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Review

Immunosuppressive Potential of Mesenchymal Stem Cells in Medicine

Adusumilli Pramod Kumar [1], Jeesa George [1 *]

[1] Department of Pharmacy Practice, Faculty of Pharmacy, Ramaiah University of Applied Sciences, Gnanagangothri Campus, Bangalore-560054, India.

* Corresponding Author: Ms Jeesa George, Assistant Professor, Department of Pharmacy Practice, M S Ramaiah University of applied sciences, Bangalore, 560054, Email: jeesamanikombel@gmail.com

Running title: Immunosuppressive Potential of MSC in Medicine

Abstract

Immunosuppressive drugs are substances that suppress or reduce the strength of the body's immune system. They are often used to manage conditions where an overactive immune response leads to tissue damage or disease progression. Mesenchymal Stem Cells (MSCs) have garnered significant attention in research due to their multifaceted immunological properties, presenting them as potential therapeutic candidates for a range of disorders, including autoimmune diseases and tumors. Initially recognized for their ability to suppress T lymphocytes, recent studies have highlighted MSCs' impact on various immune cell types, T cells, B cells, natural killer (NK) cells, dendritic cells (DCs), macrophages, and neutrophils, underscoring their complex role in immune regulation and tolerance development. MSCs primarily suppress the immune system by inhibiting T cell proliferation through the release of substances such as TGF-β, HGF, PGE2, IL-10, HLA-G5, and IDO, promoting the generation of regulatory T cells (Tregs) that further dampen immune reactions. Furthermore, MSCs influence the function of DCs by impeding their development and maturation processes, while also enhancing the production of inflammatory molecules like IL-10. Similarly, MSCs hinder the proliferation of B cells and their antibody production, particularly in inflammatory contexts. Thus, immunosuppressive potential of MSCs holds significant promise for therapeutic applications.

Keywords: Immunosuppression, MSC, Medicine, Immunomodulation, Immune cells.

Introduction

An immunosuppressive agent, also known as an immunosuppressant or immunomodulatory drug, is a substance that suppresses or modulates the activity of the immune system. These agents are used therapeutically to dampen the immune response in various medical conditions where an overactive immune system contributes to tissue damage or disease progression [1]. There are several classes of immunosuppressive agents, each with different mechanisms of action[2], [3]. Some of the most commonly used immunosuppressants are presented in table 1.

Each class of immunosuppressive agents has its own set of benefits, risks, and side effects, and the choice of drug depends on the specific condition being treated, the patient's medical history, and other individual factors. They are used in various combinations and dosages depending on the specific condition being treated, the severity of the disease, and individual patient factors to achieve optimal therapeutic

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Table 1: Different classes of immunosuppressants: examples, mechanisms of action, and applications in patients.

Immunosuppressants		Mechanisms of action	Use
Class	**Example**		
Corticosteroids or Glucocorticoids	Prednisone, Dexamethasone and Methylprednisolone	Potent anti-inflammatory drugs that suppress the activity of immune cells, particularly T cells and macrophages, and thus, reduce inflammation.	Widely used in the treatment of autoimmune diseases, organ transplant rejection, and inflammatory conditions.
Calcineurin inhibitors	Cyclosporine and Tacrolimus	Inhibit the activity of calcineurin, a phosphatase enzyme that is crucial for the activation of T cells. By blocking calcineurin, these drugs prevent the production of interleukin-2 (IL-2), a key cytokine involved in T cell proliferation and activation.	Rejection of transplanted organs and treat autoimmune diseases like psoriasis and rheumatoid arthritis.
Antimetabolites or Antiproliferative agents	Azathioprine, Mycophenolate mofetil, and Methotrexate	Inhibit the proliferation of immune cells, particularly T cells and B cells, by interfering with DNA synthesis or nucleotide metabolism.	Commonly used as maintenance therapy in organ transplant recipients and for the treatment of autoimmune diseases.
Biological therapies or Biologics	Monoclonal antibodies (e.g., Infliximab, Rituximab, Alemtuzumab, Basiliximab, Daclizumab), Tumor necrosis factor (TNF) inhibitors and Interleukin inhibitors (e.g., Ustekinumab, Secukinumab) Anti-Lymphocyte Globulin (ALG) and Anti-Thymocyte Globulin (ATG) such as ATG (rabbit or equine)	Designed to target specific components of the immune system, such as cytokines, cell surface receptors, or immune cells. For example, rituximab targets B cells. Infliximab (TNF inhibitor). Basiliximab (anti-CD25 antibody) Infliximab (anti-TNF antibody) Rituximab (anti-CD20 antibody) Muromonab (anti-CD3 antibody) Basiliximab, Daclizumab (IL-2 receptor antagonist) ALG and ATG are polyclonal antibodies that target multiple antigens on lymphocytes, leading to their destruction.	Autoimmune diseases such as rheumatoid arthritis and psoriasis, inflammatory conditions, and certain types of cancer.
mTOR Inhibitors	Sirolimus (Rapamycin) Everolimus	Inhibit the mammalian target of rapamycin (mTOR), a protein kinase involved in cell proliferation and survival.	Used to prevent organ rejection in kidney transplant recipients. Sirolimus is also used to treat certain types of

