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Mesenchymal stem cell transplantation may be able to induce immunological tolerance in systemic lupus erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) is a common, potentially fatal autoimmune disease involving a significant inflammatory response. SLE is characterised by failure of self-tolerance and activation of autoreactive lymphocytes, leading to persistent disease. Although current treatments achieve some improvement in patients, some SLE patients are refractory and others relapse after drug withdrawal. The toxicity of current drug regimens, with recurrent infections, together with ongoing inflammation, contribute significantly to the progressive decline in organ function. Therefore, the clinical management of SLE requires more effective and less toxic treatments, ideally inducing complete remission and self-tolerance. In this context, recently developed cell therapies based on mesenchymal stem cells (MSCs) represent a promising and safe strategy in SLE. MSCs inhibit the activation of B cells, prevent the differentiation of $CD4^+$ T cells into autoreactive T cells, reprogram macrophages with anti-inflammatory effects and inhibit dendritic cells (DCs), limiting their activity as antigen-presenting cells. In addition, MSCs could induce antigen-specific tolerance by enhancing anergy processes in autoreactive cells - by inhibiting the maturation of antigen-presenting DCs, blocking the T cell receptor (TcR) pathway and secreting inhibitory molecules -, increasing apoptotic activity to eliminate them, and activating regulatory T cells (Tregs) to enhance their proliferation and induction of tolerogenic DCs. Thus, induction of self-tolerance leads to immune balance, keeping inflammation under control and reducing lupus flares.

1. Introduction

Systemic lupus erythematosus (SLE) is one of the most common and potentially fatal multisystemic autoimmune diseases with variable outcome, affecting mainly young women (ratio 9:1) in their reproductive years. Although the prognosis for SLE patients has improved in recent decades, the complexity of the disease and the variety of factors involved in its progression - including genetic, endogenous and environmental factors - still make it a disease with high morbidity and mortality. SLE is prevalent worldwide, affecting all populations in a global range of 1–8.7 cases per 100,000 people [1,2]. Its severity lies in the breakdown of self-tolerance and the subsequent autoimmune response leading to inflammation and organ damage, particularly of the central nervous system and kidneys. Indeed, damage to these two organs has been identified as a marker of poor prognosis. Renal involvement is clinically evident in approximately 50% of SLE patients. The gradual decline in kidney function leading to end-stage renal disease is a major cause of death in SLE.

Even with aggressive therapy, some patients with severe manifestations of SLE will experience a progressive decline in organ function leading to chronic damage. Risk factors for progression that become apparent after initial presentation and during therapy are the frequency and severity of relapses and the degree to which the abnormal features of organ involvement are controlled. The likelihood of a successful initial outcome is greater if therapy is initiated relatively early in the course of the disease. Patients with persistent, relapsing or remitting severe clinical manifestations of SLE have active disease, causing progressive organ damage. In such cases, the standard validated first-line therapies are corticosteroids in combination with either cyclophosphamide or mycophenolate. Although these treatments result in some improvement in patients, some SLE patients are refractory and others relapse after drug withdrawal. The toxicity of common drug regimens, including recurrent infections and tumour development, together with ongoing inflammation, contribute significantly to the progressive decline in organ function. Therefore, the clinical management of SLE requires more effective and less toxic treatment that induces complete

