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Therapeutic Applications of Mesenchymal Stem Cells for Systemic Lupus Erythematosus

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Abstract

Mesenchymal stem cells (MSCs) have been intensively studied and applied in regenerative medicine and tissue engineering. Recently, their immune modulation functions make them as attractive potential approaches for autoimmune disease treatment. Systemic lupus erythematosus (SLE) is one type of chronic autoimmune diseases with multi-organ damaged by the immune system. Although current available treatments are effective for some patients, others are refractory for these therapies. The immunomodulatory and regenerative characteristics of MSCs make them as one promising candidate for treating SLE. Thus, we would discuss their immune modulation effects, pre-clinical and clinical applications, and the potentials for immune tolerance re-establishment in SLE here.

Keywords

Autoimmune diseases · Mesenchymal stem cells · MSCs · SLE · Systemic lupus erythematosus

Abbreviations

BAFF	B cell activating factor
BM	bone marrow
Breg	regulatory B cell
CCL2	C-C motif chemokine ligand 2
HSCs	hematopoietic stem cells
IDO	indoleamine 2,3-dioxygenase
IFN-γ	interferon-gamma
IL	interleukin
iNOS	inducible nitric oxide synthase
MSCs	mesenchymal stem cells
OAZ	olfactory 1/early B cell factor-associated zinc-finger protein
PD	programmed death
PGE2	prostaglandin E2
SLE	systemic lupus erythematosus
Tfh	follicular helper cell
TGF-β	transforming growth factor beta
Th	T helper cells
TNF-α	tumor necrosis factor alpha
Treg	regulatory T cells
UC	umbilical cord

1 Introduction

Mesenchymal stem cells (MSCs), also known as mesenchymal stromal cells, are spindle-shaped

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cells with multi-potent (chondrocyte, osteoblast, and adipocyte) and self-renewal abilities (Dominici et al. 2006; Pittenger et al. 1999). They could be derived from various adult tissues (Uccelli et al. 2008; Wang et al. 2014c), attach to tissue culture dishes and express certain cell surface markers (positive for CD73, CD90 and CD105; negative for CD45, CD34, CD14 or CD11b, CD79alpha or CD19 and HLA-DR) (Dominici et al. 2006). MSCs have been proposed as effective and safe cell source for stem cell therapy. They have low immunogenicity and could be safely harvested with no major ethical concerns (Wang et al. 2014c).

In addition to their applications in regenerative medicine and tissue engineering (Uccelli et al. 2008; Wang et al. 2014c), their immune modulation functions make them as attractive potential approaches for autoimmune disease treatment (Bernardo and Fibbe 2013; Keating 2012). Autoimmune diseases are characterized by local tissue destruction and chronic inflammation, which are induced by aberrant immune responses to self-constituents. This process normally includes both innate and adaptive immune responses, T and B cell auto-activation, and eventually immune tolerance collapse (Banchereau et al. 2017; van Kempen et al. 2015). So far, MSCs have been successfully applied in treating many autoimmune diseases, including systemic lupus erythematosus (SLE) (Liao et al. 2015).

Although many questions are still unsolved, the immune modulation effects of MSCs make them as the promising target for immune tolerance re-establishment in SLE. Thus, we would discuss their immune modulation effects, pre-clinical and clinical applications, and the potentials for immune tolerance re-establishment in SLE here.

2 Immune Modulations by MSCs

It has been demonstrated that the MSCs therapy is safe, without obvious side effects and malignancy in stem cell therapies for many disease (Tyndall 2014; Wang et al. 2014c). Theoretically, the transplanted MSCs should migrate into the inflamed tissues. However, the cell number is very low (Karp and Leng Teo 2009). Thus the paracrine effects have been proposed. And the immune tolerance re-construction is another promising theory for the therapeutic effects of MSCs (Ko et al. 2016). It is suggested that the MSCs induce monocytes/macrophages tolerance to autoimmunity in the eye (Ko et al. 2016). MSCs have been investigated to promote HSCs (hematopoietic stem cells) engraftment and prevent graft rejection in graft-versus-host disease (Gao et al. 2016; Le Blanc et al. 2008; Le Blanc et al. 2004; Polchert et al. 2008). MSCs also promote immune tolerance in organ transplantation (Contreras-Kallens et al. 2017). Furthermore, the MSCs have been applied in treating SLE (Sun et al. 2010).

