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Immunomodulatory Effect of Multipotent Stromal Cells

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ABSTRACT

Multipotent stromal (stem) cells are currently the subject of extensive research. Initially, special attention was given to their reparative properties; however, in recent years, the focus switched toward their immunomodulatory effects. Multipotent cells inhibit T cell proliferation (directly and via exosomes), suppress proinflammatory cytokine production, and activate anti-inflammatory cytokine synthesis. Owing to these effects, cell technologies are currently used in the treatment of Huntington disease, multiple sclerosis, autoimmune encephalomyelitis, scleroderma, systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis, and other disorders. Furthermore, multipotent stromal cells have demonstrated efficacy in acute respiratory distress syndrome models, supporting their potential use in the treatment of COVID-19 complications. They interact with target cells via both paracrine signaling and direct cell–cell interactions. However, multipotent cell-driven immunoregulation and immunosuppression mechanisms are still poorly understood. The use of multipotent cells is highly dependent on the cell source and their functions *in vivo*; moreover, functional capabilities of stem cells are known to decline with age. It is also essential to consider potential complications of immunomodulatory effects of multipotent stromal cells, including long-term, severe immunosuppression, which may result in prolonged inflammation in infections and facilitate the progression of malignant neoplasms. For the effective use of multipotent cells, changes in gene expression induced by cell culture and various disorders must be taken into account. Further research is warranted into the mechanisms behind the immunomodulatory effect of multipotent stromal cells, as well as indications and contraindications for cell therapy in humans and animals. Moreover, it will be beneficial to investigate ways to control the functions of stem cells in various microenvironments.

Keywords: multipotent stromal cells; immunomodulation; immunocompetent cells; acute inflammation; chronic inflammation; cell therapy.

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Иммуномодуляторное действие мультипотентных стромальных клеток

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АННОТАЦИЯ

Мультипотентные стромальные (стволовые) клетки являются объектом многочисленных исследований. Первоначально основное внимание уделялось их репаративным свойствам, однако в последние годы интерес сместился к иммуномодулирующим возможностям. Мультипотентные клетки напрямую и посредством экзосом супрессируют пролиферацию Т-лимфоцитов, подавляют продукцию провоспалительных цитокинов и активируют синтез противовоспалительных. Благодаря этим эффектам клеточные технологии нашли применение при лечении болезни Гентингтона, рассеянного склероза, аутоиммунного энцефаломиелита, склеродермии, системной красной волчанки, ревматоидного артрита, миастении гравис и других патологий. Кроме того, мультипотентные стромальные клетки продемонстрировали эффективность на моделях острого респираторного дистресс-синдрома, что указывает на перспективность их использования в коррекции осложнений COVID-19. Взаимодействие с клетками-мишенями осуществляется как через паракринные сигналы, так и посредством прямого межклеточного контакта. Однако механизмы иммунорегуляции и иммуносупрессии мультипотентными клетками до конца не изучены. Их применение во многом зависит от источника клеток и их функций *in vivo*, при этом известно, что с возрастом функциональные возможности стволовых клеток снижаются. Следует учитывать и возможные осложнения иммуномодулирующего действия мультипотентных стромальных клеток, включая длительную выраженную иммуносупрессию, что может приводить к затяжному воспалительному процессу при инфекциях, а также создавать благоприятные условия для прогрессирования злокачественных опухолей. Для эффективного использования мультипотентных клеток следует учитывать изменения экспрессии генов, индуцируемые культивированием и различными патологическими состояниями. Целесообразны дальнейшие исследования как механизмов иммуномодулирующего эффекта мультипотентных клеток, так и особенностей показаний и противопоказаний к применению клеточной терапии у пациентов и животных. Целесообразен поиск способов управления функциями стволовых клеток в различных микроокружениях.

Ключевые слова: мультипотентные стромальные клетки; иммуномодуляция; иммунокомпетентные клетки; острое воспаление; хроническое воспаление; клеточная терапия.

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INTRODUCTION

Multipotent stromal (stem) cells (MSCs) are nonhematopoietic progenitor cells that were first detected in the bone marrow and characterized in the mid-20th century [1]. MSCs from bone marrow create a specific microenvironment for hematopoietic and immunocompetent cells. They can differentiate into cells of various (at least mesodermal) tissues, including bone, cartilage, adipose, and muscular tissues [2, 3].

