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Review Article

Mesenchymal stem cells for immune modulation in systemic lupus erythematosus: From bench research to clinical applications

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Abstract

Systemic lupus erythematosus (SLE) is a prevalent autoimmune disease affecting multiple organ systems. Disease progression is inevitable as part of its natural course, necessitating aggressive therapeutic strategies, particularly with the use of immunosuppressants. Long-term use of steroids and other immunosuppressants is associated with significant adverse effects. Mesenchymal stem cells (MSCs) have been shown to modulate the immune response, leading to immunosuppressive effects against self-antigens. MSCs have demonstrated the ability to modulate several immune cell populations, contributing to favorable outcomes in controlling immune and inflammatory conditions. Recent evidence has shown an increase in Treg and Breg cell subsets following MSC administration, along with modulation of other immune cells, including dendritic cells, B cells, and T cells. However, the balance between MSC pro-inflammatory and anti-inflammatory phenotypic activation remains a critical factor in determining therapeutic outcomes. Various covariates also influence the efficacy of MSC therapy. The aim of this study was to provide a comprehensive overview of the utilization of mesenchymal stem cells (MSCs) in SLE treatment, leveraging their immunomodulatory and immunosuppressive capabilities. Understanding the fundamental preclinical effects of MSCs and recent findings from clinical studies may enhance the potential of MSC therapy in the management of SLE patients.

Keywords: Autoimmune, dysregulation, immunomodulation, immunosuppression, stem cell

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Introduction

Systemic lupus erythematosus (SLE) is a multifaceted autoimmune disorder that affects approximately 8% of the global population [1]. Despite advancements in the field, SLE continues to contribute significantly to mortality, particularly among females in both developed and developing countries [1]. Female patients experience a significantly increased risk of mortality,

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which may result from either disease progression or the adverse effects of conventional immunosuppressive therapies; infections account for 36.4% of reported deaths associated with SLE [2]. SLE exhibits a strong female predominance compared to males, with a ratio of 9:1 and a prevalence rate of 72.8 per 100,000 person-years. In Indonesia, hospital clinic visits by SLE patients increased from 2015 to 2017, with the highest incidence occurring at a median age of 28 years [3].

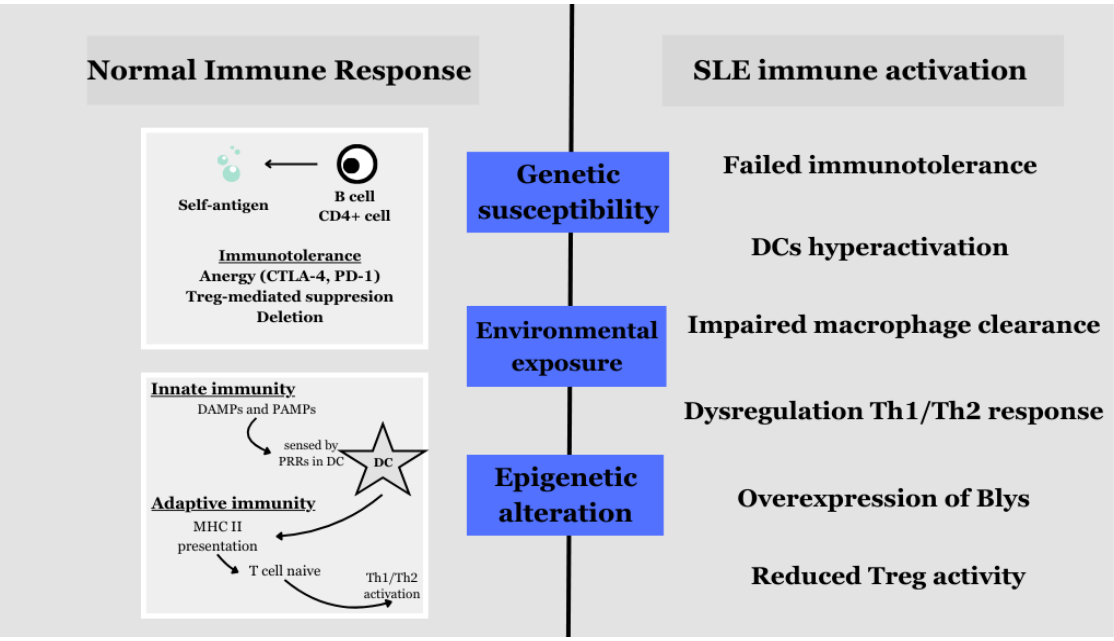

Figure 1. Normal immune response and systemic lupus erythematosus (SLE) immune activation represent two distinct milieus. The interplay of genetic susceptibility, environmental exposure, and epigenetic alterations leads to the development of clinical SLE. In a normal immune response, immunotolerance mitigates immune activation against self-antigens through anergy, suppression, and deletion. In contrast, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) recognized by pattern recognition receptors (PRRs) on dendritic cells (DCs)—including Toll-like receptors (TLRs), Nod-like receptors (NLRs), and C-type lectin receptors—initiate adaptive immune activation. BlyS: B lymphocyte stimulator; CTLA-4: cytotoxic T-lymphocyte-associated protein 4; MHC II: major histocompatibility complex-II; PD-1: programmed death-1.