The immune modulation activities of MSCs are through both cell-cell direct contact and also secretome, which is composed of extracellular vesicles and soluble factors (Heldring et al. 2015; Phinney et al. 2015). The soluble factors include IDO (indoleamine 2,3-dioxygenase), PGE2 (prostaglandin E2), soluble HLA-G5, TNF-stimulated gene-6, heme oxygenase-1, nitric oxide, IL-10 (Interleukin-10) and TGF-β1 (transforming growth factor beta 1) (Bernardo and Fibbe 2013; Keating 2012; Uccelli et al. 2008).

MSCs are low immunogenic or have immune privilege resulting from low expression of major histo-compatibility complex class I, II and the lack of co-stimulatory factors (Bernardo and Fibbe 2013, Keating 2012, Uccelli et al. 2008). Thus allogenic MSCs transplantation should be feasible with minimal immune rejections. However, it has been found that the allogenic MSCs would be rejected in the mice model (Ankrum et al. 2014). And the immune environments affect the therapeutic effects of MSCs significantly (Carrion et al. 2010). Thus understanding how the MSCs interact with the immune system is critical before clinical applications.

3 MSCs Therapy for Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is one type of chronic autoimmune diseases with multi-organ damaged by immune system (Bernatsky et al. 2006; Lee et al. 2016; Murphy et al. 2013; Tsokos 2011; Tyndall 2009). Several factors, such as genetic and environmental factors, could induce self-tolerance loss and immune system over-activation, resulting in tissue and organ injuries (Lisnevskaia et al. 2014; Tsokos et al. 2016). Current available treatments for SLE have been demonstrated to reduce morbidity and mortality effectively, such as non-steroidal anti-inflammatory drugs, anti-malarial agents, glucocorticoids, immunosuppressive agents and target depleting B cells (Xiong and Lahita 2014). Although they are effective for some patients, others are refractory for these therapies. The immuno-modulatory and regenerative characteristics of MSCs make them as one promising candidate for treating SLE.

3.1 MSCs Defects in SLE

The bone marrow MSCs derived from SLE patients have impaired proliferation capability and immune modulation functions (Che et al. 2014; Feng et al. 2014; Gao et al. 2017; Nie et al. 2010; Sun et al. 2007). They are defective in cell migration and more prone to cell death (Gu et al. 2014a; Gu et al. 2014b; Li et al. 2012; Shi et al. 2014). Furthermore, they fail to suppress the T and B cell activities (Feng et al. 2014; Wang et al. 2014a). Thus the MSCs isolated from SLE patients have no therapeutic benefits (Carrion et al. 2010). Furthermore, it has been demonstrated that in the MRL/lpr mice model of SLE, the impairment of bone marrow MSCs and their niche deficiency contribute to the pathogenesis of SLE-like diseases (Sun et al. 2009).

MSCs from SLE patients have cytokine secretion abnormality (Sun et al. 2007) and are more prone to senescence and apoptosis (Nie et al. 2010) through up-regulating Wnt/β-catenin and p53/p21 pathways (Gu et al. 2014b) or down-regulating Bcl-2 (Li et al. 2012) and IDO (Wang et al. 2014a). The MSCs derived from the bone marrow of lupus-like mice and SLE patients have decreased abilities to suppress the B cell proliferation, differentiation, and activity, resulting from CCL2 (C-C motif chemokine ligand 2) reduction. And the CCL2 over-expression could restore their immune suppression abilities in the SLE MSCs (Che et al. 2014). Furthermore, the gene OAZ (olfactory 1/early B cell factor-associated zinc-finger protein) is highly enriched in MSCs and up-regulated in the SLE patients. Knocking down OAZ could also restore the impaired immune suppression function of SLE MSCs via up-regulating CCL2 expression (Feng et al. 2014). Later studies have demonstrated that the SLE MSCs have increased reactive oxygen species production, DNA damage and repair, p53 and p16 expression, pro-inflammatory cytokine production through the mitochondrial antiviral signaling protein-Interferon-β feedback loop (Gao et al. 2017). Thus the autologous MSCs derived from SLE patients have impaired therapeutic applications and are not the suitable cell source for cell therapy. And the allogenic MSCs from healthy donors are the preferred cell source in treating SLE patients.

