

The Immunomodulatory Role of MSC as A Cell Therapy in Systemic Lupus Erythematosus

Sara Hosseini^{1,2}, Mahmoud Mahmoudi^{1,2}, Seyed-Alireza Esmaili^{1,2*}

¹Department Immunology Research Center, Mashhad University of Medical Sciences, Mashhad, Iran; ²Department of Immunology, Mashhad University of Medical Sciences, Mashhad, Iran

ABSTRACT

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 has 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- γ , 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.

Keywords: Cutaneous lupus erythematosus; Lupus; Systemic lupus erythematosus; Discoid lupus; Autoimmune; Discoid lupus erythmatosus

DESCRIPTION

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 applied 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].

Correspondence to: Seyed-Alireza Esmaili, Department of Immunology, Mashhad University of Medical Sciences, Mashhad, Iran, Tel: +989191047300; E-mail: Imunoman2009@gmail.com

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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 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 b 1 (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 T-cells, 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 interleukin-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, antinuclear 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 T-cell 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 [20,25,26].

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.

Conflict of Interests

The authors declare no competing financial and non-financial interests.

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