symptoms including leukopenia, thrombocytopenia and anemia, and also SLE-related diffuse alveolar hemorrhage symptoms.[54–60] The therapeutic effect can be so evident that, following MSCT in some studies, the prednisone and immunosuppressant doses were tapered.[59,60] One clinical trial study reported improved skin complications, arthritis, refractory hypertension and blood count following MSCT.[54] In contrast to the above-mentioned promising findings, it was demonstrated that autologous MSCT couldn't improve the disease activity and that the observed increase in Treg cells was not associated with clinical benefits. Although this study was performed on only two SLE patients, it is noteworthy that the therapy was conducted by autologous transplantation with MSCs derived from their own BM,[61] and again this finding implies lesser therapeutic potential of MSCs derived from SLE patients. Nevertheless, the MSCT has been reported to be a safe treatment to human SLE patients and no adverse complications were reported in the above-mentioned clinical trials.[54–61]

Immunological parameters improved by MSCT to humans

Decreases in complement serum levels are used as a tool for monitoring SLE activity; e.g. C3 and C4 are included as criteria in SLEDAI measurement and are used worldwide.[62] The C3 component of the complement system was measured in several MSCT clinical trials and the results demonstrated increased C3 levels following transplantation.[36,55] In addition, increased titers of ANAs and anti-ds-DNA antibody are both considered as diagnostic laboratory markers and are included in the SLEDAI criteria.[63] Furthermore, several studies demonstrated that, similar to the anti-ds-DNA antibody, ANA can have significant correlation with the SLE disease activity.[64] With this knowledge, the titers of anti-ds-DNA and ANA were measured in several studies and the results demonstrated decreased titers following MSCT,[54,55,59,60] although this was not always significant for ANA (Table 2).[54]

Another immunological finding reported by most of the MSCTs on SLE patients was increased numbers of CD4+Foxp3 + Treg cells[36,54,55,61,65] and Treg/Th17 ratio.[57,65] There were also increased TGF-β serum levels[55,65] and decreased TNF-α serum levels following transplantation.[65]

Cell and MSC senescence

Senescence, in contrast to aging, is not about the whole organism but is instead relevant at the cellular level and can be defined as "an essential arrest of cell division". These cells have changes in both their function and replicative potential. The senescent cells are arrested in G1 cellular growth phase and are large and flattened morphologically.[25] Cellular senescence can be divided in two groups regarding the molecular mechanism involved: the first is related to telomere shortening and the p53 pathway (telomere-initiated cellular senescence), and the other type is stress-induced and is mediated through the p16-pRB pathway (stress-induced or premature senescence, stasis or M0).[66] The gene expression profile in senescent cells changes dramatically. In addition to the genes related to the cell cycle, senescent cells have increased expression of secretory proteins with the potential to change the microenvironment; for example, senescent fibroblasts secrete increased amounts of extracellular remodeling proteins and inflammatory mediators to their surrounding microenvironment.[66]

MSCs mostly demonstrate senescence as follows: morphologically they are bigger without a spindle-shaped appearance; they also have reduced colony-forming unit number and size, reduced differentiation and division potential, reduced telomere length and telomerase activity, and have altered secretory profiles.[25]

MSC senescence in SLE patients

There are several studies demonstrating MSC cell senescence in SLE patients or lupus mouse models.