Environmental risk factors implicated in the development of SLE include Epstein-Barr virus (EBV) infection and ultraviolet light exposure [4]. Genetically, SLE is characterized by a multi-locus, polygenic predisposition involving several key genes, including genes related to immunomodulation (integrin subunit alpha M or ITGAM or CD11B), immune complex clearance and apoptosis encoded complement 1q, and complement 2 (C1q and C2), as well as genes involved in innate (signal transducer and activator of transcription (STAT) 4 and interferon regulatory factor (IRF) 5), and adaptive immunity (B lymphoid kinase (BLK), B cell scaffold protein with ankyrin repeats 1 (BANK1), E26 transformation-specific (ETS1), and interleukin 10 (IL-10) [5]. Dysregulation between innate and adaptive immune responses represents a central mechanism driving the systemic nature of SLE [6]. Other hallmark features include defects in complement activation, elevated levels of B lymphocyte stimulator (B lymphocyte stimulator (BlyS) or cluster differentiation-257 (CD257), which contribute to B-cell tolerance dysfunction, an imbalance between Th1 and Th2 cells, and hyperactivation of antigen-presenting cells (APCs), including dendritic cells [7]. Epigenetic modifications also play a critical role in SLE pathogenesis, with CD4+ T cell DNA hypomethylation leading to the activation of immune-related genes [8].

However, management of SLE continues to rely primarily on conventional immunosuppressants, which, while mitigating some symptoms, fail to halt disease progression and are frequently associated with adverse effects [9,10]. Cell-based therapies that exhibit both immunomodulatory and immunosuppressive properties present a promising therapeutic approach by potentially curbing abnormal immune activation in SLE and thereby reducing the

dependence on conventional immunosuppressants [11]. The aim of this study was to provide a comprehensive overview of the utilization of mesenchymal stem cells (MSCs) in SLE treatment, leveraging their immunomodulatory and immunosuppressive capabilities. The discussion encompasses the immunopathogenesis of SLE, fundamental aspects of MSCs as immunomodulators, recent in vitro findings related to immunomodulation, current challenges in clinical studies of MSC therapy in SLE patients, and future therapeutic prospects.

Systemic lupus erythematosus initiation: From physiological response to autoimmune disease

Innate and adaptive immune responses are tightly coordinated to generate effective immunity against external antigens while maintaining tolerance to self-antigens, as presented in **Figure 1** [12]. The innate immune system serves as the first line of defense, initiating two primary responses: inflammation and antiviral activity [13]. Dendritic cells play a key role by processing and presenting antigens via major histocompatibility complex-II (MHC-II) molecules to CD4+ T lymphocytes [14,15], thus bridging innate and adaptive immune activation. Subsequently, cytokines are released into the local environment, guiding CD4+ T cells to differentiate into specific subtypes [16]. For instance, interferon gamma (IFN-γ promotes the development of type 1 immunity (Th1), while interleukin 4 (IL-4) induces type 2 immunity (Th2) [17]. A balance between Th1 and Th2 responses is essential for an appropriate immune reaction [18]. Dysregulation of Th1/Th2 polarization has been implicated in certain infections and autoimmune disorders, including SLE [12].

Interplay between innate and adaptive immunity

Impaired innate and adaptive immune responses contribute significantly to the pathogenesis of SLE [5]. Dysfunction of the innate immune system is characterized by the hyperexpression of interferon-alpha (IFN-α) and its gene products, primarily driven by the activation of dendritic cells [19]. This immune activation promotes autoimmunity rather than maintaining tolerance [20]. One hypothesis for the early events in SLE development involves infection and subsequent autoantibody formation [21]. Microbial components, such as double-stranded RNA (dsRNA), single-stranded RNA (ssRNA), or double-stranded DNA (dsDNA), are recognized by endosomal Toll-like Receptors (TLRs), which stimulate IFN-α secretion and activate downstream nuclear factor kappa beta (NF-κB) signaling pathways [22]. The cumulative effect of this signaling cascade is an increase in IFN-α levels, which drives the production of autoantibodies by B cells, specifically targeting nuclear antigens released from apoptotic cells [23].

In SLE, a disproportionate increase in apoptotic cell death combined with impaired clearance mechanisms leads to the accumulation of autoantigen-antibody complexes, perpetuating a cycle of inflammation [24]. IFN-α plays a key role in this process by transforming monocytes into potent dendritic cells, which further amplify the inflammatory response through the production of more IFN-α [25]. Dendritic cells are also central to immune activation, serving as primary activators of T-cells and disrupting immune tolerance, a critical event in the initiation and perpetuation of SLE [26]. Additionally, the presence of abnormal CD4+ T cells, known as autoantibody-inducing CD4+ T cells, is a major factor in the pre-diseased period of autoimmune process [27]. These cells promote autoantibody production by activating both B cells and CD8+ T cells, thereby driving the pathogenesis of SLE [28].

An advance to immune dysregulation in systemic lupus erythematosus (SLE)

The imbalance between Th1 and Th2 responses is also implicated in the pathogenesis of SLE. Th2 responses predominantly stimulate B cell activation and suppress Th1-mediated immunity, leading to B cell hyperactivation, increased autoantibody production, and subsequent tissue damage [17,18,29]. However, previous study has revealed a more complex interplay between Th1 and Th2 responses in SLE patients, indicating that their relationship may vary throughout disease progression [29]. Type 1 interferons (particularly IFN-α), a hallmark of Th1 immunity, are involved in the early stages of SLE pathogenesis and act as potent inducers of dendritic cells, which breach self-tolerance [30]. In contrast, type 2 interferon (IFN-γ) promotes T cell differentiation into the Th1 subset while also inducing antibody class switching in pathogenic B

cells, as demonstrated in murine models [31]. The San Roque lupus model has highlighted the central role of IFN-γ, showing that its inhibition reduces follicular helper T cells and autoantibody production [32]. Additionally, IL-2-deficient mice exhibit impaired regulatory T cell (Treg) function, which is crucial for maintaining immune tolerance and preventing autoimmunity [33].