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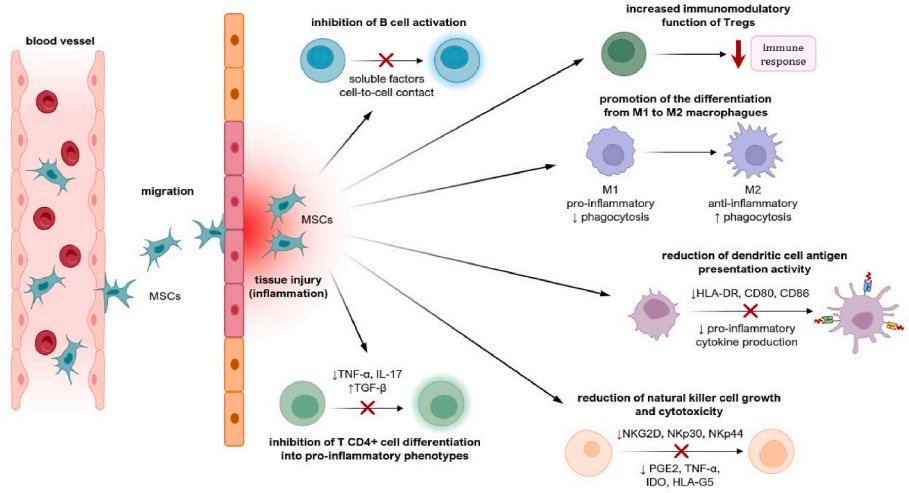

Fig. 1. Mechanisms by which mesenchymal stem cells (MSCs) migrate to peripheral tissues and target active immune cells: inhibition of active B cells and T CD4⁺ cell differentiation; increase in regulatory T cells (Tregs); promotion of differentiation from pro-inflammatory macrophages (M1) to anti-inflammatory macrophages (M2); reduction in antigen-presenting activity of dendritic cells (DCs); reduction in the number and activity of natural killer (NK) cells.

remission and ideally contributes to the promotion of self-tolerance.

On the other hand, new treatments for SLE that specifically inhibit a component of the immune system, such as biologic therapies, are being investigated and are becoming increasingly important in the treatment of SLE. Several promising biologic agents are being tested in clinical and preclinical studies to find new reliable therapies [3]. Although the mechanisms of action of these drugs are more specific, biologic agents lead to a decrease in non- and self-antigen-activated lymphocytes, which can lead to various adverse events, such as relapses after drug withdrawal. Induction of antigen-specific tolerance may overcome these problems by targeting the disease-causing lymphocytes. This concept represents a further step forward in the treatment of SLE. In this context, mesenchymal stem cell (MSC) therapy is in the spotlight because of its immunomodulatory capacity regarding both innate and adaptive immunity [4]. Therefore, depending on their mechanism of action, the question is whether MSCs could replace the autoimmune environment by favouring immunological tolerance in SLE.

2. The inflammatory process in SLE

SLE is defined by multiple defects in the innate and adaptive immune systems that promote chronic inflammation in tissues. In terms of molecular mechanisms, SLE is characterised by several abnormalities in cell and cytokine regulation. Patients with SLE are almost universally characterised by an excess of autoantibodies, especially those directed against nuclear antigens (anti-dsDNA, RNP particles), but also anti-DNA and antiphospholipid. These autoantigens are released during dysregulated cell death and contribute to the release of damage-associated molecular patterns (DAMPs) due to defective clearance of dying cells [5]. These defective processes lead to a loss of self-tolerance caused by multiple dysregulations, including excessive secretion of cofactors and cytokines that control and amplify B cell activation [6], mutations associated with B cell receptors (BCR) [7], a less efficient complement system [8], and involvement of the CD40 ligand [9] and Toll-like receptors (TLR) 7 and 9 signalling pathways [6]. This aberrant activation leads to excessive levels of activated B cells, memory B cells and plasma cells in patients with SLE, whose checkpoints responsible for eliminating autoreactive B cells are defective.

B cell activation and antibody production are known to be regulated by T cells through cytokine release and direct cellular contact. The levels of different T cell subsets have been reported to be altered in SLE patients, including upregulation and accumulation of T follicular helper (Tfh) cells, gamma-delta (γδ) T cells, T helper 17 (Th17) cells, and double negative (DN) T cells ($CD4^-$ TCRδ), Th2 cells and double negative (DN) T cells ($CD4^-$ $CD8^-$ TCRαβ+), as well as the downregulation of Th1 and the immunosuppressive function of the different regulatory T cell subsets, thus contributing to the amplification or perpetuation of the specific pathogenic process. Alterations in the number and/or function of these cell types, together with inappropriate overactivation of dendritic cells (DCs) producing type I interferon (IFN–I) - the main signature in lupus [10] - and monocytes acting as DCs in this context [11], cause changes in the levels of the various cofactors and cytokines they produce, including interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-10 (IL-10), transforming growth factor beta (TGFβ), interferon gamma (IFNɣ), interleukin-17 (IL-17), interleukin-21 (IL-21), which contribute to the control and amplification of T and B cell activation.