3.2 Pre-clinical Studies of MSCs Therapy for SLE

In the mice model of SLE, MSCs transplantation improves renal functions, reduces renal and lung pathology, decreases serum levels of autoantibody and proteinuria, and prolongs the survival of lupus prone mice through inhibiting monocyte, B cell, follicular helper cell (Tfh), and inducing Treg (regulatory T cells) and IL-10 (Table 1) (Chang et al. 2011; Choi et al. 2012; 2015; Deng et al. 2015; Gu et al. 2010; He et al. 2016; Jang et al. 2016; Ji et al. 2012; Ma et al. 2013; Park et al. 2015; Schena et al. 2010; Sun et al. 2009; Thiel et al. 2015; Zhang et al. 2014; 2017; Zhou et al. 2008).

Table 1 Therapeutic applications of MSCs for SLE in pre-clinical studies

Disease Model	Cell Origin	Delivery Method	Follow-up Period	Outcomes	References
MRL/lpr mice	hBM-MSCs	1×10^6 cells; tail vein; once	16 weeks	Auto-antibody reduction; proteinuria reduction; renal pathology reduction	Zhou et al. (2008)
MRL/lpr mice	mBM-MSCs	0.1×10^6 cells/10 g; tail vein; twice	11 weeks	Osteoblastic niche reconstruction; multiple organ function improvement	Sun et al. (2009)
MRL/lpr mice	hUC-MSCs	1×10^6 cells; tail vein; three times	11 weeks	Auto-antibody reduction; proteinuria reduction; renal pathology reduction	Gu et al. (2010)
(NZBxNZW) F1 mice	mBM-MSCs	$1.25x10^6$ cells; tail vein; three times;	5 weeks	Reduction in glomerular immune complex deposition and lymphocytic infiltration	Schena et al. (2010)
(NZBxNZW) F1 mice	hUC-MSCs	1×10^6 cells; tail vein; once	8 weeks	Auto-antibody reduction; proteinuria reduction; renal pathology reduction; prolonged the life span	Chang et al. (2011)
(NZBxNZW) F1 mice	hAD-MSCs	0.5×10^6 cells; tail vein; every 2 weeks	54 weeks	No adverse effects; higher survival rate; auto-antibody reduction; proteinuria reduction; renal pathology reduction	Choi et al. (2012)
MRL/lpr mice	mBM-MSCs	0.2×10^6 cells/10 g; tail vein; twice	4 weeks	Disease activity reduction; T cell proliferation inhibition	Ji et al. (2012)
MRL/lpr mice	mBM-MSCs	1×10^6 cells; tail vein; once	8 weeks	Decreased BAFF expression; auto-antibody reduction; proteinuria reduction	Ma et al. (2013)
MRL/lpr mice	hUC-MSCs	1×10^6 cells; tail vein; three times	11 weeks	Interstitial pneumonitis, lung peribronchiolar lesion, and lung perivascular lesion reduction	Zhang et al. (2014)
MRL/lpr mice	hAD-MSCs; CTLA4Ig-overexpressing hAD-MSCs	1×10^6 cells; tail vein; every 2 weeks	18 weeks	Auto-antibody reduction; proteinuria reduction; kidney inflammation reduction	Choi et al. (2015)
MRL/lpr mice	hUC-MSCs	1×10^6 cells; tail vein; once	4 weeks	Improved the proportion of $CD206^+$ macrophages and their phagocytic activity	Deng et al. (2015)
Roquin (san/san) mice	hAD-MSCs	1×10^6 cells; tail vein; once weekly	5 weeks	Auto-antibody reduction; proteinuria reduction; decreased $ICOS^+CD44^+$ Tfh cells, Th1 cells and Th17 cells; increased Treg cells; Bregs expansion induction	Park et al. (2015)
(NZBxNZW) F1 mice	hESC-MSCs	0.5×10^6 cells; tail vein; 3 times weekly	12 weeks	Auto-antibody reduction; proteinuria reduction; preserved renal architecture; kidney inflammation reduction	Thiel et al. (2015)
MRL/lpr mice	mAD-MSCs	1×10^6 cells; tail vein; every 2 weeks	10 weeks	Auto-antibody reduction; proteinuria reduction; kidney inflammation reduction	He et al. (2016)
(NZBxNZW) F1 mice	hBM-MSCs	1×10^6 cells; retro-orbital; every 2 weeks, 3 times	11 weeks	Attenuated glomerulonephritis; auto-antibody reduction; proteinuria reduction; improved survival; Tfh cell reduction	Jang et al. (2016)