In Th2 immunity, three key cytokines—IL-6, IL-10, and IL-13—play pivotal roles in promoting B cell proliferation and differentiation [18]. These cytokines work synergistically to defend against extracellular pathogens and stimulate antibody production [34]. IL-6 levels are notably elevated in patients with SLE, particularly in those with lupus nephritis [35]. In addition, disease activity triggers IL-10 overexpression, especially in patients experiencing disease flare-ups [36], enhancing B cell survival and cytotoxic T cell (CD8+) function. While IL-10 is generally recognized for its anti-inflammatory properties, reducing Th1 activity, its role in SLE is paradoxical, contributing to both immune regulation and disease progression [37]. IL-13 contributes to SLE pathogenesis by inducing the expression of surface self-antigens, such as CD23, CD71, and MHC-II [38]. A recent study has highlighted the importance of regulatory B cells (Bregs) in modulating the autoimmune response through IL-10 secretion [39]. Two primary subsets of Bregs have been identified: transitional type 2 marginal zone precursor B (T2-MZP B) cells (marginal zone B cell precursors) and B10 cells (CD19+CD5+CD1dhi B cells) [40]. In murine models of lupus, B10 cells have demonstrated a suppressive effect, suggesting their potential role in regulating autoimmune activity in SLE [41].

Mesenchymal stem cells (MSCs): Introduction

Stem cells represent a promising therapeutic strategy for ameliorating hyperinflammatory and autoimmune diseases [42]. These cells possess self-renewal properties and multilineage differentiation potential, functioning as progenitors capable of regenerating damaged tissues. Human stem cells can be sourced from various adult and perinatal tissues, including adipose tissue, fetal tissue, umbilical cord, dental pulp, and placental tissue [43]. However, the therapeutic efficacy and outcomes of stem cell-based treatments vary considerably across studies, which may be attributed to differences in the immunogenic characteristics, paracrine effects, and secreted products of stem cells from different sources [44-55].

Among the various stem cell sources, the three most commonly utilized are umbilical cord blood-derived mesenchymal stem cells (UC-MSCs), bone marrow-derived mesenchymal stem cells (BM-MSCs), and adipose tissue-derived mesenchymal stem cells (A-MSCs) [44]. MSCs, a subset of stromal cells, possess the ability to differentiate into multiple cell types, including chondrocytes, osteoblasts, myofibroblasts, and other stromal lineage cells [56]. The therapeutic potential of MSCs lies in their robust tissue regenerative and immunomodulatory properties, making them a key focus of research for the treatment of inflammatory and autoimmune diseases [57].

Immunotolerance and immunosuppression effect of mesenchymal stem cells

MSCs serve as immunomodulators in both innate and adaptive immune responses, interacting primarily with Tregs, dendritic cells, natural killer cells, and neutrophils to exert their therapeutic potential [44]. Additionally, MSCs secrete a variety of paracrine molecules packaged in vesicles, collectively known as the secretome [58]. These vesicles contain growth factors, cytokines, and chemokines such as transforming growth factor-beta 1 (TGF-β1), tumor necrosis factor-alpha (TNF-α), IFN-γ, hepatocyte growth factor (HGF), nitric oxide, and other bioactive substances [59]. Through the secretion of these molecules, MSCs can inhibit leukocyte recruitment, suppress T helper 17 (Th 17) differentiation, reduce natural killer cell proliferation, and modulate other immune processes [44]. Co-culture of these products has been shown to independently suppress immune responses in mouse models by inhibiting peripheral blood mononuclear cell (PBMC) proliferation and preserving Treg function [60].

MSCs promote immunotolerance by modulating follicular helper T cells through the increased secretion of anti-inflammatory cytokines, including transforming growth factor-β (TGF) and IL-10 [61]. This mechanism has been highlighted in the context of transplantation, where MSCs help reduce host rejection by enhancing Treg function, with TGF-β playing a key role in upregulating Tregs [61,62]. Additionally, MSC-derived exosomes have been shown to decrease

silent mating type information regulation 2 homolog 1 (SIRT-1) expression in CD4+ T cells, which further promotes Treg expansion, ultimately contributing to immunotolerance [63]. In a non-inherited maternal antigen (NIMA) rat model, MSC immunization induced immunotolerance, largely attributed to the action of Tregs, thus supporting the potential application of MSCs in treating autoimmune diseases [64]. Tregs are a focal point in MSC-mediated immunomodulation due to their critical role in maintaining peripheral immune tolerance and preventing self-antigen-triggered immunosuppression [65].

MSCs inhibit the differentiation and proliferation of B cells into antibody-secreting cells, a process mediated through the suppression of activated dendritic cells [66]. A study demonstrated an upregulation of Bregs following MSCs infusion, with Bregs playing an immunosuppressive role that contributes to the maintenance of peripheral tolerance [67]. However, a universally accepted definition of Bregs has yet to be established in international literature. Bregs represent a recently identified subpopulation of B cells, distinct from the conventional B1, B2, and plasma cells [40]. The interaction between Bregs and MSCs has significant implications for cell-based therapies in autoimmune diseases, highlighting the potential of soluble cytokines and Breg-mediated immunosuppressive mechanisms in the modulation of immune responses [68].

Mesenchymal stem cells and immune microenvironment

The local microenvironment plays a crucial role in determining MSC phenotypes, particularly through exposure to varying cytokine compositions and TLR ligation [69,70]. High levels of IFN-γ promote the anti-inflammatory response of MSCs, classified as MSC subtype 1. Conversely, low inflammatory activity induces a pro-inflammatory response, characteristic of MSC subtype 2 (**Figure 2**). MSCs do not inherently possess immunosuppressive properties; rather, their immunosuppressive activity is triggered by the local environment [69]. Specifically, MSCs exhibit immunosuppressive effects after interacting with activated immune cells in vitro [71], indicating that MSCs are not innately inhibitory but require exposure to inflammatory cytokines to activate this function. This has been demonstrated by studies showing that blocking IFN-γ receptor antibodies can reverse the inhibitory effects of MSCs [72,73]. Therefore, high concentrations of IFN-γ act as a licensing signal to induce MSC-mediated immunosuppression [44].