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			cancer, like renal cell carcinoma.
Janus Kinase (JAK) inhibitors	Tofacitinib and Baricitinib	Block the activity of Janus kinases, enzymes involved in cytokine signaling pathways. By inhibiting cytokine signaling, JAK inhibitors reduce inflammation and suppress immune responses.	Autoimmune diseases such as rheumatoid arthritis and psoriasis.
Fusion Proteins	Engineered proteins such as Abatacept (CTLA-4-Ig), Belatacept	Inhibit the costimulatory signals required for T-cell activation.	Abatacept (CTLA-4-Ig): Used in rheumatoid arthritis and juvenile idiopathic arthritis. Belatacept: Used to prevent organ rejection in kidney transplant recipients.
Cytotoxic agents	Cyclophosphamide, Methotrexate (at higher doses), Azathioprine (at higher doses)	Kill rapidly dividing cells, including activated immune cells	Autoimmune diseases and organ transplant rejection

outcomes while minimizing adverse effects. In the medical field, thus, the use of immunosuppressive agents is essential because of their critical role in managing various conditions by modulating the immune response and preventing immune-mediated damage to tissues and organs. Autoimmune Diseases Management, Organ Transplantation, Graft-versus-Host Disease (GVHD), Management of Allergic Reactions, Control of Chronic Inflammatory Conditions, Prevention of Organ Damage in Autoimmune Disorders, Balancing Immune Response, and Chronic Inflammatory Diseases are few of the areas where immunosuppressive agents are indispensable. However, their use requires careful monitoring to balance the benefits of immunosuppression with the risk of infections and other adverse effects[3]. It is crucial for healthcare providers to tailor the treatment regimen according to the specific needs and condition of each patient, taking into account factors such as disease severity, comorbidities, and potential drug interactions. Additionally, regular monitoring of immune function, as well as screening for infections and other complications, is essential to ensure the safety and efficacy of immunosuppressive therapy. Through diligent management and surveillance, the benefits of immunosuppressive agents can be maximized while minimizing the risks associated with their use. Thus, the need of the immunosuppressive agents in medical field cannot avoided.

MSC as Immunomodulator

Mesenchymal Stem Cells (MSCs) have garnered significant attention in scientific research due to their remarkable immunological properties, which have been rigorously tested and confirmed across laboratory experiments, animal studies, and human trials[4]. These cells play pivotal roles in modulating the immune response, offering promising avenues for therapeutic intervention in conditions ranging from autoimmune and inflammatory diseases to cancer[5]. The immunomodulatory properties of MSCs were first recognized in the late 1990s and early 2000s. Key research during this period demonstrated that MSCs could modulate immune

