World Journal of Biology Pharmacy and Health Sciences
eISSN: 2582-5542
Cross Ref DOI: 10.30574/wjbphs
Journal homepage: https://wjbphs.com/

(REVIEW ARTICLE)

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Immunomodulatory effects of mesenchymal stem cells on B and T cells

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World Journal of Biology Pharmacy and Health Sciences, 2023, 15(03), 006–010

Publication history: Received on 20 July 2023; revised on 31 August 2023; accepted on 03 September 2023

Article DOI: https://doi.org/10.30574/wjbphs.2023.15.3.0365

Abstract

Mesenchymal stem cells (MSCs) or adult multipotent progenitor cells with the ability to self-renew and differentiate, are extracted from a variety of tissues, including bone marrow, adipose tissue, umbilical cord blood, Wharton's jelly, tooth pulp, menstrual blood, and others. Since they are multipotent, cultured MSCs can differentiate into the adipogenic, chondrogenic, and osteogenic lineages after being isolated. Due to their immunomodulatory, immunosuppressive, and regenerative potentials, multipotent mesenchymal stem cells (MSCs) have received extensive scrutiny as an efficient tool for cell-based therapy of inflammatory, immune-mediated, and degenerative illnesses. Mesenchymal stem cells (MSCs) have been the subject of numerous preclinical and clinical research that looked into their therapeutic potential. This potential is primarily supported by MSCs' immunosuppressive characteristics. Even while there is still much to learn about the therapeutic characteristics of MSC transplantation, mounting evidence suggests that T and B cells undergo changes after MSC infusion, most notably the induction of regulatory T (T_{regs}) and B (B_{regs}) cells. T_{regs} and B_{regs} have been shown to exhibit immunosuppressive properties, and these cells are being considered as potential novel targets for the therapy of inflammatory disorders.

Keywords: MSC; Immunomodulatory; T cells; B cells

1. Introduction

1.1. Insight into MSCs

Mesenchymal stem cells or mesenchymal progenitor cells are a subgroup of non-hematopoietic cells found in the bone marrow stroma. Ex vivo cell expansion and induction can be carried out on MSCs, which can be in vivo or in vitro, to terminally differentiate them into osteoblasts, chondrocytes, adipocytes, tenocytes, myotubes, neural cells, and hematopoietic-supporting stroma. These cells are a desirable therapeutic tool due to their multipotency, ease of isolation and culture and strong ex vivo expansion potential [1]. MSCs can be extracted from many different tissues, including the umbilical cord, adipose tissue, menstrual blood, endometrial polyps, etc. However, MSCs have recently been discovered in new sources, including endometrium and menstrual blood [2]. MSC treatments are the focus of clinical studies due to their capacity for regeneration and immunomodulation, however, from the standpoint of clinical research, there are a few possible dangers of MSC therapeutics that need to be considered: (i) the cells' immunogenicity; (ii) the culture/medium components' biosafety; (iii) the potential risk of ectopic tissue formation; and (iv) the possibility that the cells may undergo an in vitro transformation during cultural expansion that could result in cancer [3].

As a result of the discovery of MSC immunomodulatory capabilities in more recent years, the field of regenerative medicine has gradually made way to the study of autoimmunity. This is because traditional immunosuppressants may be dangerous in this category of illnesses caused by immune system activation that is out of control and results in loss of self-tolerance and auto-reactivity. One advantage of MSC-based therapy may be the immunological flexibility of MSCs,

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which results in an immunosuppression that is only momentary and spatially restricted [4]. MSCs have a dynamic immunomodulatory profile as a result of their exceptional capacity to recognize injury or inflammation and then switch to the appropriate response [5]. Theoretically, the MSC secretome is capable of correcting aberrant immune regulation (i.e., establishing immunological homeostasis) due to a wide range of biological activities connected to the secretome that have been demonstrated thus far, including anti-inflammatory, anti-apoptotic, and immunomodulatory capabilities. The extremely biocompatible secretome might be thought of as the best alternative for cell-free therapy because it exerts similar biological effects but is far less immunogenic than MSCs. Additionally, because the MSC secretome's composition is modifiable, it has the potential to serve as a component of a nanomedicine delivery system that would enable us to specifically target diseased cells or tissues in the future [6].