(continued)

Table 1 (continued)

Disease Model	Cell Origin	Delivery Method	Follow-up Period	Outcomes	References
MRL/lpr mice	hUC-MSCs	1×10^6 cells; tail vein; once	4 weeks	Tfh cell reduction; auto-antibody reduction	Zhang et al. (2017)

hBM-MSCs human bone marrow derived mesenchymal stem cells, *hUC-MSCs* human umbilical cord derived mesenchymal stem cells, *hAD-MSCs* human adipose tissue derived mesenchymal stem cells, *hESC-MSCs* human embryonic stem cell derived mesenchymal stem cells, *mAD-MSCs* mouse adipose tissue derived mesenchymal stem cells, *mBM-MSC* mouse bone marrow derived mesenchymal stem cells

One single dosage of MSCs transplantation shows significant therapeutic effects, which could be further promoted by multiple treatment (Choi et al. 2012; Gu et al. 2010). And the long-term serial administrations do not show any adverse effects (Choi et al. 2012). Furthermore, it would be more effective at the early stage of SLE progress than the late stage (Choi et al. 2012). The transplanted cells could be detected in the kidney even after 3 months post cell infusion (Gu et al. 2010).

MSCs prevent disease associated inflammation, protein cast deposition, and infiltration of $CD3^+$ lymphocytes and complement C3 in the kidneys (Thiel et al. 2015; Zhou et al. 2008). This therapy also leads to significant reductions in serum levels of tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), two inflammatory cytokines associated with SLE (Chang et al. 2011; He et al. 2016; Thiel et al. 2015). They also decrease T-helper (Th) 1 cytokines (Interferon-γ, IL-2), Th17 cytokine (IL-17) and increase Th2 cytokines (IL-4, IL-10) (Chang et al. 2011; Choi et al. 2012; He et al. 2016).

MSCs can significantly decrease marginal zones, T1, T2, activated B cells, and plasma cells (Ma et al. 2013; Park et al. 2015). Moreover, serum levels of B cell activating factor (BAFF) decrease significantly after MSCs transplantations (Ma et al. 2013). MSCs inhibit antigen-dependent proliferation and differentiation to plasma cells of follicular and marginal zone B cells. This inhibitory effect is dependent on cell-to-cell contact, interferon-gamma (IFN-γ) and the programmed death 1 (PD-1)/PD ligand pathways (Schena et al. 2010). The infiltration of long-lived plasma cells into the inflamed kidney is also reduced in the hBM-MSCs (human bone marrow derived mesenchymal stem cells) treated mice (Jang et al. 2016).

The auto-antibodies are predominantly produced with the help of Tfh cells and then form immune complexes that trigger widespread inflammatory damages, including nephritis (Jang et al. 2016). MSCs decrease the percentage of Tfh cells, which is increased in lupus and positively correlated to plasma cell proportions and serum total IgG as well as anti-dsDNA antibody levels (Park et al. 2015; Zhang et al. 2017). The proliferation and differentiation of Tfh cells are markedly suppressed by MSCs through iNOS (inducible nitric oxide synthase) production and a cell-contact-dependent manner (Jang et al. 2016; Park et al. 2015; Zhang et al. 2017). In addition, MSCs decrease the Th1 cells and Th17 cells while increase the Foxp3-expressing Treg cells and IL-10 expressing Breg (regulatory B cell) cells (Choi et al. 2012; He et al. 2016; Park et al. 2015; Zhou et al. 2008). MSCs also inhibit the G1/S transition of the abnormal lupus T lymphocytes through up-regulating p21 and p27 and down-regulating cyclin-dependent kinase 2 (Ji et al. 2012)

MSCs transplantation increases the proportion of $CD206^+$ and $CD68^+$ macrophages and their phagocytic activities (Deng et al. 2015; He et al. 2016). What is even more interesting is that the MSCs transplantation is capable of reconstructing the bone marrow osteoblastic niche and more effectively reverses the multi-organ dysfunction when compared with medical immuno-suppression with cyclophosphamide (Sun et al. 2009).