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responses, which opened up new therapeutic possibilities for their use in treating various inflammatory and autoimmune diseases. A pivotal study by Krampera et al. in 2003 highlighted the ability of MSCs to inhibit the proliferation of T-cells, which was a significant finding in understanding their effects[6]. Recent advancements in the field have unveiled a broader spectrum of interactions, demonstrating that MSCs exert profound effects on a myriad of immune cell types, including B-lymphocytes, dendritic cells, and natural killer cells. This expanded understanding underscores the intricate network through which MSCs exert their immunomodulatory influence. Furthermore, MSCs have emerged as key players in the maintenance of peripheral tolerance, a critical mechanism in preventing autoimmune responses and facilitating the acceptance of transplanted organs. Their ability to induce immune tolerance extends beyond individual cells to encompass complex interactions within the immune microenvironment. In addition to their roles in immune regulation, MSCs have demonstrated remarkable potential in tumor immunology. Studies have highlighted their capacity to suppress tumor defenses and promote an immunosuppressive tumor microenvironment, thereby facilitating tumor growth and metastasis[7], [8]. Conversely, harnessing MSCs' immunomodulatory capabilities holds promise for developing innovative cancer therapies aimed at enhancing anti-tumor immune responses. The evolving understanding of MSCs' immunosuppressive potential underscores their significance in immunology research and their therapeutic implications across a broad spectrum of immune-related disorders. Further exploration of the intricate mechanisms underlying MSC-mediated immunomodulation is poised to unlock novel therapeutic strategies with profound clinical impact.

MSC as Immunosuppressant

MSCs possess immunosuppressive properties that make them an attractive candidate for various therapeutic applications, particularly in the field of regenerative medicine and immune-related disorders. They can interact with various immune cells, including T cells, B cells, natural killer cells, dendritic cells, and macrophages. They can inhibit the proliferation and activation of these immune cells, thereby suppressing immune responses. MSCs also secrete a variety of anti-inflammatory molecules, such as interleukin-10 (IL-10), transforming growth factor-beta (TGF-β), indoleamine 2,3-dioxygenase (IDO), prostaglandin E2 (PGE2), and many others. Many of these molecules help to dampen inflammation and promote tissue repair. MSCs can induce the generation and activation of regulatory T cells (Tregs), which are a subset of T cells known for their immunosuppressive functions[9]. Tregs help maintain immune tolerance and prevent excessive immune responses. MSCs can inhibit the maturation and function of dendritic cells, which are antigen-presenting cells involved in initiating and regulating immune responses. By modulating dendritic cell activity, MSCs contribute to immune suppression[10]. MSCs can induce the polarization of macrophages toward an M2 phenotype, which is associated with anti-inflammatory and tissue repair functions[11]. This modulation of macrophage polarization helps to resolve inflammation and promote tissue healing. MSCs secrete a diverse array of soluble factors and extracellular vesicles that exert their effects on neighboring cells and tissues. These paracrine signaling mechanisms contribute to the immunosuppressive properties of MSCs. In addition to their immunosuppressive effects, MSCs have the ability to differentiate into various cell types, and contribute to tissue regeneration and repair. By promoting tissue healing, MSCs indirectly modulate immune responses and reduce inflammation. The immunosuppressive properties of MSCs make them promising

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Table 2: A list of few immunosuppressors originated from MSCs.

Source	Immunosuppresor	Mode of Action	
		Inhibition	Promotion or activation
MSCs	TGF-β	Inhibiting the proliferation and function of various immune cells, including T cells, B cells, and dendritic cells.	Promotes the differentiation of regulatory T cells
MSCs	HGF	Anti-inflammatory and tissue repair properties.	Activation of immune cells and promote the regeneration of damaged tissues
MSCs	PGE2	Inhibiting the activation and function of immune cells such as T cells and dendritic cells.	Promotes the generation of regulatory T cells, which further suppress immune responses.
MSCs	IL-10	Anti-inflammatory cytokine that suppresses the activation and function of immune cells.	Promotes the differentiation of regulatory T cells and regulatory B cells, which contribute to immune tolerance.
MSCs	HLA-G	Inhibition of natural killer (NK) cell activity, suppression of T cell responses,	Induction of regulatory T cells, and modulation of dendritic cell function.
MSCs	IDO	IDO, an enzyme that catabolizes tryptophan, an essential amino acid required for T cell proliferation.	By depleting tryptophan levels, IDO inhibits T cell activation and proliferation, contributing to immunosuppression
MSCs	TSG-6	Inhibits the activity of pro-inflammatory cytokines such as TNF-α and IL-1β, reducing the inflammatory response.	Promotes tissue regeneration by enhancing the proliferation and migration of fibroblasts and endothelial cells, crucial for wound healing. Additionally, it activates macrophage polarization towards an anti-inflammatory (M2) phenotype, aiding in the resolution of inflammation and tissue repair.