Table 2 Summary of treatment trials of MSCs in SLE patients

Cell source	*Recipient*	*Number of patients*	*Sex*	*Age (years)*	*Ethnicity*	*Graft type*	*Route of injection*	*Concomitant therapy (maintenance therapy)*	*Results*	*Reference*
Human BM-derived MSCs	Human	4	3 (F), 1 (M)	16–23	Chinese	Syngeneic	IV	Tapering doses of steroids and CTX	Increased Treg number, no change in SLEDAI	[61]
Human BM- MSCs or umbilical cord MSCs	Lupus nephritis patients resistant to conventional therapy	15	14 (F), 1 (M)	12–44	Chinese	Allogeneic	IV	tapering doses of steroids (prednisone) and CTX	Renal remission, represented by proteinuria and serum creatinine levels. Improved overall disease activity score, increased total serum albumin and decreased anti-ds-DNA antibody level.	[59]
BM MSCs	SLE patients with refractory cytopenia	16	14 (F), 2 (M)	17–56	Chinese	Allogeneic	IV	Tapering doses of steroids and (13) CTX	In SLE with refractory cytopenia SLEDAI decreased; leukopenia, thrombocytopenia and anemia were improved and increased the Treg/Th17 ratio	[57]
BM-MSCs	Human SLE patients	58	51 (F), 7 (M)	12–54	Chinese	Allogeneic	IV	Tapering prednisone and immunosuppressive drug (CTX, LEF or MMF)	Decreased SLEDAI, anti-ds-DNA, ANA, proteinuria, creatinine, and BUN. Improved skin complications, arthritis, refractory hypertension and increased Tregs	[54]
Human umbilical cord MSCs	Diffuse alveolar hemorrhagic SLE patient	35	34 (F), 1 (M)	16–62	Chinese	Allogeneic	IV	Tapered prednisone and reduced doses of immunosuppressive drug (CTX, MMF, LEF, CsA or tacrolimus)	Improved hemoptysis, dyspnea, hypertension, gingival and vaginal bleeding. Amelioration of anemia, thrombocytopenia and serum albumin. Decreased immune cell infiltration and DAH	[58]
C3H/HeJ BM-MSCs and human BM-MSC	MRL/*lpr* mice SLE patients	4	4 (F)	19–46	Chinese	Allogeneic	IV	Tapered doses of steroid and immunosuppressive drugs	Improved kidney and liver function, increased bone and marrow generation, increased HSC niche creation, increased Treg/Th17 ratio	[36]
Human umbilical cord-MSCs	Human SLE	81	74 (F), 7 (M)	12–55	Chinese	Allograft	IV	Tapered prednisone and CTX	Decreased SLEDAI, 24-hour proteinuria and BUN, serum albumin, anti-ds-DNA and ANA, and increased C3 level.	[55]
Human BM MSCs from healthy family donors (if not present umbilical cord MSCs)	Refractory SLE patients	40	38 (F), 2 (M)	17–54	Chinese	Single or double allogeniec MSCs	IV	Tapering prednisone and immunosuppressive drugs	Reduced SLEDAI score, proteinuria and serum creatinine level, but no difference between single or double allogeneic MSCs.	[56]

(continued)

Table 2 Continued

Cell source	*Recipient*	*Number of patients*	*Sex*	*Age (years)*	*Ethnicity*	*Graft type*	*Route of injection*	*Concomitant therapy (maintenance therapy)*	*Results*	*Reference*
Human umbilical cord MSCs	Human SLE	2	2 (F)	19–25	Chilean	Allogeneic MSCs	IV	Not mentioned	Increased Treg cells. Reduced CD8-IL17A+/CD3+Th17 cells. Increased TGF-β and decreased TNF-α levels in serum.	[65]
Umbilical cord-derived MSCs	Human SLE	51	48 (F), 3 (3)	17–56	Chinese	Allogeneic MSCs	IV	Not mentioned	Decreased disease activity, anti-ds-DNA, serum albumin, complement proteins, proteinuria, BUN and creatinine serum levels.	[60]
Human umbilical cord MSCs and BM MSCs	Human SLE	87	80 (F), 7 (M)	12–56	Chinese	Allogeneic MSCs	IV	Tapering of steroid and immunosup-pressive drugs (CTX, MMF, or LEF)	Follow-up 4 years (mean follow-up period of 27 months) following experiment: SELENA-SLEDAI scores signifi-cantly improved for up to 4 years after MSCT. 24-hour proteinuria decreased (improved renal involvement) serum creatinine, BUN, and GFR. Improved hemoglobin and platelet counts became normal	[86]

BM: bone marrow; BUN: blood urea nitrogen; CTX: cyclophosphamide; CsA: Cyclosporine A; DAH: diffuse alveolar hemorrhage; ds: double-stranded; IV: intravenous infusion; LEF: leflunomide; MMF: mycophenolate mofetil; MSC: mesenchymal stem cell; MSCT: MSC transplantation; SELENA: ; SLE: systemic lupus erythematosus; SLEDAI: SLE disease activity index; Th: T helper; Treg: regulatory T cell.