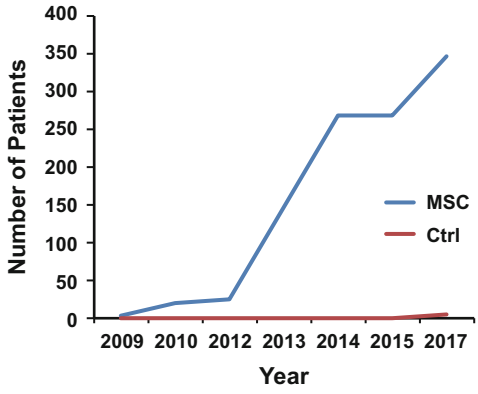

Fig. 1 Number of SLE patients subjected to MSCs therapy in clinical studies. *SLE* systemic lupus erythematosus, *MSCs* mesenchymal stem cells, *Ctrl* control

3.3 Clinical Studies of MSCs Therapy for SLE

In clinical studies, MSCs transplantation is safe and effective in treating SLE patients, with improved renal functions and decreased autoantibody productions (Fig. 1, Table 2; Deng et al. 2017; Gu et al. 2014a; Li et al. 2013; Liang et al. 2010; Phillips et al. 2017; Shi et al. 2012; Sun et al. 2009; 2010; Wang et al. 2013, 2014b, 2015, 2017a, b, c).

Allogenic bone marrow or umbilical cord (UC)-derived MSCs transplantation has shown the disease activity amelioration and renal function improvement in the SLE patients refractory to conventional treatment (Gu et al. 2014a; Sun et al. 2009; Wang et al. 2013). MSCs also reduce many SLE markers significantly. And the improvement is followed by peripheral Treg up-regulation and the balance re-establishment between Th1- and Th2-related cytokines (Sun et al. 2010). The MSCs transplantation has cured the SLE patients with diffuse alveolar hemorrhage, who was refractory to the methylprednisolone and immunoglobulin treatment (Liang et al. 2010; Shi et al. 2012), and SLE patients with refractory cytopenia (Li et al. 2013). Another study also shows that the umbilical cord derived MSCs have the therapeutic effect in severe and refractory SLE patients (Wang et al. 2014b). And this therapeutic effect is partially through up-regulating Treg and down-regulating Th17 cells by MSCs (Li et al. 2013; Sun et al. 2010; Wang et al. 2015, 2017a). The up-regulation of Treg is mediated by increasing the serum levels of TGF-β while the down-regulation of Th17 cells is by PGE2 up-regulation (Wang et al. 2017a). Moreover, the higher levels IFN-γ could predict a good response to MSCs therapy in active lupus patients (Wang et al. 2017c).

3.4 Mechanisms of MSCs Therapy for SLE

Thus both pre-clinical and clinical studies have shown that MSCs are safe and effective for treating SLE. However, most of the underlying mechanisms still remain unclear. Now it is clear that MSCs could suppress the immune response, reduce the pro-inflammatory factors and up-regulate anti-inflammatory factors (Chang et al. 2011; Choi et al. 2012; He et al. 2016; Thiel et al. 2015). Furthermore, they could suppress the B cell (Jang et al. 2016; Ma et al. 2013; Park et al. 2015; Schena et al. 2010), Th1 and Th17 cells (Choi et al. 2012; He et al. 2016; Park et al. 2015; Zhou et al. 2008). And they increase Treg and Breg cells (Choi et al. 2012, He et al. 2016, Park et al. 2015, Zhou et al. 2008; Fig. 2).

MSCs suppress the B cell activities through inhibiting Tfh cells via iNOS production and cell contact (Jang et al. 2016; Park et al. 2015; Zhang et al. 2017). Furthermore, the inhibition of B cell proliferation and antibody production by MSCs is mediated by both $CD4^+$ and $CD8^+$ T cells. Moreover, the cell-cell contact between the MSCs and T cells, but not between the MSCs and B cells, is necessary to inhibit the B cell proliferation. (Rosado et al. 2015).

