MINI-REVIEW

The immunomodulatory role of MSC as a cell therapy in systemic lupus erythematosus

Seyed-Alireza Esmaeili[1,2*], Sara Hosseini[1,2], Mahmoud Mahmoudi[1,2], Afsaneh Foolady Azarnaminy[3]

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Systemic Lupus Erythematosus (SLE) is a chronic multisystemic inflammatory autoimmune disorder. By far there aren't any certain and clear etiopathogenesis for SLE, however, it has been well indicated that genetic susceptibility along with environmental factors drive the disturbance in immune tolerance so that SLE development will occur, through which both the innate and adaptive arms of the immune response exacerbate disease condition. To date, no absolute cure for SLE have been illustrated and current therapeutic strategies are primarily in terms of application of immunosuppressive drugs. Mesenchymal Stem Cells (MSC) are multipotent stem cells with low immunogenicity that can differentiate into different kinds of cells. Recently, Immunomodulatory functions of MSCs bring them as potential candidate for treating SLE. MSCs play a role in suppression of the antigen-presenting cells maturation (*DC and MQ*), T cells proliferation (*Th1, T17, and Th2*), proliferation and immunoglobulin production of *B cells*, the cytotoxic activity of CTL and NK cells as well as increasing regulatory cytokines (*TGF-β and IL10*), and decreasing inflammatory cytokines (*IL17, INF-Y, TNF-α, and IL12*) levels. The aim of this study is to show the worthwhile and therapeutic properties of MSCs with regards to the results of animal model studies, preclinical studies, and clinical trials of MSC therapy in SLE from the immunoregulatory aspect.

Key Words: *Systemic lupus erythematosus; Autoimmune disorder; Mesenchymal stem cells; T cells; B cells*

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic heterogeneous autoimmune disease through which anti-nuclear autoantibodies as well as excessive inflammatory responses are highly produced, affecting several organs. The clinical manifestations are raging from mild rash to severe organ involvement such as nephritis and even neuropsychiatric complications, depending on the organ system that is affected. It is generally accepted that genetic predisposition in combination with environmental and hormonal factors trigger immune responses that lead to disease progression, however the exact etiopathology is still intricate. Not only current SLE treatments including anti-malarial, steroidal and non-steroidal immunosuppressive drugs in addition to anti-inflammatory agents are not highly curative, but also often accompanied with notable toxicities. Therefore, further therapeutic strategies are urgently required in order to treat SLE more efficiently [1-5].

IMPORTANCE OF MESENCHYMAL STEM CELL

Mesenchymal stem cells are small cell bodies with a large nucleus resembling fibroblasts along with self-renewal and multipotent differentiation potentials. Functional and Phenotypic Features of MSCs are plastic adherence ability, expression of *CD105, CD90, and CD73* markers and no expression of CD34, CD45, CD11b, CD14, CD19, or CD79a and HLA-DR markers. One of the most significant features of these cells is their capability to bring about mesodermal and non-mesodermal cell lineages both *in vitro* and *in vivo*, namely osteoblasts, chondrocytes, cardiomyocytes, endothelial cells, lung epithelial cells, hepatocytes, and neurons, which can be applicated as a wealthy candidate for in regenerative medicine [6,7]. It has been well demonstrated that multiple fetal and adult tissue sources are available as possible sources of MSCs and MSC like cells for experimental investigations. It comprises Bone Marrow (BM) (as one of the most readily sources), Adipose Tissue (*AT-MSCs*), peripheral blood, umbilical cord blood, synovial fluid and membrane, dental pulp, fetal tissues, deciduous teeth, tendon, skeleton, dermis, muscle, thymus, spleen, fallopian tubes, brain, liver, periosteum, placenta, synovial, and amniotic fluids. Despite similar phenotypic characteristics, MSCs express distinguished tendencies for proliferation as well as differentiation in terms of being stimulated by various growth factors [8,9].