candidates for therapeutic interventions aimed at modulating immune responses, reducing inflammation, and promoting tissue repair in various diseases and conditions, including autoimmune disorders, graft-versus-host disease (GVHD), and inflammatory disorders.

Immune Cells and MSC Immunosuppressive Impact

MSCs can impede T lymphocyte activation and proliferation in vitro[12], [13], [14]. They inhibit T cell proliferation induced by alloantigens, mitogens, and activation via CD3 and CD28 antibodies. Additionally, MSCs reduce the cytotoxic effects of antigen-primed cytotoxic T cells (CTLs), likely by limiting CTL proliferation rather than directly inhibiting their cytolytic activity. The suppression of T cell proliferation by MSCs is consistent, showing similar effects regardless of whether the responder cells are autologous or allogeneic. Although physical segregation of MSCs and peripheral blood mononuclear cells fails to completely nullify the suppressive effect, It is widely believed that MSCs primarily exert their immunosuppressive effects on activated T lymphocytes by secreting anti-proliferative and immunosuppressive soluble factors[15]. The IDO enzyme, TGF-β, hepatocyte

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growth factor (HGF), PGE2, IL-10, and human leukocyte antigen G isoform (HLA-G5) are some of the factors widely studied for MSC immunosuppressive effects (Table 2).

The enzyme IDO, which catalyzes the metabolism of tryptophan into kynurenine breakdown products upon stimulation with interferon-gamma (IFN-γ), has emerged as a potential contributor to MSC-mediated T-cell proliferation suppression. However, IDO's precise role in MSC-induced suppression remains elusive, with conflicting findings regarding its involvement in T cell apoptosis[16]. Furthermore, nitric oxide (NO) production by MSCs has been implicated as another potential mechanism underlying the inhibition of T-cell proliferation. However, published data suggest that some of MSCs' immunosuppressive effects on alloantigen-induced T-cell activation may occur through cell-to-cell contact mechanisms[17].

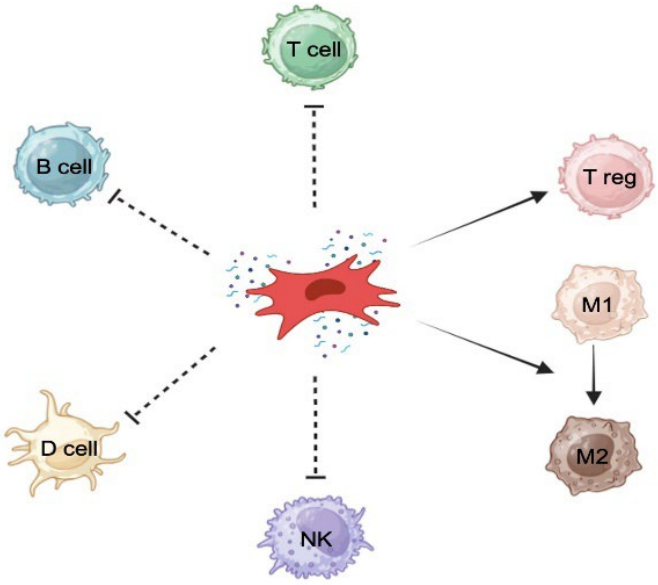


Figure 1 MSC impact on immune cells.