It has been demonstrated that the bone marrow derived MSCs could induced the T cell apoptosis via the FAS ligand-dependent FAS pathway, resulting in disease phenotype ameliorates. MSCs could secrete monocyte chemotactic protein 1, recruit T cells and mediate T cell apoptosis. The apoptotic T cells then induce macrophages to produce high levels of TGF-β, which up-regulates of $CD4^+CD25^+Foxp3^+$ regulatory T cells and, ultimately, immune tolerance (Akiyama et al. 2012).

Table 2 Therapeutic applications of MSCs for SLE in clinical studies

	No. of Patients					
Cell origin	**MSCs treatment**	**Ctrl**	**Delivery method**	**Follow-up period**	**Outcomes**	**References**
hBM-MSCs	4	0	Intravenously	12–18 months	Disease activity reduction; renal function improvement; serologic markers improvement	Sun et al. (2009)
hUC-MSCs	1	0	Intravenously	5 weeks	Improvements in the clinical condition, oxygenation level, radiographic and hematological status	Liang et al. (2010)
hUC-MSCs	16	0	Intravenously	3–28 months	Significant improvements in the SLEDAI score, levels of serum ANA, anti-dsDNA antibody, serum albumin, complement C3, and renal function	Sun et al. (2010)
hUC-MSCs	4	0	Intravenously	9–24 months	Dramatic improvements of their clinical manifestations; amelioration of oxygen saturation as well as hematological and serologic changes	Shi et al. (2012)
hBM-MSCs hUC-MSCs	35	0	Intravenously	6–45 months	Decline of disease activity; increased Treg and decreased Th17; reverse hematological aberration in SLE patients with refractory cytopenia	Li et al. (2013)
hBM-MSCs hUC-MSCs	87	0	Intravenously	4 years	Significant changes in the SLEDAI score, levels of serum auto-antibodies, albumin, and complements	Wang et al. (2013)
hBM-MSCs hUC-MSCs	81	0	Intravenously	12 months	Obvious amelioration of renal function; lomerular filtration rate improved; no adverse event	Gu et al. (2014a)
hUC-MSCs	40	0	Intravenously	12 months	No adverse events; proteinuria declined; serum antinuclear antibody and anti-double-stranded DNA antibody decreased	Wang et al. (2014b)
hHSCs plus hBM-MSC	1	0	Intravenously	36 months	Clinical symptoms caused by SLE were remitted; $CD4^+CD25^+FoxP3^+$Treg cells increased	Wang et al. (2015)
hUC-MSCs	12	6	Intravenously	6 months	No obvious positive treatment effect.	Deng et al. (2017)
hUC-MSCs	1	0	Intravenously	12 months	Auto-antibodies declined	Phillips et al. (2017)
hUC-MSCs	30	0	Intravenously	12 months	Treg increased; Th17 decreased; increase in serum TGF-β; decrease in serum TNF-α	Wang et al. (2017a)
hUC-MSCs	9	0	Intravenously	6 years	No adverse events; long-term safety proved	Wang et al. (2017b)
hUC-MSCs	26	0	Intravenously	12 months	IFN-γ predicts clinical response to MSCs in SLE	Wang et al. (2017c)

hBM-MSCs human bone marrow derived mesenchymal stem cells, *UC-MSCs* human umbilical cord derived mesenchymal stem cells, *hHSCs* human hematopoietic stem cells, *Ctrl* control, *SLE* systemic lupus erythematosus, *IFN-γ* interferon-gamma, *TNF-α* tumor necrosis factor alpha, *TGF-β* transforming growth factor beta, *Treg* regulatory T cells, *Th17* T helper cells, type 17