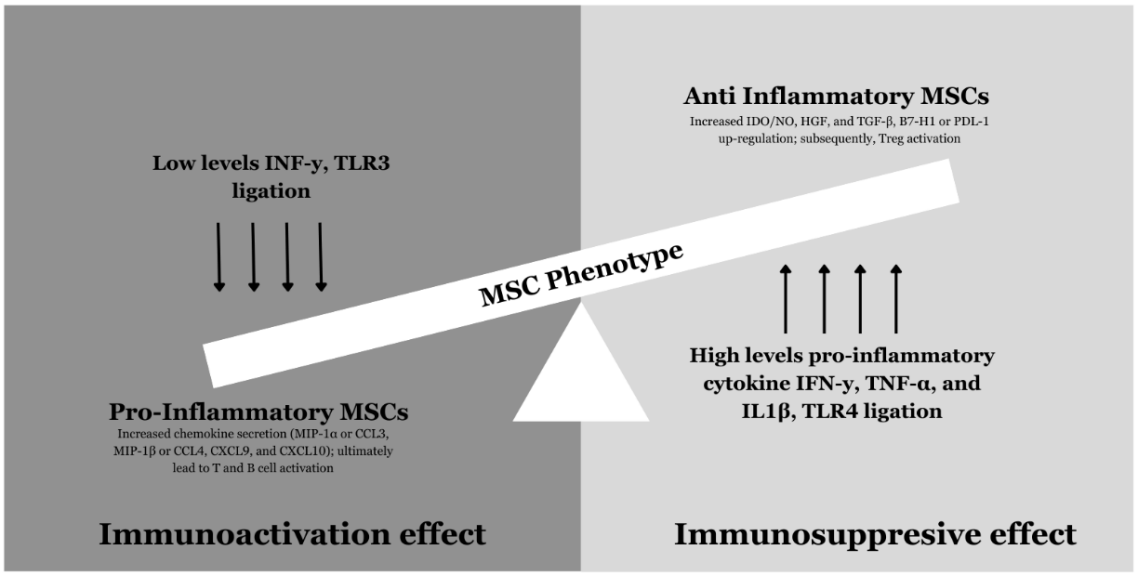

Figure 2. The licensing procedure determines mesenchymal stem cells (MSC) phenotype. High inflammatory cytokine provokes MSC to exert its immunosuppressive effect; this becomes the basis of MSC utilization for several autoimmune diseases, including systemic lupus erythematosus (SLE). B7-H1 or PDL1: programmed death ligand-1; CXCL9/10: chemokine (C-X-C motif) ligand 9/10; HGF: hepatocyte growth factor; IDO: indolamine dioxygenase; IFN: interferon; MIP-1α/β: macrophage inflammatory protein 1α/β; NO: nitric oxide; TGF-B: transforming growth factor β; TLR: Toll-like receptor; TNF-alfa: tumor necrosis factor alfa.

MSCs respond to varying concentrations of IFN-γ. When treated with low levels of IFN-γ, MSCs can induce the formation of antigen-specific CD8+ T cells and increase interleukin-2 (IL-

2) production, suggesting that low IFN-γ concentrations transform MSCs into APCs or polarize them into a pro-inflammatory phenotype [74]. However, As IFN-γ levels rise, MSCs lose immune reactivity, marked by decreased expression of MHC class II molecules, and shift toward an immunosuppressive role [44]. MSCs are crucial in sensing pro-inflammatory cytokines such as IFN-γ, TNF-α, and interleukin-1 beta (IL-1β) from the local environment, which initiates a 'licensing step' that enables them to modulate immune responses [75]. Following exposure to IFN-γ and TNF-α, MSCs can secrete superoxide dismutase 3 (SOD3), an anti-inflammatory enzyme [76]. Moreover, IFN-γ stimulates MSCs to produce indoleamine 2,3-dioxygenase (IDO) and upregulates the expression of B7-H1, also known as programmed death-ligand 1 (PD-L1), which exerts immunosuppressive effects via signal transducer and activator of transcription 1 (STAT-1) [77]. This mechanism leads to T-cell anergy, a state in which activated T cells fail to respond to antigenic stimulation, further contributing to MSC-mediated immunosuppression [78].

MSCs acquire their immunosuppressive properties primarily in response to a highly inflammatory environment, though other key factors also play a role [44]. TLRs on MSCs influence their subsequent polarization [79]. While TLRs (toll-like receptors) function as pattern recognition receptors, they also possess significant immunomodulatory properties. The engagement of TLR ligands, known as TLR priming, serves as an additional determinant in modulating MSC function [70]. In inflammatory environments, MSCs express high levels of TLR2, TLR3, and TLR4, while suppressing TLR6 [80]. For instance, TLR3 agonists, such as lipopolysaccharide, enhance bactericidal activity and cytokine production in equine MSCs, fostering a pro-inflammatory local environment [81]. Initial studies indicated that TLR3 ligands stimulate pro-inflammatory cytokine secretion from MSCs [82]. However, more recent evidence suggests that TLR3 can also induce an immunosuppressive effect in MSCs, depending on the exposure duration and ligand concentration, further contributing to the polarization of MSC phenotypes [83].

TLR expression varies across MSCs derived from different sources [70]. UC-MSCs exhibit high levels of TLR4 and TLR6 but show low expressions of TLR1, TLR3, TLR5, and TLR9. In contrast, bone marrow-derived and adipose tissue-derived MSCs share similar TLR expression patterns, expressing TLR1-6 and TLR9 while lacking TLR7 [25,80]. This variation in TLR expression influences the responsiveness of MSCs to their environment, determining their functional plasticity [80,84]. TLR activation has been implicated in the pathogenesis of several autoimmune diseases, including inflammatory bowel disease and rheumatoid arthritis. As a result, TLR-primed MSCs could be pre-conditioned to enhance their immunosuppressive effects [84]. Notably, low TLR signaling in MSCs has been associated with increased immunosuppressive properties, including the upregulation of human leukocyte antigens G (HLA)-G, elevated prostaglandin levels, IL-10/IFN-γ exposure, and the activation of the Notch signaling pathway [81].