Although, human mesenchymal stem cells (hMSCs) have the potential to cure a wide range of illnesses and disorders and are a promising therapeutic tool in regenerative medicine, their precise mechanisms of action remain unclear, though they are likely related to all or a combination of the following: multipotent differentiation, functional incorporation, immunomodulation, and secretion of paracrine factors [7], [8]. Due to their capacity to inhibit T cell proliferation, hMSCs are particularly intriguing as a therapeutic approach for inflammatory disorders [7], [9]–[12]. Through antigen presentation, antibody release, and complement activation, B cells, which are crucial immunological effector cells in adaptive immune responses, contribute to autoimmunity. Previous studies have demonstrated that MSCs can control not just B cell proliferation and differentiation, but also prevent B cell apoptosis. Through this review study, we hope to shed light on such immunomodulatory effects of MSCs on T and B cells.

1.2. Current Definition and Understanding of B and T cells

B cells, which are crucial for the adaptive immune response, have been linked to autoimmune disorders, infections, and cancer because of their capacity to present antigens, make antibodies, and stimulate the immune system [13]. Regulatory B cells (B_{regs}) are a collective term for a number of subsets of B cells that perform regulatory tasks resembling those of regulatory T cells (T_{regs}). Previous research has demonstrated that B_{regs} can suppress Th1 and Th17 responses and activate forkhead box P3+ ($FoxP_3$+) T_{reg} pools, which are essential for maintaining peripheral tolerance [14]. Different B cell subpopulations, such as B1 B cells, B2 B cells, and plasma cells, have been discovered to contain regulatory B cells [15]. Immunosuppression which is B_{reg} mediated plays a significant role in maintaining peripheral tolerance. B_{regs} may express one or more regulatory factors, such as programmed cell death ligand 1 (PD-L1), transforming growth factor (TGF), interleukin-10 (IL-10), and IL-35, because to their heterogeneity and have inhibitory or suppressive effects on related T cells [16], [17]. However, there is still no clear consensus on the definition and classification of B_{regs} [18].

The immune system's T cells are specialized to target particular foreign substances. T cells circulate until they come into contact with their particular antigen, rather than attacking all antigens at once. T cells are therefore essential for developing immunity to foreign particles. Although they begin in the bone marrow, T cells develop in the thymus. They do not get activated, though, until they come across their unique antigen. On the surface of antigen-presenting cells (APCs), they bind to this antigen. The major histocompatibility complex (MHC) is often made up of several different types of T cells, primarily CD4 helper and CD8 cytotoxic T cells. T cells come in three different subtypes: cytotoxic (T_c), helper (T_h), and regulatory (T_{reg}). To be effective for immunity, each of them must have a significant response to foreign antigens. Following activation, cytokines are used for communication. What kind of responder the cells become is determined by the cytokines. Helper T cells develop into IL-17, T_{h1}, or T_{h2} cell types. Each of these categories plays a unique part in the ongoing evolution of new immune responses [19].

2. Immunomodulatory Effects of MSCs

MSCs have several means by which they can affect the individual immune cell types. Overall, MSCs exercise their immunomodulatory effects by inhibiting proliferation and maturation of pro-inflammatory or effector immune cells, as well as driving certain immune cells toward tolerogenic and anti-inflammatory phenotypes [20].

2.1. Immunomodulatory Effects of MSCs on B cells

Numerous studies have demonstrated how MSCs impact B cells by acting as immunomodulators. In a previously done research study, the ability of hMSCs to engage directly with B cells to inhibit their growth and demise while promoting arrest in the G0-G1 phase of the cell cycle was observed for the very first time. They discovered that the reduction of human B cell proliferation, differentiation into antibody-secreting cells, and chemotaxis in vitro resulted in downregulation of the expression of C-X-C motif chemokine receptors ,CXCR4, CXCR5 and CCR7, in B cells [21].

In another study it was observed that third-party MSCs may be able to suppress allo-specific antibody production in vitro, which suggests they can modulate B cell allo-responses by inhibiting antibody production. This could help sensitized transplant recipients avoid a positive cross-match [22].

In a different research study, it was discovered that bone marrow MSCs can encourage the proliferation of transitional cells and naive B cells and their differentiation into immunoglobulin-secreting cells. In addition, an observation was made that suggested MSCs strongly encourage the proliferation of memory B cells and their differentiation into plasma cells through polyclonal stimulation of B cells isolated from children with systemic lupus erythematosus and healthy donors [23].

MSCs' key roles in the regulation of regulatory B cells are crucial in the treatment of numerous illnesses. For instance, $CD1d^{high}CD5+$ regulatory B cells were upregulated following MSC administration, which in turn exerted anti-inflammatory and immunosuppressive effects in experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis (MS) in humans [24].