3. Mesenchymal stem cells promote an anti-inflammatory environment in SLE

Multipotent mesenchymal stromal cells, or more commonly mesenchymal stem cells (MSCs), can be isolated from a variety of tissues such as umbilical cord or bone marrow [12]. Their immunomodulatory effects have been shown to affect and reprogram immune cells [13] - reversing both their numbers and function [14] - as well as the concentration of cytokines and other soluble factors [15], resulting in the execution of anti-inflammatory responses. Recent studies have shown that MSCs interact with immune cells - both innate and adaptive immunity, such as natural killer (NK) cells, macrophages, monocytes, DCs, T and B cells - through cell-to-cell contact and paracrine activity. The function of MSCs is based on environmental signals. In the absence of tumour necrosis factor α (TNF-α) and IFN-I - very strong markers of inflammation - MSCs promote T-cell production by adopting a pro-inflammatory phenotype. Conversely, when MSCs are exposed to high levels of TNF-α and IFN-I, they act as anti-inflammatory regulators by producing TGF-β1, indoleamine 2,3-dioxygenase (IDO) and prostaglandin E2 (PGE2) [16]. Another example is the maturation of M1 to M2 macrophages, which is dependent on interleukin-6 (IL-6) levels in the environment [17].

In this context, MSCs inhibit B cell activation, proliferation and differentiation into plasma B cells via soluble factors and cell-to-cell contact, reducing autoantibody production [18] and other processes. MSCs are also able to inhibit T $CD4^+$ cell differentiation into Tfh, Th1 and Th17 cells, reduce abnormal T cell activation by decreasing levels of pro-inflammatory factors such as TNF-α or IL-17 and increasing levels of anti-inflammatory cytokines such as TGF-β [18,19]. MSCs can also

influence regulatory T cells (Tregs) by increasing their immunomodulatory functions. In addition to cells of adaptive immunity, MSCs also affect cells of innate immunity. For example, macrophages can be reprogrammed, limiting their aberrant activation in autoimmune diseases such as SLE and exerting an anti-inflammatory effect, both by promoting their differentiation from M1 type - pro-inflammatory functions - to M2 type - anti-inflammatory functions - and by increasing their phagocytic activity [20,21]. MSCs also affect DCs by inhibiting their maturation and function, limiting their antigen presentation cell (APC) activity by reducing the expression of presentation molecules such as HLA-DR, CD80 or CD86 [22]. Thus, like macrophages, MSCs can convert DCs to an anti-inflammatory phenotype by down-regulating the production of pro-inflammatory cytokines [23,24]. Finally, MSCs can reduce the growth and cytotoxicity of NK cells, possibly through both decreased expression of activating receptors, including NKG2D, NKp30 and NKp44, and increased expression of inhibitory receptors, such as CD158a and CD158b [25]. This lack of activation has also been linked to the secretion of cytokines by MSCs, such as PGE2, TNF-α, IDO or HLA-G5 molecules [24,26].

In addition, MSCs remain hypo-immunogenic [27] due to both their low expression of major histocompatibility (MHC) class I molecules and their null expression of MHC class II or co-stimulatory molecules (CD40, CD40L, CD80, CD86), making them ideal candidates for allogeneic treatment. Indeed, there is evidence that autologous therapies with MSCs - despite increasing Tregs concentration - do not sufficiently improve disease prognosis and are therefore not a suitable cell source for cell therapy in SLE [28]. In addition, treatment with allogeneic MSCs has been shown to have a long-term effect in reducing SLE autoimmunity [29] (Fig. 1).