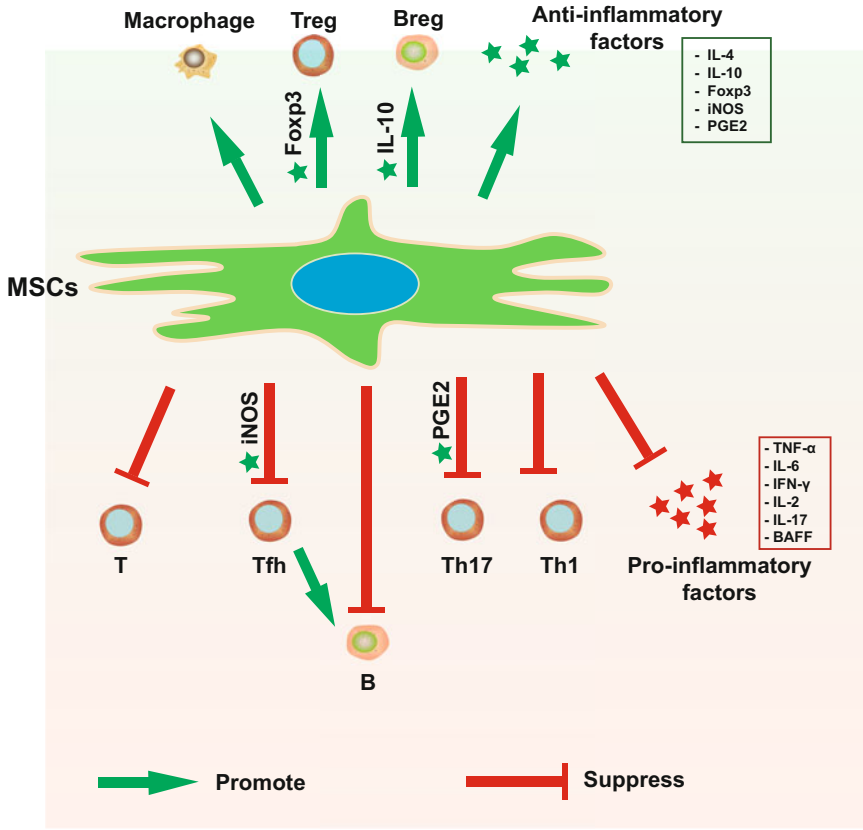

Fig. 2 Mechanisms of MSCs therapy for SLE. MSCs could up-regulate the expression and secretion of anti-inflammatory factors, and promote the immune suppressive functions of macrophage, Treg and Breg cells. MSCs induce Treg production through up-regulating Foxp3 expression and Breg via IL-10 expression. On the other hand, MSCs also could suppress the functions of T, B, Tfh, Th1, and Th17 cells with decreased the expression of pro-inflammatory factors. MSCs suppress the Tfh through iNOS production and Th17 via PGE2. In addition to the direct inhibition, MSCs also suppress the B cell activities through Tfh inhibition. *MSCs* mesenchymal stem cells, *Treg* regulatory T cells, *Breg* regulatory B cells, *T* T cells, *B* B cells, *Tfh* follicular helper T cells, *Th1* helper T cell, type 1, *Th17* helper T cell, type 17

4 Targeting MSCs for Re-Establishing the Immune Tolerance

SLE is characterized by local tissue destruction and chronic inflammation, which are caused by aberrant immune responses to self-constituents. This process normally includes both innate and adaptive immune responses, T and B cell auto-activation, and eventually immune tolerance collapse (Banchereau et al. 2017; van Kempen et al. 2015) (Fig. 3). The chronic inflammation would induce genomic instability and produce mutated proteins, which might generate cross-reactivity against the native proteins according to the "antigen mimicry" theory (Joseph et al. 2014; van Kempen et al. 2015). Thus inflammation suppression is important for autoimmune disease treatment as this process might continually produce new auto-antigens.

Conventional therapies for SLE, such as hydroxychloroquine, corticosteroids, cyclophosphamide, belimumab, mycophenolate mofetil and others, have significantly improved the survival of SLE patients (Hahn 2013). However, they often cause serious side effects including infection, secondary malignancy, bone marrow suppression, and disease relapses after drug