MSCs have been proposed to induce a state of T-cell anergy, attributed to the absence of certain surface costimulatory molecules like CD80 and CD86 involved in T-cell activation[18]. T cell anergy is a tolerance mechanism in which the lymphocyte is intrinsically functionally inactivated following an antigen encounter, but remains alive for an extended period of time in a hyporesponsive state. Alternatively, MSCs have been found to induce anergy by arresting T-cell division even after their removal, maintaining inhibited T-cell proliferation despite restored IFN-γ production, suggesting a persistent state of immunosuppression. Discrepancies in these findings may arise from variations in experimental conditions or MSC origin.

Furthermore, MSCs play a crucial role in modulating immune responses, primarily through the facilitation of regulatory T cell (Treg) generation. Research indicates that MSCs promote the development of CD8+ regulatory T cells, which effectively restrain the proliferation of allogeneic lymphocytes. Experiments have shown that MSCs increase the subset of CD4+CD25+ regulatory cells in PBMC cultures stimulated with immune triggers. However, the exact role of these cells in suppressing T-cell proliferation is not fully understood.

Interestingly, MSCs continue to inhibit T-cell proliferation even after CD4+CD25+ regulatory T cells are depleted, indicating the presence of additional mechanisms yet to be clarified. A recent discovery shows that MSCs can not only stop T-cells from growing but also slow down the growth of various types of cancer cells. This finding changes the traditional view of MSCs as only immune system regulators, suggesting they have a wider and more significant impact[7].

MSCs have exhibited the capacity to impede the proliferation of B cells across various activating conditions in different in vivo models. For instance, in experiments employing anti-CD40L and IL-4 to stimulate B cells, MSCs demonstrated inhibitory effects[19]. These findings are similar to observations in human studies, where MSCs effectively stopped the proliferation of B cells activated by anti-Ig

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antibodies, soluble CD40 ligand, and cytokines. Experiments showed that soluble factors released by MSCs can stop B cells from multiplying. However, the liquid from MSC cultures alone had no effect, indicating that MSCs need signals from B cells to release these inhibitory factors[20].

MSCs profoundly affect dendritic cell biology by disrupting their differentiation, maturation, and function. In the presence of MSCs, monocytes and CD34+ progenitors struggle to become CD1a+ dendritic cells (DCs). These DCs also show reduced maturation signals, like lower CD83 expression and inadequate upregulation of key molecules such as HLA-DR and costimulatory molecules[21]. Immature DCs generated with MSCs struggle to activate T cells, producing fewer proinflammatory cytokines like TNF-α, IFN-γ, and IL-12, while increasing anti-inflammatory IL-10 production. PGE2 and IL-10 released by MSCs play significant roles in inhibiting DC differentiation and function. Blocking PGE2 synthesis helps restore TNF-α and IFN-γ secretion by DCs, emphasizing PGE2's regulatory role.

Natural killer (NK) cells are innate immune cells that primarily target cells lacking HLA class I molecules, using a balance of activating and inhibitory receptors to regulate their cytolytic activity. MSCs suppress IL-2 or IL-15-driven NK cell proliferation and IFN-γ production. Additionally, Sotiropoulou et al. found that MSCs selectively impairs NK cell ability to kill HLA class I-positive tumor cells, while their cytotoxicity against HLA class I-negative cells remains unchanged. This highlights MSCs' specific inhibition of NK cell activity against targets with higher HLA class I expression, which are generally less susceptible to NK cell-mediated destruction [17]. Previously considered immunoprivileged, MSCs can be targeted and lysed by activated NK cells due to different ligands recognized by activating NK receptors[22].

These findings provide valuable insights into the intricate mechanisms underlying MSC-mediated immunosuppression, with significant implications for the development of therapeutic strategies targeting immune-related disorders.

Clinical Applications

MSCs' immunosuppressive properties hold significant clinical promise across diverse medical domains, particularly in hematopoietic stem cell transplantation (HSCT) and regenerative medicine with the aim of stimulating tissue repair and modulating immune responses in a variety of immune-mediated and inflammatory diseases (Table 3).