4. Loss of immunological tolerance in SLE

Tolerance, or self-tolerance, is defined as the absence of an immunological response to self-antigens. Healthy individuals maintain tolerance because their immune systems have competent central and peripheral tolerance mechanisms, and the immunological pathways of tolerance take place in the immune cells of innate and adaptive immunity. In healthy individuals, if activation is not followed by co-stimulation, the activated immune cell undergoes an inactivation process that can lead to anergy or elimination by apoptosis. Cell suppression by regulatory cells is another interesting strategy to keep the immune response low. The function of regulatory cells as immunoregulators is indirectly one of the fundamental mechanisms of tolerance induction, and they promote the elimination of autoreactive cells.

In SLE, some of these effector mechanisms fail and immunological abnormalities result in autoimmunity. Aberrant signalling by TcR is known to contribute to the breakdown of immune tolerance to self-antigens. The structure of the TcR has been shown to be altered in SLE patients - the ζ chain is replaced by a γ chain of the FcεR. Signalling by this altered TcR in SLE has been shown to be 100-fold stronger than normal signalling. Increased activity of the intracellular calcium and protein kinase signalling pathways has also been studied, leading to changes in the activation of early-stage T lymphocytes. In addition, the normal production of IL-2 may be altered due to both the defective MAP kinase activity and the decrease in CD80 ligand, leading directly to a lack of tolerance maintenance [30,31].

The aberrant differentiation of monocytes into antigen-presenting DCs is another way of losing self-tolerance. T-cell activation requires monocytes to differentiate into mature DCs together with co-stimulatory molecules expressed on the DC membrane, such as CD80, CD86 or HLA-DR [32]. Alterations in this differentiation process can lead to chronic maturation and activation of DCs. Monocyte-derived DCs from SLE patients have been shown to spontaneously overexpress CD86, a co-stimulatory molecule in the membrane of DCs, which means that DCs are likely to be more efficient activators of T cells due to their enhanced antigen-presenting capacity. This would facilitate the breaking of immune tolerance [33].

On the other hand, the homeostatic suppressive effect of Tregs on effector T cells is crucial for the maintenance of self-tolerance, as Tregs reduce the activity of autoreactive effector cells that have escaped tolerance. The homeostatic suppressive effect starts with the inhibition of their expansion, either in a contact-dependent manner or by consuming local IL-2 thanks to their higher level of CD25. Tregs can also downregulate the expression of some co-stimulatory molecules such as CD80/86 to reduce the number of antigen-presenting cells by binding CTLA4 expressed on their membrane to CD80/86 with a higher affinity than CD28 [34]. Finally, CTLA4-mediated signals can induce indoleamine 2,3-dioxygenase (IDO) in antigen-presenting cells, leading to the starvation of effector T cells by depriving them of energy factors [35,36]. Valencia et al. [37] described that the number of Tregs was lower in the peripheral blood of patients with active SLE compared to patients with inactive SLE and healthy donors. The authors also showed that these Tregs from patients with active SLE had lower levels of FoxP3 and were less efficient in suppressing T cell proliferation and cytokine secretion in vitro. In contrast, Tregs from inactive SLE patients were more efficient in their suppressive capacity, as were healthy controls [38]. Knowing that there is a crucial imbalance of pathogenic T helpers vs. Tregs in SLE patients, parallelisms have been observed between IL-2 and TGF-β signalling deficiency and the reduction of Tregs, meaning that the uncontrolled activation of effector mechanisms could be a result of Tregs deficiency [39].