Mesenchymal stem cells utilization in some diseases

Previous clinical trials have documented successful outcomes with MSC therapy in transplant recipients, particularly in patients with steroid-resistant graft-versus-host disease (GVHD) [61,85]. In these cases, MSC therapy has been shown to prolong graft survival and rescue transplanted tissues. Additional studies have demonstrated significant therapeutic benefits in severe and refractory GVHD cases where conventional immunosuppression has failed [85]. MSCs exert immunomodulatory effects on both innate and adaptive immune cells, primarily suppressing excessive immune responses, which offers a promising alternative to traditional immunosuppressive therapies that are often associated with more severe side effects [44,72]. MSCs inhibit the activation of T cells, including CD4+ and CD8+ lymphocytes [71,77]. The immunosuppressive effects of MSCs are mediated through the release of soluble cytokines such as IL-10, TGF-β, prostaglandin E2 (PGE2), IDO, and nitric oxide, which together modulate the local immune environment and suppress immune activation [86].

Several autoimmune diseases have demonstrated improvement following the application of MSCs. In Crohn's disease with strictures, MSC injections administered over 11 sessions resulted in clinical resolution [87]. MSC infusion modulates immune responses by affecting IFN-γ

production, while interleukin-17a (IL-17a) levels are elevated in Crohn's disease models, creating a non-inflammatory microenvironment with minimal activation of CD4+ and CD8+ T cells [87]. Additionally, efferocytosis of apoptotic human MSCs (hMSCs) has shown long-term efficacy in inflammatory models of the small intestine, promoting a shift toward M2 macrophages, a subset associated with tissue repair, following MSC administration [88]. In collagen-induced arthritis, a model for rheumatoid arthritis, MSCs modulate immune responses by increasing Tregs and Tr1 cells (CD4+ T cells expressing IL-10), while suppressing Th1 and Th17 cell activity in peripheral blood and secondary lymphoid organs [89,90]. Furthermore, MSC therapy reduces pro-inflammatory cytokine levels, including IFN-γ, TNF-α, interleukin-14 (IL-14), and IL-17, following administration [91].

Systemic sclerosis, or scleroderma, is characterized by a predominantly Th1-mediated immune response [92]. MSCs counteract this by suppressing immune reactivity, thereby preventing lymphocyte infiltration into exocrine glands. MSCs promote a shift toward Th2 responses and Tregs while reducing the activity of follicular helper T cells (Tfh) and Th17 cells [93]. In rat models, MSCs help balance Th1/Th2 responses and have been clinically shown to improve the scleroderma disease activity index (SSDAI) following MSC injection [94].

In type 1 diabetes mellitus, MSCs have been demonstrated to enhance pancreatic endocrine function, evidenced by increased C-peptide levels, while also reducing fasting glucose and HbA1c [95]. This therapeutic effect is attributed to the MSCs' ability to mitigate the destructive infiltration of CD4+ T cells into pancreatic beta cells [96]. Additionally, MSCs show potential for differentiating into insulin-producing cells, as indicated by the expression of pancreatic and duodenal homeobox 1 (PDX-1) [96,97]. In multiple sclerosis, MSCs reduce CCL (CC chemokine ligand)-2 levels, which blunt the response of helper T cells and dendritic cells, while increasing hepatocyte growth factor (HGF) levels, CXC chemokine ligand (CXCL) 12, and IL-8 [98,99]. The reduction of CCL-2 in cerebrospinal fluid has been associated with clinical improvement in multiple sclerosis patients [98]. Thus, MSCs' immunomodulatory and proliferative capacities serve as promising therapeutic strategies for autoimmune and hyperinflammatory diseases.

Mesenchymal stem cells and immune cell interaction in systemic lupus erythematosus

Previous in vitro studies have demonstrated the effects of MSCs on specific subsets of immune cells, leading to a wide range of immunomodulatory properties [61,70,72,99-101]. Understanding the detailed interactions between MSCs and various immune cells could provide a strong foundation for further exploration of MSC therapy in SLE patients. Dendritic cells are key initiators of immune activation; however, their persistent activation in SLE contributes to aberrant immune responses [20,30]. Within adaptive immunity, proper coordination between T cells and B cells is crucial, typically regulated by the suppressive functions of Tregs and Bregs [93,102]. In SLE, dysfunctions in these regulatory mechanisms have been widely observed in several studies, highlighting the potential for MSCs to restore immune balance in SLE [103].

Mesenchymal stem cells inhibit dendritic cells activation

Hyperactivation of dendritic cells plays a pivotal role in immune reactivity against self-antigens in SLE through their function as APCs [15]. In SLE patients, dendritic cells exhibit an enhanced capacity for activation, as evidenced by the overexpression of CD80, a co-stimulatory molecule [20]. MSCs modulate dendritic cell function by promoting an anti-inflammatory phenotype, largely through inhibiting the secretion of pro-inflammatory cytokines [100]. An in vitro study demonstrated that MSCs quantitatively reduced CD11c+ expression (a dendritic cells marker) in co-cultured SLE peripheral blood mononuclear cells (PBMCs), downregulating human leukocyte antigen-DR (HLA-DR), CD80, and CD86, thereby preventing monocyte differentiation into dendritic cells, highlighting the anti-proliferative effect of MSCs on dendritic cells [100]. In SLE, a deficiency of tolerogenic dendritic cell subsets, particularly CD1c+ dendritic cells, has been observed [104]. These cells play a crucial role in regulating antigen presentation via an IL-10-dependent mechanism to maintain peripheral tolerance [105]. Supporting this, MSCs have been shown to increase IL-10 production and promote the generation of CD1c+ dendritic cells, along with their activator, Fms-related tyrosine kinase 3-ligand (FLT3L) [104].