In the realm of stem cell transplants, MSCs emerge as vital players. They wield potent immunosuppressive capabilities, crucial for bolstering HSC engraftment post-transplantation, dampening graft rejection, and alleviating the ravages of graft-versus-host disease (GvHD). Clinical trials stand testament to the safety and efficacy of MSC co-infusion in transplant recipients, heralding accelerated hematological recovery and a diminished incidence of acute GvHD. Moreover, MSCs exhibit remarkable efficacy in combating steroid-resistant acute GvHD, heralding significant improvements in patient survival rates. Experimental evidence, both in animal models and clinical trials, underscores the profound immunosuppressive potential of MSCs in fortifying hematopoietic stem cell engraftment and thwarting graft rejection and GvHD[23], [24]. Grounded in in vivo experimentation and bolstered by the intrinsic immunomodulatory role of MSCs in hematopoiesis, these findings provide a robust rationale for exploring their capacity to facilitate hematological recovery after stem cell transplantation in humans. Pioneering clinical endeavors, such as the infusion of MSCs in breast cancer patients during autologous transplantation, have not only unveiled the immunological safety of MSC administration but have also heralded rapid hematopoietic recovery without any immunosuppression-related toxicity[25]. Subsequent multicenter trials, conducted in allogeneic stem cell transplant

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settings, further validate these findings, alongside a reassuring absence of adverse underscoring prompt hematopoietic recovery immunological events.

Table 3: Clinical applications of MSCs' immunosuppressive properties.

Disease	Pathology	Mechanism of Action of MSCs
Graft-versus-host disease (GVHD)	Donor T cells recognize recipient tissues as foreign Activation and expansion of donor T cells Migration to target organs Tissue damage through cytotoxicity Persistent inflammation and tissue fibrosis	Immunomodulation: Suppress T cell activation and expansion Tissue Repair: Promote tissue regeneration Anti-inflammatory Effects: Dampen inflammation Induction of Immune Tolerance: Promote regulatory T cell expansion
Rheumatoid arthritis (RA)	Autoimmune inflammation in joints Destruction of cartilage and bone Synovial inflammation and hyperplasia	Immunomodulation: Suppress inflammation and immune cell activation Anti-inflammatory Effects: Reduce cytokine production Tissue Repair: Stimulate tissue regeneration Inhibition of Osteoclastogenesis: Protect bone and cartilage
Crohn's disease	Chronic inflammation of gastrointestinal tract Mucosal ulcerations and fibrosis Abdominal pain, diarrhea, and weight loss	Immunomodulation: Suppress inflammation and immune cell activation Tissue Repair: Promote mucosal healing and regeneration Anti-inflammatory Effects: Reduce cytokine production Restoration of Gut Barrier Function: Improve intestinal integrity
Multiple sclerosis (MS)	Autoimmune attack on myelin sheath in the central nervous system Neuroinflammation and demyelination Impaired nerve signaling Motor and cognitive dysfunction	Immunomodulation: Suppress inflammation and immune cell activation Neuroprotection: Protect neurons and promote remyelination - Anti-inflammatory Effects: Reduce cytokine production Modulation of Microglial Activation: Attenuate neuroinflammation
Systemic lupus erythematosus (SLE)	Autoimmune attack on multiple organs and tissues Production of autoantibodies against self-antigens Immune complex deposition and tissue damage Systemic inflammation and organ dysfunction	Immunomodulation: Suppress autoantibody production and immune cell activation Anti-inflammatory Effects: Reduce cytokine production and inflammation Immune Tolerance Induction: Promote regulatory T cell expansion Tissue Repair: Facilitate tissue regeneration and repair
Type 1 diabetes	Autoimmune destruction of pancreatic beta cells Insulin deficiency and hyperglycemia Immune cell infiltration in pancreatic islets	Immunomodulation: Suppress autoimmune response and immune cell activation Beta Cell Protection: Preserve pancreatic beta cell function and survival