In addition, Bregs also contribute to self-tolerance. The most studied Bregs are those that produce IL-10. Bregs regulate macrophage responses and DC functions by suppressing TNFα production [40,41] and inhibiting Th1 and Th17 responses. Interestingly, Bregs induce FoxP3+ Tregs expansion via $CD72^{-}CD5$ interaction, implying that they contribute to self-tolerance maintenance [42]. Studies have shown that levels of IL-10-producing Bregs are reduced in SLE, particularly in SLE-nephritis [43]. One possible explanation for the reduced levels of Bregs in SLE patients is that the regulatory interaction between Bregs and DCs is altered due to the hyperactivation of DCs. This, together with the overproduction of IFNα, causes the DCs not to activate the Bregs [44].

5. Mesenchymal stem cell therapy may have a role in the induction of tolerance in SLE

In SLE, there are a number of immunological changes associated with the emergence of the loss of tolerance process that promote the development of autoimmunity. Loss of self-tolerance in SLE has several aspects, including defects in deletion and/or inactivation of T and B cells, defects in apoptosis, inappropriate function of inhibitory receptors and loss of number or function of regulatory T and B cells. Restoration of self-tolerance mechanisms may be an attractive step towards successful treatment of SLE. It would therefore be interesting to speculate which of these could be normalised by MSC treatment.

In this context, it is known that MSCs can promote the proper functioning of the anergy mechanism by inhibiting the maturation of antigen-presenting DCs, reducing the expression of co-stimulatory molecules such as HLA-DR, CD80 or CD86, resulting in the suppression of monocyte differentiation into DCs - the most antigen-presenting cells [24]. Alternatively, the in vitro assay performed by Zheng S. et al. [45] showed that MSCs can reduce T cell TcR signalling by secreting the protein ICAM-1, which reduces the transcription factors necessary for T-cell proliferation and differentiation, thus implementing another anergy mechanism that stimulates the induction of tolerance. However, the mechanisms of TcR blockade are still poorly understood. Finally, MSCs can induce an anergic state in immune cells by secreting inhibitory molecules that bind to inhibitory receptors on T cell membranes. For example, MSCs produce PD-1L [46] which binds to PD-1 - a family of CD28 receptors - on the surface of T cells whose function is to inactivate the cell once it has interacted with its ligand.

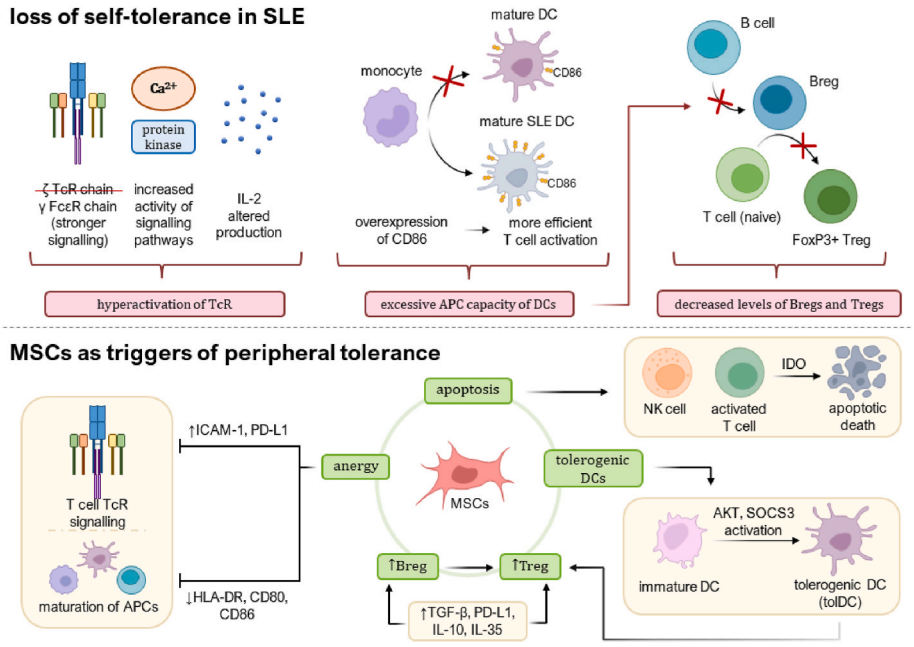

Fig. 2. Pathways of immune tolerance induced by mesenchymal stem cells (MSCs) that may promote tolerance in systemic lupus erythematosus (SLE): Establishment of proper anergy mechanisms via T cell receptor (TcR) signalling and secretion of inhibitory molecules, CD80, CD86 acting on antigen-presenting cells (APCs); development of early apoptotic death on activated immune cells; induction of dendritic cell (DC) differentiation towards a tolerogenic phenotype; differentiation of T and B cells into regulatory T subsets (Tregs) and regulatory B subsets (Bregs).