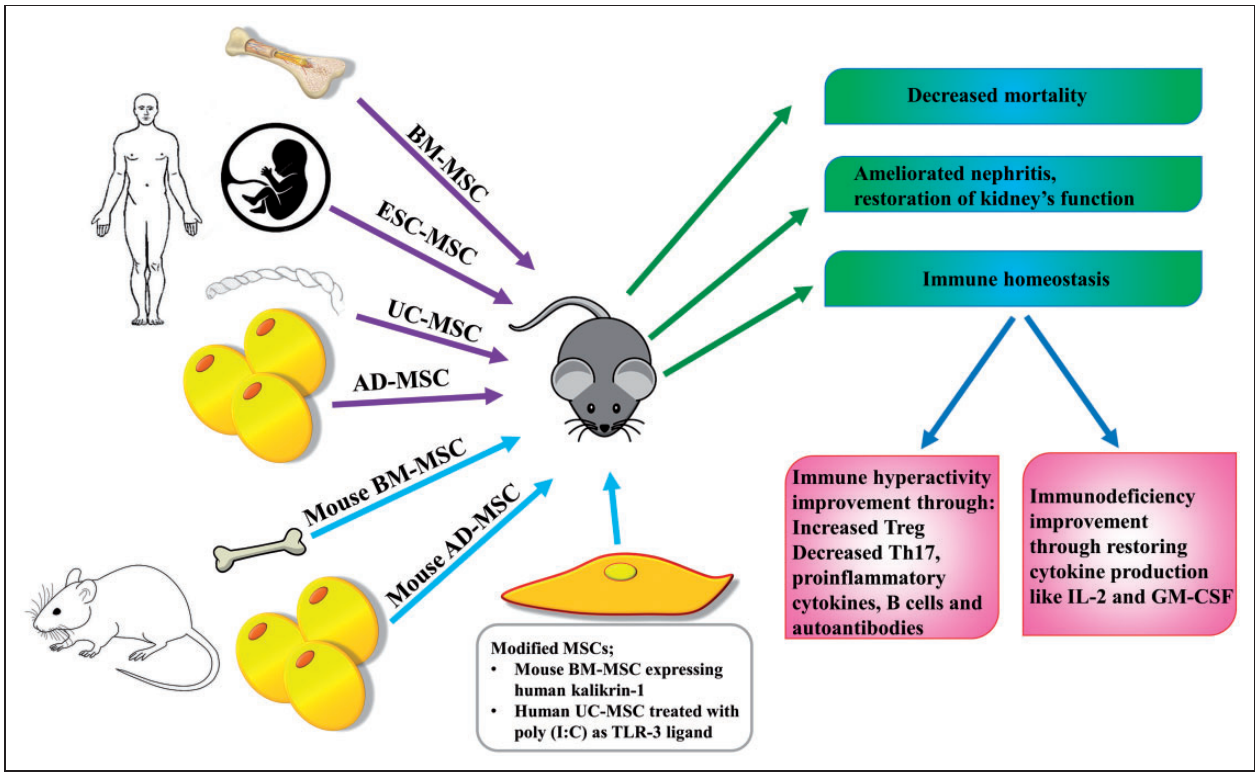

Figure 1 Summary of MSCT in human and mice model of lupus.