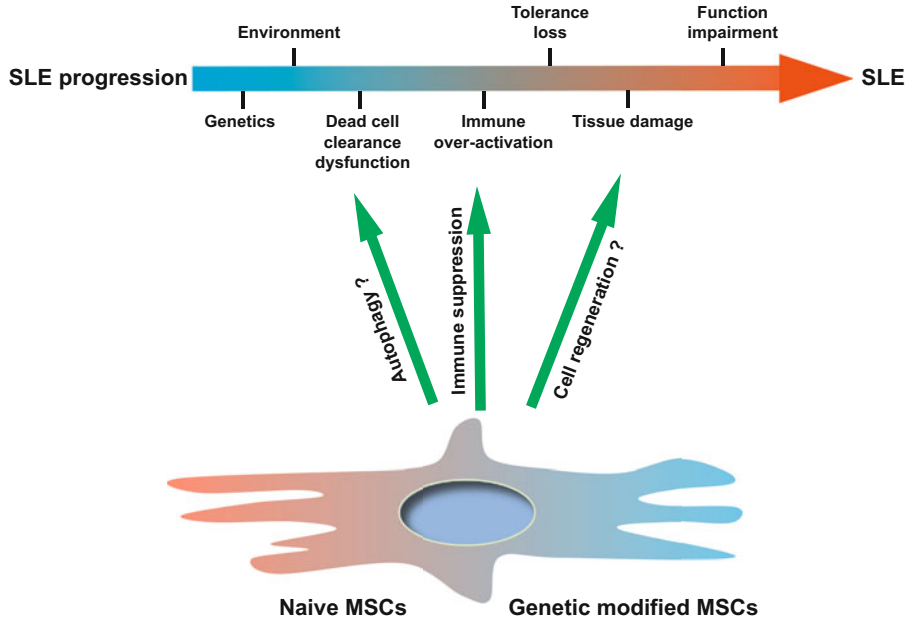

Fig. 3 Targeting MSCs for re-establishing the immune tolerance. During the SLE progression, dysfunctions in the dead cell debris clearance, over-activation of the immune system, and the tissue damaged by self-attack are critical. Naïve or genetic modified MSCs could suppress the immune response to alleviate the SLE symptoms. Potentially, MSCs might also promote the self-antigen clearance through autophagy and cell regeneration via stem cell differentiation. *SLE* systemic lupus erythematosus, *MSCs* mesenchymal stem cells

withdrawal (Bernatsky et al. 2006; Lee et al. 2016). Immune cell targeted therapy, such as Treg transplantation and B cell depletion have been evaluated in animal models or SLE patients. Regulatory T cell ($CD4^+CD25^+$ Treg) based immunotherapy shows effectiveness in the treatment of SLE animal models (Liao et al. 2015). And B cell depletion therapy has also been demonstrated as effective and safe treatment for SLE patients (Kamal and Khamashta 2014). Although they are effective for some patients, others are refractory for these therapies. Thus, novel alternative therapies are needed (Murphy et al. 2013). Both tissue regeneration with healthy stem cells and immune tolerance re-construction are important for treating SLE. In addition to their immune suppression abilities, the autophagy and cell regeneration might also contribute to the SLE therapy. Thus MSCs might provide a promising candidate for immune tolerance re-construction in SLE treatment (Fig. 3).

MSCs stimulated with strong inflammation signals or bacteria have enhanced immune suppressive activities (Chan et al. 2016). In contrast, low inflammatory signal, such as in SLE mice model or patients, reduces significantly the immune suppressive effects of MSCs (Che et al. 2014; Rasmusson et al. 2007). Thus, genetic modified or chemical primed MSCs would be more optimal for treating SLE (Fig. 3).

5 Limitations and Future Perspectives

MSCs are multi-potent stem cells isolated from many tissues (Bianco et al. 2008). However, there is no specific cell surface markers for MSCs so far and diverse markers have been applied to isolate MSCs (Lv et al. 2014; Mo et al. 2016). MSCs are composed of phenotypically and functionally diverse cells (Mo et al. 2016). Genome-wide

methylation, transcription, and *in vivo* analysis have shown that the MSCs isolated from different origins have different characteristics, although they share similar MSC cell surface markers and differentiation abilities *in vitro* (Acar et al. 2015; Reinisch et al. 2015). Thus more efforts must be made to screen MSCs specific markers. Purifying the MSCs subpopulation with specific cell surface markers may enhance their differentiation or immune modulation abilities. MSCs lineage and subtype analysis would also help to define the pure populations and the mechanisms of MSCs for their therapeutic applications.

Another concern is that the MSCs might differentiate into myofibroblast and cause organ fibrosis (El Agha et al. 2017; Trial et al. 2016). Thus carefully characterization and function assessment should be critical analyzed before clinical applications.

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Ethical Approval The authors declare that this article does not contain any studies with human participants or animals.

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