Mesenchymal stem cell-induced Treg upregulation

SLE is characterized by a dysregulated T-cell response, particularly involving the balance between Th1 and Th2 cells. Although initially proposed as a Th2-dominant response, this has been debated in several studies [18]. During SLE flare-ups, the inflammatory environment—marked by elevated levels of interferon type I (IFN-I) and TNF-α levels—acts as a licensing event for MSCs to exert their immunosuppressive effects [71,73]. MSCs inhibit CD4+ T cell proliferation, promote the transformation of macrophages from the M1 to the M2 subset, and enhance Treg function and proliferation, thereby inducing immune tolerance [106]. These immunosuppressive properties are mediated by the secretion of IL-10, TGF-β1, IDO, and PGE2 [101].

MSCs also modulate T cell signaling by increasing intercellular adhesion molecule 1 (ICAM-1) binding to CD43, which inhibits the formation of the T cell receptor (TCR) micro cluster during T cell activation [107]. Furthermore, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) expressed by MSCs binds to CD80/86 with a higher affinity than CD28, resulting in increased IDO expression in APCs and impaired antigen presentation [108]. Additionally, Tregs, which are deficient and functionally impaired in many SLE patients, further reduce CD80/86 expression on dendritic cells [102]. The cumulative effect of MSCs on T lymphocytes plays a crucial role in supporting immune tolerance in MSC-treated SLE patients [109].

Mesenchymal stem cells versus B cell

B lymphocytes and their secreted products play a central role in several manifestations of SLE [23]. Co-culture experiments involving MSCs and B cells under controlled conditions have demonstrated significant immunoregulatory changes, including inhibition of IgM-secreting plasma cells, suppression of B cell proliferation, and reduced B cell differentiation [110]. Inflammatory conditions can influence the polarization of MSCs, shifting them towards an anti-inflammatory phenotype that suppresses B cell activity [110]. MSCs inhibit B-cell activation by downregulating the expression of B-cell activating factor (BAFF) [110].

Additionally, toll-like receptor 7 (TLR7) overexpression in SLE promotes B cell autoreactivity through IFN-γ induction [111]. MSCs downregulate the TLR7/NF-κB pathway, resulting in reduced TNF-α production while simultaneously enhancing IL-10 secretion via activation of the extracellular signal-regulated kinase (ERK) pathway [111]. Furthermore, MSCs impair B cell development by upregulating CCL2 expression and disrupting the MST (macrophage stimulating)1-mTOR (mammalian target of rapamycin)-STAT (signal transducer and activator of transcription)1 signaling axis, further contributing to the modulation of B cell function in SLE [112].

Newly discovered Breg and mesenchymal stem cells interaction

A newly identified subset of immune cells, known as regulatory B cells or B10 cells, has been shown to counteract autoreactivity through the secretion of IL-10. These cells are characterized by the markers CD19+CD5+CD1dhi [41,113]. The primary function of B10 cells is to regulate T cell-mediated immunity by sensing surges of pro-inflammatory cytokines [38]. As previously discussed, B10 cells contribute to the diversity of Breg phenotypes, alongside B-1a and marginal zone B cells, in their immunoregulatory roles [40].

In SLE, a deficiency in Breg populations, including B10 cells, has been associated with increased autoreactivity and hyperactivation of B cells [102]. In patients with lupus nephritis, B10 cell numbers were significantly reduced compared to healthy controls but were restored with immunosuppressive therapy [114]. Interestingly, Treg levels remained unaffected by immunosuppression [102]. Animal studies have shown that MSC administration expands the B10 cell population in the spleen, which concurrently alleviates autoimmune activity in SLE models [115]. The role of Bregs, particularly B10 cells, is becoming increasingly recognized as a hallmark in controlling disease by suppressing systemic immunity, presenting a potential novel therapeutic target in SLE management [114].

Table 1. Chronological overview of clinical studies on mesenchymal stem cells (MSC) therapy for systemic lupus erythematosus (SLE) from 2010 to 2022

Author	Study characteristics	Findings	Adverse events	Limitation
Liang *et al.*, 2010 [45]	Source: BM-MSCs administered at a dosage of 1×10^6 cells/kg BW. Study design: Clinical pilot study. Participants: Fifteen patients with refractory SLE who did not respond to induction doses of immunosuppressants (CYC and MMF), including patients with refractory secondary ITP and refractory LN.	BM-MSC treatment improved renal function, serological markers (ANA and anti-dsDNA antibodies), and subjective symptoms such as fatigue and weight loss. Additionally, there was an observed increase in Tregs.	One patient experienced a significant herpes zoster infection one week after the BM-MSC injection.	The study did not include cytokine profiling, although the authors referenced Th1 polarization in their findings. The follow-up period was also brief.
Wang *et al.*, 2012 [46]	Source: Allogeneic BM-MSCs administered in two dosages: 1×10^6 cells/kg BW and 2×10^6 cells/kg BW. Study design: Open-label randomized study. Participants: Fifty-eight patients with refractory SLE presenting with hematologic and nephritis manifestations.	The lower BM-MSC dosage (1×10^6 cells/kg BW) demonstrated greater efficacy compared to the higher dosage, leading to remission based on SLEDAI, hematologic parameters, and renal function.	One patient experienced disease recurrence, while infections were observed in seven patients in the single-transplant group and nine patients in the double-transplant group during the four-year follow-up period.	The study did not include cytokine or autoantibody profiling, and no data were provided on prior immunosuppressant use before MSC administration.
Wang *et al.*, 2013 [47]	Source: BM-MSCs. Study design: Prospective cohort with a four-year follow-up (Phase II). Participants: Eighty-seven patients with refractory SLE (SLEDAI score ≥8), unresponsive to immunosuppressants (CYC, MMF, AZT, or LEF) for six months, or requiring ongoing prednisone treatment (≥20 mg).	Complete remission was achieved in 28% of patients after one year and 31% after two years. The overall relapse rate was 23%. Over the four-year period, improvement in SELENA-SLEDAI scores was observed, with a sustained positive effect on renal function, including reduced proteinuria. Patients maintained on immunosuppressants remained stable in 65% of cases.	One patient developed a disseminated pulmonary infection, and two patients experienced diarrhea.	Variability in pre-treatment immunosuppressant use was noted, and some patients received multiple MSC injections, though this was not explicitly detailed in the study.
Li *et al.*, 2013 [48]	Source: BM-MSCs. Study design: Pre- and post-test study. Participants: Thirty-five patients with cytopenia related to SLE, refractory to immunosuppressants (CYC, AZT, LEF, MMF, and prednisone ≥20 mg).	Significant improvement in SLEDAI scores was observed (mean baseline 12.1 vs 5.5 at six-month follow-up). Leukopenia improved (baseline 2.47×10^3/μL vs 4.89×10^3/μL at three months), and thrombocytopenia also showed improvement (baseline 52×10^3/μL vs 91×10^3/μL at three months). Additionally, Treg levels increased at one and three months, while Th17 levels decreased persistently over 12 months.	Diarrhea occurred in two patients, pneumonia in one patient, and two deaths were reported. One case of agranulocytosis was also noted.	The study lacked a control group, cytokine profiling was not performed, and there was variability in pre-treatment immunosuppressant use, raising concerns about baseline uniformity.
Gu *et al.*, 2014 [49]	Source: BM-MSCs from healthy donors. Study design: Open-label clinical trial. Participants: Eighty-one patients with refractory lupus nephritis.	At 12 months, 60.5% of patients achieved either complete or partial remission. The overall relapse rate was 22.4%. Secondary outcomes included	Two patients developed pulmonary infections.	The study lacked a control group and randomization, and different maintenance dosages