Another study found that human synovial membrane-derived MSCs could induce $CD21^{high}CD23^{high}$ transitional 2 (T2) cells, $CD23^{low}CD21^{high}$ marginal zone (MZ) cells, and CD5+CD1d+IL-10 cells in the spleen, as well as increase the number of immature transitional B cells, such as IL-10+ cells, thereby minimizing the severity of arthritis in mice [25].

In a different study, MSC infusions helped stabilize renal allograft function over time. This was probably accomplished by causing recipients of kidney allografts to develop long-lasting immunophenotypes for naive and $CD24^{high}CD38^{high}$ transitional B cell subsets [26]. Additionally, a recent study demonstrated that the B_{reg} cell subset $CD19+CD24^{high}CD38^{high}$ also demonstrated crucial roles in the long-term acceptance of lung graft [27].

In an acute graft-versus-host disease (aGVHD) mouse model with complete MHC mismatch, allogeneic MSC transplantation was found to increase levels of IL-4 and IL-10, induce B_{regs}, and significantly reduce the expression of CD69 and CD86 on B cells to prolong survival, demonstrating that B cells are targets of the immune regulatory cascade in MSCs and that they play a significant role in the development of aGVHD [18]

2.2. Immunomodulatory Effects of MSCs on T cells

A study showed that (1) both autologous or allogeneic BMSCs strongly inhibit T cell proliferation, (2) this phenomenon, which is triggered by both cellular and nonspecific mitogenic stimuli, has no immunologic restriction, and (3) T cell inhibition is not attributable to the induction of apoptosis and is likely attributable to the production of soluble factors [8].

Numerous cytokines are present in hMSC serum-free conditioned media (SFCM), and prior research has connected physoxia to altered secretome composition. The data obtained from this study are consistent with the hypothesis that IL-10 inhibits Jurkat T cell growth and activation in hMSC SFCM. It was further established that transforming growth factor beta TGF-β is unimportant to SFCM-mediated immunosuppression [28].

The findings of this recent study demonstrated that human umbilical cord mesenchymal stem cells (hUCMSCs) decreased T_{h17} cell ratio, elevated forkhead box P3 (Fox-P3) mRNA and protein expression, and boosted Treg cell ratio in the spleen while increasing apoptosis and downregulating ROγt mRNA and protein expression in T cells. Additionally, they reduced retinoic-acid-receptor-related orphan nuclear receptor gamma (ROγt) and Fox-P3 expression in the joints, blocked IL-17, and increased transforming growth factor- β (TGF-β) expression in the serum, which improved arthritis and slowed the progression of radiological damage [29].

Another study suggested that adipose-derived mesenchymal stem cells (Ad-MSCs) significantly upregulated the transcription factors for T_{h2} and T_{reg} cells, such as GATA-binding protein-3 (GATA3) and Fox-P3 ($p<0.05$), while significantly downregulated the transcription factors for T_{h1} and T_{h17} cells, such as T-box 21 (T-bet) and ROγt ($p<0.05$). These findings show that Ad-MSCs can induce a situation that is immunosuppressive by suppressing pro-inflammatory T cells and inducing T cells with a regulatory phenotype. The clinical consequences for inflammatory and autoimmune illnesses like RA may therefore be significant [30].

Another study demonstrated that ageing had no impact on dental pulp MSCs (DP-MSCs') abilities to regulate CD4+ T cells or their impacts on T_{h1} and T_{h2} cells. However, the expression of the pleiotropic molecules like interleukin-6 (IL-6) and hepatocyte growth factor (HGF), which are crucial for bone and dental tissue regeneration, drastically decreased in

old DP-MSCs. This circumstance might have had an indirect impact on how young and old DP-MSCs modulated the T_{h17} and T_{reg} cells [31].

In one of the more recent research studies, it was found that Fox-P3, transforming growth factor (TGF), and IL-10 gene expression were elevated in collagen-induced arthritis (CIA) mice; ROγt, IL-17, and IL-6 gene expression were also increased in these mice that were administered with miR-146a-transduced MSC-derived exosomes. This goes to show that exosomes from MSCs that have been modified with anti-inflammatory miRNA may produce more T_{reg} cells and anti-inflammatory cytokines [32].

3. Conclusion

From this review, we get an insight into the immunomodulatory effects of MSCs on B and T cells. We still do not completely understand the molecular machinations of how MSCs and their derived secretomes lead to immunomodulation of lymphocytes. These properties, however, can be used for therapeutic purposes to alleviate the symptoms of different inflammatory conditions, the pathogenesis of which involves abnormal B and T cell proliferation. This requires more extensive research and study so that these treatments can be well understood and established before they are brought down to clinical trials.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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