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		Anti-inflammatory Effects: Reduce inflammation and cytokine production Induction of Immune Tolerance: Promote regulatory T cell expansion
Sepsis	Systemic inflammatory response to infection Dysregulated immune activation Endothelial dysfunction and organ damage Circulatory collapse and multi-organ failure	Immunomodulation: Modulate immune response and suppress cytokine storm Anti-inflammatory Effects: Reduce systemic inflammation and cytokine release Endothelial Protection: Improve endothelial function and vascular integrity Organ Protection: Attenuate organ damage and dysfunction
Inflammatory bowel disease (IBD)	Chronic inflammation of gastrointestinal tract Mucosal ulcerations, diarrhea, and abdominal pain Immune cell infiltration and tissue damage -Intestinal barrier dysfunction	Immunomodulation: Suppress inflammation and immune cell activation Tissue Repair: Promote mucosal healing and regeneration Anti-inflammatory Effects: Reduce cytokine production and inflammation Restoration of Gut Barrier Function: Improve intestinal integrity
Liver cirrhosis	Chronic liver injury and fibrosis Hepatocyte apoptosis and necrosis Hepatic stellate cell activation and collagen deposition Portal hypertension and liver dysfunction	Immunomodulation: Suppress inflammation and immune cell activation Anti-fibrotic Effects: Inhibit hepatic stellate cell activation and collagen synthesis Tissue Repair: Stimulate hepatocyte regeneration and inhibit apoptosis Angiogenesis Promotion: Enhance vascularization and improve liver blood flow
Acute respiratory distress syndrome (ARDS)	Acute lung injury and severe hypoxemia Alveolar damage and inflammation Pulmonary edema and impaired gas exchange Respiratory failure and multi-organ dysfunction	Immunomodulation: Modulate immune response and reduce inflammation Anti-inflammatory Effects: Suppress cytokine storm and immune cell activation Endothelial Protection: Preserve pulmonary vascular integrity and reduce permeability Alveolar Epithelial Repair: Promote alveolar epithelial cell regeneration and repair

Notably, co-transplantation of HSC and MSCs emerges as a promising strategy for modulating host alloreactivity and augmenting the engraftment of donor hematopoiesis, thereby mitigating the risk of early graft failure, particularly in scenarios marked by HLA disparity. The most striking clinical manifestation of MSCs' immunosuppressive prowess unfolds in the crucible of acute GvHD management post-allogeneic stem cell transplantation. A remarkable anecdote recounts the rescue of a pediatric patient grappling with severe GvHD after their transplant through the infusion of maternal BM-derived MSCs[26]. Subsequent clinical investigations, encompassing a diverse cohort of patients, validate the efficacy of MSC therapy in steroid-resistant acute GvHD, heralding a paradigm shift in immunosuppressive treatment approaches with notable improvements in patient survival rates.

The promising results from exploring MSCs for autoimmune diseases have led to

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scrutiny of their clinical potential. In a study involving 76 severe Rheumatoid Arthritis (RA) patients resistant to standard treatments, Autologous HSCT (AHSCT) showed encouraging responses, though complete eradication of the disease wasn't achieved[27]. Another trial with 33 severe RA patients didn't find significant benefits with antigen selection but confirmed the immunomodulatory effects of HSCs in the joint environment[28]. For severe Juvenile Idiopathic Arthritis (JIA), a successful AHSCT protocol has been proposed involving various steps to safeguard against infections while maximizing immune recovery[29]. In the case of severe Systemic Lupus Erythematosus (SLE), AHSCT showed positive outcomes for most patients, albeit with some experiencing symptom recurrence and elevated mortality rates, prompting further investigation[30].