Author	Study characteristics	Findings	Adverse events	Limitation
		improvements in renal function, BILAG and SLEDAI scores, and a reduction in immunosuppressant dosage following BM-MSC injection.		of immunosuppressants were used.
Wang *et al*., 2014 [50]	Source: UC-MSCs administered in two infusions with a one-week interval. Study design: Multi-center prospective cohort. Participants: Patients with SLE refractory to immunosuppressive agents (CYC, MMF, or LEF induction doses), or requiring prednisone ≥20 mg.	After 12 months, a MCR was achieved in 32.5% of patients, and a PCR in 27.5%. SLEDAI scores improved from a baseline mean of 10.83 to 6.48, with a reduction in proteinuria from 2.24 g to 1.41 g over the same period.	Adverse events were reported as unrelated to MSC infusion, with three patients developing herpesvirus infections and three deaths.	The study lacked randomization and a control group, and there was variability in the pre-treatment use of immunosuppressants.
Deng *et al*., 2017 [51]	Source: UC-MSCs, 2×10^8 cells. Study design: Randomized, double-blind, controlled trial. Participants: Patients with LN WHO class III or IV, with a SLEDAI score >8, BILAG score A/B, and proteinuria >1 g/day.	Proteinuria decreased in both groups: in the placebo arm, proteinuria reduced from 4.49 g at baseline to 3.11 g at 6 months, while in the UC-MSC group, it decreased from 3.08 g to 0.97 g. There were no significant differences between the groups in terms of renal function, lupus activity scores, or patient outcomes.	Two cases of severe pneumonia were reported.	The study lacked baseline uniformity, with a disproportionate reduction in participants in the placebo group.
Liang *et al*., 2018 [52]	Source: BM-MSCs and UC-MSCs. Study design: Retrospective cohort study. Participants: 404 patients with various autoimmune diseases, including SLE, Sjögren's syndrome, systemic sclerosis, polymyositis/dermatomyositis, rheumatoid arthritis, mixed connective tissue disease, autoimmune liver disease, and primary vasculitis.	Outcome measures include hyperacute-acute adverse events and long-term events (death) in different autoimmune disease groups.	11.9% of patients experienced mild to moderate hyperacute adverse events, including fever, headache, palpitations, facial flushing, insomnia, and gastrointestinal discomfort.	There were multiple autoimmune backgrounds of involved participants, no efficacy indicator was measured, the study design was retrospective, and there was no control group.
Wen *et al*., 2019 [53]	Source: BM-MSCs/UC-MSCs at a dose of 1×10^6 cells/kg. Study design: Retrospective cohort study. Participants: Sixty-nine adult patients with SLE, refractory to standard treatments, with a SLEDAI score ≥8.	The study identified several factors associated with a poor clinical response, including older age, presence of arthralgia, serositis, and lack of HCQ use. Improvement in SLEDAI scores was observed.	NA	Variability in pre-treatment immunosuppressant use, the retrospective study design, and the inclusion of patients receiving MSCs from two different sources (UC-MSCs vs BM-MSCs) were noted.
Kamen *et al*., 2022 [54]	Source: UC-MSCs from two healthy donors, with a dosage of 1×10^6 cells/kg body weight. Study design: Phase I clinical trial. Participants: Six patients with active SLE, with SLEDAI scores between 6 and 12 points, and BILAG scores of A or B.	Five patients met the primary response criteria by 24 weeks, showing improvements in laboratory markers, including proteinuria, lymphocyte counts, and autoantibody levels. B cell composition shifted, with reductions in double-negative 2 and activated naïve B cells following MSC injection. No significant changes were observed in T-cell responses.	Mild nausea, paresthesia, and flushing were reported.	Phase I clinical trial with a small sample size

Author	Study characteristics	Findings	Adverse events	Limitation
Ranjbar *et al*., [55]	Source: Adipose-derived MSCs at a dosage of 2×10^6 cells/kg BW. Study design: Phase I clinical trial. Participants: Nine patients with refractory LN, previously treated with CYC and/or MMF or LEF, and prednisolone 20 mg/day for a minimum of three months.	Complete remission was achieved in 33.3% of patients. Although MSC treatment initially reduced proteinuria (median baseline 1.8 g vs 1.0 g at one month), the effect was not sustained, with proteinuria increasing to >1.5 g by three months. SLEDAI scores improved from a median of 16 at baseline to 8 at 12 months post-MSC infusion.	NA	Phase I clinical study with a small sample size.