THERAPEUTIC APPLICATIONS OF MSC

Over the last decade, MSC-based therapies are attracting considerable attention as innovative therapeutic alternatives in a vast panel of inflammatory as well as degenerative medicine owing to their antimicrobial activity, anti-apoptotic, neuroprotective, antioxidant, angiogenic immunomodulatory properties. In addition, isolated tumors and metastatic diseases can be treated by application of MSCs as vehicles for targeted drug delivery systems in terms of their special features such as homing ability, fast *ex-vivo* expansion, immunoregulation, feasibility of autologous transplantation properties, and their multilineage potential. Nonetheless, it is worth noting that their vehicle role is not limited to cancer treatment [10,11]. To put it in a nutshell, their self-renewal, multipotency, regenerative ability, and immunomodulatory features, bring MSCs as a promising type of cell therapy in the treatment of various diseases particularly ischemia, diabetes, inflammatory, autoimmune and even neurological diseases, tissue injury, organ transplantation, and hepatic diseases [12,13].

THE IMMUNOMODULATORY ROLE OF MSCs

Looking beyond the characteristics mentioned above, it has also been reported that MSCs have potent immunomodulatory, anti-proliferative, and anti-inflammatory capacities, however, their molecular basis is still elusive. Since MSCs are capable of escaping from immune recognition and recognition by alloreactive T cells, they can be potentially useful for transplantation objectives. This is likely because of the fact that MSCs lack the expression of class II Major Histocompatibility Complex (MHCs) in

[1]*Department of Immunology Research Center, University of Mashhad Medical Sciences, Mashhad, Iran;*[2]*Department of Immunology Department, University of Mashhad Medical Sciences, Mashhad, Iran;*[3]*Department of Anesthesiology, University of Mashhad Medical Sciences, Ardabil, Iran*

Correspondence: *Seyed-Alireza Esmaeili, Department of Immunology Research Center, University of Mashhad Medical Sciences, Mashhad, Iran, Tel: +985138002379; E-mail: Imunoman2009@gmail.com*

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addition to costimulatory molecules, such as *B7-1, B7-2, CD40, or CD40L*. Thus, they tend to favor tolerance/anergy induction rather than allogeneic responses [14,15]. It is a well-known fact that MSCs exhibit a notable immunological role toward both humoral and cellular immune responses. The immunosuppression mediated by MSCs is a complex mechanism through which, T cell subsets polarization from a *Th1 and Th17* cell promoted to *Th2* and *Treg,* respectively. It has also been reported that in the MSC-treated animals, On the one hand, the inflammatory cytokines level produced by *Th1* and *Th17* including *IFN- γ, IL-2, IL-12p70, IL-17, IL-22,* and *TNF-α* were significantly reduced, which are believed to be significant drivers of tissue damage as well as disease pathology in autoimmune diseases [16,17]. On the other hand, the anti-inflammatory cytokines such as *IL-4 and IL-5* produced by *Th2* in addition to *IL-10 and TGF-β* by Tregs were substantially increased. The suppression of T cells mediated by MSCs follows certain mechanisms consisting inducing G0 arrest in the T cell cycle, apoptosis, IDO expression, modulatory effects on antigen- presenting cells, secretion of Prostaglandin E2 (*PGE2*), Transforming Growth Factor b1 (TGF-b1), human leukocyte antigen-G5, Fas ligand (*FasL*), and Programmed Death-Ligand 1 and 2 (*PDL1 and PDL2*) [18-20].

Moreover, a significant number of studies have also reported that CTL formation is inhibited by MSCs in which CTL-mediated cytotoxicity is markedly decreased. At odds with Tcells, the immunosuppressive features of MSCs on the humoral arm of adaptive immunity, namely B cells, remains disputable. There are several studies indicating that MSCs interfere with maturation, proliferation and differentiation into plasma cells. On the contrary, other studies stated that MSCs advocate B-cell proliferation and differentiation into plasma cells and memory B-cell population [21]. It has been also reported that MSCs exert numerous modulatory effects on innate immune cells. DCs are the most critical innate immune cells that play determining role in the initiation, maintenance, and regulation of immune responses which will be further get affected with MSCs so that differentiation, migration, maturation, and antigen presentation of DCs may then end up triggering tolerogenic T-cells. To be more precise, the low proliferation and expression of costimulatory molecules, *HLA-DR, CD80, and CD86*, along with blocking of proinflammatory cytokine secretion of DCs can lead to the immune tolerance induction. Macrophages bear a very similar outcome as DCs did by the affection of MSCs, bringing on a major immunosuppressive response, increased levels of Inter Leukin-10 (*IL-10*) expression and diminished levels of *TNF-α, IL- 12*, low costimulatory molecule CD86, and human leukocyte antigen class II molecules. It should be noted that MSCs promote a shift from an inflammatory M1 phenotype to the anti-inflammatory M2 phenotype so that their balance will get modulated. Another relevant target for the immunomodulatory properties of MSCs is NK cells. In fact, both resting and pre-activated NK cells seem to be suppressed by MSCs *via IDO1, TGF-b, HLA-G, and PGE2* secretion [22,23].