Some of the first evidence for the impaired function of BM stromal cells in SLE pathogenesis was obtained from ta study by Papadaki et al. in 2001;[67] however, Sun et al. were the first group to directly pointed to MSC defects in the BM of SLE patients and reported some findings related to the aging of these cells in comparison to healthy donor MSCs, including slower growth, earlier aging and decreased vitality during passages.[68] This issue has also been reported by Badri et al. as structural and functional defects of MSCs from a moue model of SLE.[69] The gene expression profiles of BM-MSCs from SLE patients assessed by microarray demonstrated that the expression of genes involved in the regulation of the cell cycle, actin cytoskeleton, and TGF-β, focal adhesion and MAPK pathways are changed. Consistent with altered gene expression in the cell cycle and actin cytoskeleton pathways in MSCs, the protein level of cyclin E was reduced, and actin cytoskeleton distribution was abnormal in the cytoplasm, respectively.[70] These can both be considered as signs of cell senescence. In addition, the only observed upregulated gene in the TGF-β pathway that was also confirmed at the protein level was bone morphogenetic protein (BMP)-5.[70] The signaling related to the TGF-β pathway can be done through two collections of Smad molecules, the Smad2/3 and Smad1/5/8 pathways. The latter pathway's activity contributes to the aging and terminal differentiation of cells and has been reported to contribute to the pathogenesis of other rheumatologic diseases including osteoarthritis. The Smad1/5/8 signaling pathway is also exploited by BMP molecules, hence the increased BMP-5 can be considered as another sign of cell senescence.[71–73] Several features pertaining to cell senescence have been reported in MSCs derived from the BM of SLE patients, including slower growth and proliferation, distorted morphology and F-actin distribution, increased number of β-galactosidase-positive cells, increased number of cells restricted in G1 phase, and decreased immunomodulatory properties including reduced TGF-β secretion and Treg/Th17 ratio and reduced B cell inhibition, the latter of which is due to reduced CCL2 production.[74–78] However, somewhat unexpectedly, MSCs from patients with higher SLEDAI have demonstrated activated telomerase, which is perceived to be triggered in response to early senescence.[74] Furthermore, the expression of $p16^{INK4A}$ has been found to be increased in MSCs isolated from SLE patients. $p16^{INK4A}$, which is involved in cell cycle control through preventing CDK4/6-cyclin D1 complex expression, is considered as a marker of

cell senescence. The important role of this molecule in MSC senescence can be highlighted by the finding that knock down of $p16^{INK4A}$ expression can reverse the senescence phenotype in these cells. $p16^{INK4A}$ inhibits the ERK1/2 signaling pathway and, furthermore, direct inhibition of this pathway can mimic the senescence related-phenotype in MSCs; hence, ERK1/2 is one of the signaling pathways that is involved in the senescence of MSCs in SLE patients.[76]

Other identified pathways that are involved in MSC senescence in SLE patients include the p53/p21 pathway through Wnt/β-catenin signaling,[79,80] p27-dependent cell cycle arrest due to endoplasmic reticulum stress,[81] the PTEN/Akt-$p27^{kip1}$ pathway,[77] the PI3/Akt pathway[82] and the mTOR pathway.[83]

Due to this effect of the mTOR pathway on the induction of MSC senescence and consequently the impaired functions of MSCs including defected immunoregulation, it is hypothesized that the lupus nephritis improvement following rapamycin (RAPA) therapy in MRL/*lpr* mice can be attributed to this effect of RAPA on MSC senescence.[83] Another intriguing point is that SLE serum can induce MSC senescence. This effect is due to the elevated levels of leptin and neutrophil-activating peptide 2 in the SLE serum that, through activating the PI3/Akt pathway, can promote MSC senescence.[82]

In addition to senescence-associated defects such as distorted cell morphology, defective proliferation and differentiation, and reduced immunoregulatory properties, MSCs isolated from SLE patients also demonstrate other abnormalities including increased apoptosis and impaired migration and homing capacity.[77,84,85]

Conclusion

The immunomodulatory and regenerative potentials of MSCs have led researchers to employ MSCs obtained from various tissues to treat SLE. Actually, the supportive function for HSCs in the BM niche, as well as the immunomodulatory properties of MSCs, suggest their capacity to be used in cell therapy. Studies have demonstrated insufficient results when using autologous MSCTs to treat SLE in mice and humans.[43,61] In addition, in contrast to healthy human MSCs, MSCs from human SLE patients cannot improve the defective bone and BM formation in mice model of SLE.[36]

On the other hand, there is satisfying evidence that SLE is also an MSC-mediated disorder. There is a bulk of studies emphasizing that MSCs from SLE patients may undertake a senescence process that is accompanied by defects in the phenotype and, in particular, the function of these cells. In addition, these cells have impaired migration and homing capacities and are also more susceptible to apoptosis. One therapeutic lesson that can be inferred from these findings is the possibility of more promising results from allogeneic MSCT and the preference of this approach to autologous MSCT. The second lesson that needs to be more confirmed in the future is the benefit of designing next-generation therapeutics and therapeutic approaches with special attention to MSCs and their disorders in SLE patients. Further studies to disclose the precise pathobiology of MSCs will hopefully open up new horizons in SLE therapy.

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