In Systemic Sclerosis (SS), AHSCT demonstrated improvements in skin and pulmonary conditions, but studies present conflicting results regarding long-term remission rates. Nonetheless, AHSCT holds promise in extending the lifespan of severe SS patients. The AHSCT has proven safe and effective in inducing and maintaining remission in previously treatment-resistant patients with Crohn's disease. When combined with Cyclophosphamide (CY), this approach has led to clinical remission, with improvements in diarrhea, abdominal pain, and disease activity. Recent phase-I trials have successfully utilized autologous, adipose tissue-derived MSCs for treating fistulizing Crohn's disease, paving the way for phase II and III trials using MSCs derived from different sources[31]. In immune thrombocytopenia purpura (ITP), a combination therapy of CY and AHSCT has demonstrated efficacy in achieving long-term responses, suggesting that Stem Cells (SCs) may expedite hematological recovery compared to conventional immunotherapy. However, responses to AHSCT in ITP patients have varied, ranging from transient responses to continuous remission or transplantation-related mortality. AHSCT has also shown promise in improving B-cell function and inducing persistent insulin independence in type 1 diabetes mellitus (DM) patients[32]. This therapeutic approach involves the destruction of the patient's immune system and autoimmune processes, potentially allowing pancreatic cells to resume insulin secretion once the auto-aggressive mechanism is halted. Furthermore, allogeneic human adipose tissue-derived MSCs transfused with cultured bone marrow cells have demonstrated efficacy in reducing insulin requirements in insulinopenic DM patients without adverse effects. In the realm of neurodegenerative diseases, MSCs have been explored for their potential in neural differentiation. Intrathecal injection of selected HSCs or MSCs has shown safety and partial improvement in neurological function in patients with severe Amyotrophic lateral sclerosis (ALS) and other neurodegenerative diseases. Additionally, ex vivo expanded AHSCT spinal injection has demonstrated improvements in lower limb function in ALS patients. Thus, in tissue repair and regenerative medicine, MSC-based therapies have shown promise in conditions such as osteogenesis imperfecta (OI), osteoarthritis (OA), and cardiac regeneration. Additionally, MSCs have been utilized in vascular regeneration, correction of urological disorders, promotion of vaginal tissue repair, and improvement of liver parameters in cirrhotic patients. MSC-based therapies offer diverse therapeutic applications across various medical conditions, highlighting their potential as a valuable tool, such as immunosuppressor, in regenerative medicine and tissue repair.

Conclusion

MSCs have demonstrated significant potential as immunosuppressive agents across various medical applications. Their unique ability to modulate immune responses, reduce inflammation, and promote tissue repair has positioned them as valuable tools in the treatment of autoimmune diseases, graft-versus-

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host disease (GVHD), and organ transplantation. Clinical trials and research studies have underscored their efficacy, showcasing their capacity to suppress the proliferation and activity of immune cells, secrete anti-inflammatory cytokines, and enhance tissue regeneration. These findings highlight the promising role of MSCs in improving patient outcomes in conditions where immune modulation is crucial.

Future Prospects and Way Forward

The future of MSCs as immunosuppressors is bright, but several critical areas need attention to fully harness their potential. First, there is a need for standardization and quality control in MSC culturing. Establishing standardized protocols for the isolation, expansion, and characterization of MSCs is essential to ensure consistency and reproducibility in clinical applications. Implementing rigorous quality control measures to monitor the purity, viability, and potency of MSC preparations will further enhance their safety and effectiveness.

A deeper mechanistic understanding of MSCs' immunosuppressive effects is also crucial. Continued research to elucidate the precise mechanisms by which MSCs modulate immune responses will help optimize their use and predict patient responses. Additionally, developing biomarkers to predict and monitor the therapeutic efficacy of MSCs in individual patients will enable more personalized treatment approaches, improving the overall success rates of MSC-based therapies.

Expanding clinical trials and applications is another vital step forward. More clinical trials are needed to explore the use of MSCs in a broader range of diseases and conditions, including chronic inflammatory diseases. This expansion will not only validate the efficacy of MSCs in new therapeutic areas but also refine existing treatments, making MSC-based immunosuppressive therapies a mainstay in modern medicine. By addressing these challenges and focusing on these future directions, the application of MSCs as immunosuppressors can be significantly advanced, offering new hope and improved outcomes for patients with various immune-related conditions.

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