MSC-BASED THERAPY

The overall outcome of the investigations upon mice treated with MSCs demonstrated a decline in proteinuria, Anti-Nuclear Antibodies (ANA), anti-dsDNA Abs, creatinine, glomerulonephritis, blood urea nitrogen, interstitial inflammation, T lymphocyte proliferation, and the *CD4/CD8* ratio and a rise in serum albumin level highlighting that immune cell responses could be modified by MSCs. Furthermore, these studies have reported a decrease in the level of proinflammatory cytokines, such as *TNF-α , IL-6, IL-12 and IL-17*, in addition to an increase in the level of immunoregulatory mediators including IL-10 and IL-4 [24]. Evidences according to human study who intravenously injected umbilical cord MSCs into 16 patients showed a dramatic decrease in the level of serum ANA, anti-dsDNA anti- body, proteinuria, serum creatinine, and urea nitrogen as in addition to an increase in serum albumin, complement C3, hemoglobin level, and platelet count. On top of that, polarization of Tcell from Th2 toward Th1 phenotype, reduction of circulating Th17 level along with the expansion of *CD4+CD25+*Foxp3+ T cells following the application of MSCs in patients with active SLE, consequently resulted in a remarkable reduction in disease activity as well as clinical remission [20-26].

CONCLUSION

SLE as a systemic autoimmune disorder are engaged with multi organ involvement through autoantibodies, inflammatory T Cells and cytokines. Current therapeutic strategies in SLE are predominantly based on the administration of immunosuppressive drugs, however, they are not highly beneficial for the progression and prevention of SLE. Recently, Immunomodulatory functions of MSCs in addition to their differentiation potential bring them as potential candidate for treating SLE. The mechanisms underlying immunosuppressive properties include inhibition of the pathogenic T cell responses, inducing regulatory T cells generation, decreasing B cell activation and induction, and proliferation of antigen-presenting cells into a regulatory like profile. All in all, these findings implies that MSCs can be used as a safe type of therapy with minimum toxicity which may lead to clinical remission by their immunomodulatory effects on innate and adaptive immunity maintaining immunological homeostasis.

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REFERENCES

1. Carter EE, Barr SG, Clarke AE, et al. The global burden of SLE: prevalence, health disparities and socioeconomic impact. Nature Reviews Rheumatology. 2016; 12: 605-620.
2. Sciascia S, Radin M, Roccatello D, Sanna G and Laura M. iris-AperTO. Ann Rheum Dis. 2018.
3. Momtazi-Borojeni AA, Haftcheshmeh SM, Esmaeili S-A, et al. Curcumin: A natural modulator of immune cells in systemic lupus erythematosus. Autoimmunity Reviews. 2018; 17: 125-35.
4. Vahidi Z, Samadi M, Mahmoudi M, et al. Lactobacillus rhamnosus and Lactobacillus delbrueckii ameliorate the expression of miR-155 and miR-181a in SLE patients. Journal of Functional Foods. 2018; 48: 228-33.
5. Yazdanpanah E, Mahmoudi M, Sahebari M, et al. Vitamin D3 alters the expression of toll-like receptors in peripheral blood mononuclear cells of patients with systemic lupus erythematosus. Journal of Cellular Biochemistry. 2017; 118(12): 4831-483 5.
6. Kitada M and Dezawa M. Parkinson's disease and mesenchymal stem cells: potential for cell-based therapy. Parkinson's Disease. 2012; 2012: 873706.
7. Wang L, Zhao Y, Shi S, et al. Interplay between mesenchymal stem cells and lymphocytes: Implications for immunotherapy and tissue regeneration. Journal of Dental Research. 2012; 91(11): 1003-10.
8. Kyurkchiev D, Bochev I, Ivanova-Todorova E, et al. Secretion of immunoregulatory cytokines by mesenchymal stem cells. World Journal of Stem Cells. 2014; 6(5): 552-70.
9. Moghaddam AS, Afshari JT, Esmaeili S-A, et al. Cardioprotective microRNAs: Lessons from stem cell-derived exosomal microRNAs to treat cardiovascular disease. Atherosclerosis. 2019; 285: 1-9.
10. Maykowski P, Smithgall M, Zachariah P, et al. Seasonality and clinical impact of human parainfluenza viruses. Influenza and other Respiratory Viruses. 2018; 12: 706-716.
11. Tomchuck SL, Norton EB, Garry RF, et al. Mesenchymal stem cells as a novel vaccine platform. Frontiers in Cellular and Infection Microbiology. 2012; 2: 140.
12. Silva LH, Antunes MA, Dos Santos CC, et al. Strategies to improve the therapeutic effects of mesenchymal stromal cells in respiratory diseases. Stem Cell Research & Therapy. 2018; 9(1): 45.
13. Colpo GD, Ascoli BM, Wollenhaupt-Aguiar B, et al. Mesenchymal stem cells for the treatment of neurodegenerative and psychiatric