ANA: antinuclear antibodies; anti-dsDNA: anti-double stranded DNA; AZT: azathioprine; BILAG: British Isles Lupus Assessment Group; BM-MSC: bone marrow-derived mesenchymal stem cells; BW: body weight; CYC: cyclophosphamide; HCQ: hydroxychloroquine; ITP: immune thrombocytopenia purpura; LEF: leflunomide; LN: lupus nephritis; MCR: major clinical response; MMF: mycophenolate mofetil; NA: not available; PCR: partial clinical response; SLE: systemic lupus erythematosus; SLEDAI: systemic lupus erythematosus disease activity index; Tregs: regulatory T cell; UC-MSC: umbilical cord-derived mesenchymal stem cells.

Therapeutic potentials of mesenchymal stem cells in systemic lupus erythematosus

Clinical trials and observational studies investigating the use of MSCs in SLE patients have fluctuated in activity over the past few decades (**Table 1**). Despite early discoveries, large-scale trials involving significant participant numbers have yet to be conducted. One of the ongoing challenges in advancing cell-based therapy for SLE is the variability in immune responses across different SLE populations. Current conventional therapies rely on nonspecific immunosuppressants, which often result in increased side effects, particularly with prolonged treatment—an unfortunate necessity in the lifelong management of SLE immune activity [116]. As a result, stem cell-based therapy presents a potential alternative for a subset of SLE patients, particularly those who are refractory to standard treatments.

Several clinical studies have demonstrated the efficacy of MSC therapy in treating advanced and refractory SLE (**Table 1**) [45-49]. In these trials, MSCs have been administered at doses of one to two million cells per kilogram of body weight (kg BW), leading to remission in refractory SLE cases, as measured by improvements in the SLE Disease Activity Index (SLEDAI) score, hematological indices, and renal function [45,47,51,54]. These findings suggest that MSC therapy may offer a promising option for managing severe forms of SLE.

In SLE MSCs, it has been shown to maintain a normal phenotype, characterized by the expression of CD29+, CD44+, and CD105+, with the absence of CD14-, CD45-, CD34-, and HLA-DR- markers. However, genotypic analysis reveals differences, particularly in the secretion of cytokines such as TGF-β1, IL-6, and IL-7 in SLE patients [117]. These findings reflect the underlying immune pathology in SLE, underscoring the importance of further research into MSC applications.

MSC therapy serves as an alternative immunomodulatory and immunosuppressive strategy in SLE management [60]. Significant advancements in understanding the mechanisms of MSCs have led to promising outcomes in controlling SLE, as demonstrated by preclinical and clinical studies [54,61,108]. The first phase I clinical trial, published in 2009, reported an increase in Tregs and clinical improvement within one year of MSC transplantation [54,55,118]. Phase II trials have shown similar efficacy, with a 50% clinical response rate after four years of follow-up, despite differences in study design and protocols. This trial has provided crucial insights into the potential of MSC therapy for refractory SLE patients [47].

Future prospects

The application of MSCs in SLE leverages their immunomodulatory and immunosuppressive properties, offering an alternative to conventional therapies. However, it is essential to recognize that SLE creates a unique immune environment characterized by heightened reactivity to self-antigens and persistent inflammation, which drives its primary pathogenesis. Cytokine and TLR signaling play critical roles in this environment, and if not carefully considered, they may interfere with MSC-mediated modulation, potentially leading to unwanted outcomes.

Additionally, MSC dysfunction is commonly observed in SLE patients (referred to as SLE-MSC), making autologous MSC transplantation less viable. Conversely, allogeneic MSC transplantation has been shown to be safe and effective, offering a promising alternative in cell-based therapy. Identifying suitable patients and selecting the appropriate MSC sources are critical factors in optimizing outcomes and minimizing side effects in this emerging therapeutic approach.

Future clinical trials utilizing MSCs should encompass a broader spectrum of SLE patients, including newly diagnosed, current, and refractory cases. To date, most studies have focused on refractory SLE patients, who are resistant to conventional treatments [45-49]. However, no study has yet explored the safety and efficacy of MSC therapy in newly diagnosed SLE patients, largely due to the difficulty in achieving uniformity in baseline characteristics, especially when comparing newly diagnosed to advanced-stage SLE patients.

Phase I trials of MSC therapy have consistently shown promising results, but several challenges remain [54,55]. These include patient selection, achieving baseline uniformity, lack of comparison group, and determining the precise MSC dosage. Furthermore, future studies are

essential to standardize study entry criteria, define clinical responses, and optimize the use of adjunct immunosuppressants and maintenance MSC dosages. Larger sample sizes will also be necessary to validate the efficacy and safety of MSC therapy across the diverse SLE patient population.

Conclusion

The application of MSCs in SLE has long been recognized as a promising avenue in cell-based therapies. MSCs exert their therapeutic effects both through direct cell-cell interactions and indirectly via their paracrine activity, which modulates immune responses. However, several confounding factors continue to affect the efficacy of MSCs in suppressing SLE activity. A key factor is the influence of the immune microenvironment on MSC functionality, particularly the role of licensing or alternative licensing processes. These processes, driven by the inflammatory milieu and cytokine profiles, critically determine MSCs' immunomodulatory capabilities. Additionally, certain TLR activations can impair MSC responses to inflammation, further complicating their effectiveness. Therefore, a deeper understanding of these interactions is crucial for optimizing MSC-based interventions in SLE treatment.

Ethics approval

Not required.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

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