In addition, MSCs can affect several cell subsets, inducing their apoptosis in a dose-dependent manner, such as activated NK and T cells [47]. The recent in vitro study by Plumas J et al. [48] demonstrated that the presence of MSCs causes early apoptotic death of activated T cells, probably via mitochondrial apoptosis, and identified the presence of intracellular functional IDO in MSCs. IDO catalyses the conversion of tryptophan to kynurenine, leading to tryptophan depletion and T-cell death.

On the other hand, MSCs produce TGF-β and IL-10, which enhance the production of FoxP3 - an important biomarker and transcription factor for the differentiation of T cells into Tregs. Another subset of regulatory cells, Bregs, play an important role in promoting tolerance [49]. Although the specific mechanisms by which MSCs regulate the generation of Bregs are still unclear, an in vivo study by Wang H et al. demonstrated that PD-L1 expression on MSCs is required for the development of IL-10-producing Bregs and MSC-mediated suppression of B cell activity and antibody production, thus contributing to tolerance induction [50]. Furthermore, this study also mentions that IL-10$^+$ Bregs are not the only tolerance-inducing Bregs subset, as at least TGF-β$^+$ and IL-35$^+$ Bregs are also present. This was confirmed by Garcia SG et al., who showed that MSC-induced Bregs can suppress T cell proliferation independently of IL-10 action [51].

In addition to the aforementioned immunoregulatory capacity of MSCs towards DCs, MSCs can also induce DC differentiation towards a tolerogenic phenotype. Chiesa et al. [52] showed that tol-DCs can be induced by MSC-derived activation of AKT, which affects NF-κβ signalling without affecting IL-10 secretion. Alternatively, Zhang et al. [53] found that the Tol DC subset may be generated via activation of the suppressor of cytokine signalling 3 (SOCS3). The most interesting and widely studied role of these tol-DCs is their ability to promote the production of Tregs, with all the associated benefits (Fig. 2).

6. Conclusions

SLE is an autoimmune disease with a wide range of clinical manifestations and severity. Lupus nephritis and neurological damage are the most prominent events leading to morbidity and mortality. Severe organ damage in SLE is treated with high doses of corticosteroids and immunosuppressive drugs, at a significant cost in terms of adverse events. Despite intensive treatment, SLE is prone to flares that cause chronic tissue damage. And while corticosteroids and immunosuppressants reduce inflammation, they do not alter the underlying autoimmune milieu that is likely to be at the centre of organ damage, either clinically or subclinically. Severe SLE requires treatments that have an important ability to induce immune tolerance, acting on the inflammation and promoting a new environment.

This review aims to explore how mesenchymal stromal cells, or the most common mesenchymal stem cells (MSCs), could reduce self-antigen-activated lymphocytes and induce antigen-specific immune tolerance, thereby reducing the inflammatory milieu and promoting immune balance. Firstly, MSCs can act on both innate and adaptive immunity, reversing abnormal levels and function of T and B cell subsets. Secondly, MSCs modify levels of soluble factors, redirecting macrophages and enhancing their anti-inflammatory function, while at the same time MSCs regulate DC and NK cells. Most importantly, MSCs could replace the autoimmune environment by promoting immune tolerance, enhancing anergy processes in autoreactive cells, increasing apoptotic activity to eliminate them, activating Tregs and Bregs cells to enhance their proliferation and induce tolerogenic DCs.

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