disorders. Anais da Academia Brasileira de Ciências. 2015; 87: 1435-49.

14. MacDonald GI, Augello A, De Bari C, et al. Role of mesenchymal stem cells in reestablishing immunologic tolerance in autoimmune rheumatic diseases. Arthritis & Rheumatism. 2011; 63(9): 2547-57.
15. Ryan JM, Barry FP, Murphy JM, et al. Mesenchymal stem cells avoid allogeneic rejection. Journal of Inflammation. 2005; 2: 8.
16. Duffy MM, Ritter T, Ceredig R et al. Mesenchymal stem cell effects on T-cell effector pathways. Stem Cell Research & Therapy. 2011; 2(4):34.
17. Ghannam S, Pène J, Torcy-Moquet G, et al. Mesenchymal stem cells inhibit human Th17 cell differentiation and function and induce a T regulatory cell phenotype. The Journal of Immunology. 2010; 185: 302-12.
18. Newman RE, Yoo D, LeRoux MA et al. Treatment of inflammatory diseases with mesenchymal stem cells. Inflammation & Allergy-Drug Targets (Formerly Current Drug Targets-Inflammation & Allergy) (Discontinued). 2009; 8: 110-23.
19. Rawat S, Gupta S, Mohanty S. Mesenchymal stem cells modulate the immune system in developing therapeutic interventions. Immune Response Activation and Immunomodulation. 2019: 103.
20. Radmanesh F, Mahmoudi M, Yazdanpanah E, et al. The immunomodulatory effects of mesenchymal stromal cell-based therapy in human and animal models of systemic lupus erythematosus. IUBMB life. 2020; 72: 2366-2381.
21. Wang LT, Ting CH, Yen ML, et al. Human mesenchymal stem cells (MSCs) for treatment towards immune-and inflammation-mediated diseases: review of current clinical trials. Journal of Biomedical Science. 2016; 23(1): 76.
22. Leyendecker Jr A, Pinheiro CCG, Amano MT et al. The use of human mesenchymal stem cells as therapeutic agents for the in vivo treatment of immune-related diseases: a systematic review. Frontiers in Immunology. 2018; 9: 2056.
23. Galland S, Vuille J, Martin P, et al. Tumor-derived mesenchymal stem cells use distinct mechanisms to block the activity of natural killer cell subsets. Cell Reports. 2017; 20(12): 2891-2905.
24. Liu J, Lu X, Lou Y, et al. Xenogeneic transplantation of human placenta-derived mesenchymal stem cells alleviates renal injury and reduces inflammation in a mouse model of lupus nephritis. BioMed Research International. 2019; 2019: 9370919.
25. Li X, Wang D, Liang J, et al. Mesenchymal SCT ameliorates refractory cytopenia in patients with systemic lupus erythematosus. Bone Marrow Transplantation. 2013; 48: 544-50.
26. Carrion F, Nova E, Ruiz C, et al. Autologous mesenchymal stem cell treatment increased T regulatory cells with no effect on disease activity in two systemic lupus erythematosus patients. Lupus. 2010; 19: 317-22.