To date, MSCs have been isolated from various tissues. These cells exhibit therapeutic plasticity and low immunogenicity due to their immunomodulatory properties and repair-promoting ability, which are crucial for effective cell-based immunotherapy [1, 3–5]. MSCs functionally regulate crucial immunocompetent cells that recognize and eliminate allo- and autoantigens [4]. They can directly interact with cells involved in innate and adaptive immunity or by secreting specific cytokines [3, 5–9]. Following the discovery of the immunomodulatory properties of MSCs, cell-based therapy began to be used for treating autoimmune diseases, in addition to regenerative medicine [1, 10–13].

This work aimed to summarize the published data on the general and specific immunomodulatory effects of cell therapy.

PubMed was searched for the articles published between 2017 and 2024 using the keyword combination *immunomodulatory + stem + cell*. More than 400 papers were identified and collected. After title, abstract, and full-text screening, 71 publications on the mechanisms and primary effects of inflammation-modulating cell therapy were included.

EFFECT OF MULTIPOTENT STROMAL CELLS ON IMMUNOCOMPETENT CELLS

All MSCs suppressed the proliferation of hetero- and autologous T cells in a dose-dependent manner [14]. MSCs inhibit T cell proliferation, activate apoptosis, and suppress the production of T cell-mediated proinflammatory cytokines, such as tumor necrosis factor- α (TNF- α) [7, 13]. Umbilical cord-derived MSCs suppressed mitogen-stimulated rapid lymphocyte proliferation, decreased interferon- γ (IFN- γ) secretion, and increased interleukin-4 (IL-4) production, with a significant elevation in CD8⁺ counts and minor changes in CD4⁺ T cell counts [15, 16]. However, wound fluid-derived MSCs markedly suppressed CD4⁺ T cell proliferation during cocultivation [17]. MSCs likely interact with immunocompetent cells via paracrine signaling, such as the transforming growth factor- β (TGF- β) and hepatocyte growth factor pathways. Furthermore, direct interactions with cells to induce apoptosis are also possible [12].

Tissue transplantation using pluripotent stromal cells that were induced to differentiate into MSCs promoted foreign cell survival and reduced leukocytic infiltration. In a mouse model of graft-versus-host disease, subcapsular *in vitro* and *in vivo* injections of kidneys with MSCs inhibited T cell proliferation.

The Th1 and Th2 phenotypes declined, but Th17 and Treg subsets (IL-10⁺ CD4⁺) enhanced. High synthesis of certain soluble factors, such as TGF- β 1/2/3, IL-10, and monocyte chemoattractant protein-1 (MCP-1), which suppress T cells and caspases, has been reported [18]. Furthermore, TGF- β partially inhibited the *in vivo* immunosuppressive effects of MSCs in a graft rejection model [19].

MSCs partially regulate the mature myeloid cells involved in inflammation, such as macrophages and neutrophils. They inhibit the expression of differentiation markers on myeloid progenitor cells during inflammation. This effect is determined by a direct contact between the MSCs and target cells via an interaction between the MSC-expressed CD200 and myeloid progenitor cell-expressed CD200R1. Reduced CD200 expression in MSCs decreases their immunomodulatory functions. Furthermore, an injury model of sterile inflammation revealed that MSCs suppress leukocytic infiltration in the affected tissues. Thus, MSCs inhibit the differentiation of myeloid progenitor cells into mature cells that delimit and infiltrate inflamed tissues [20].

Jackson and Krasnodembskaya [21] isolated primary human monocytes from donor blood and then induced their differentiation into macrophages. Donor bone marrow-derived MSCs were labeled with a mitochondria-specific fluorescent stain. The cells were then added to the macrophage culture at a ratio of 1:20 and co-cultured for 24 h. The formation of tunneling nanotubes that served as pathways for MSC mitochondrial transfer to macrophages was visualized by confocal microscopy and semi-quantified by flow cytometry. Such transport enhances macrophage phagocytosis and oxidative phosphorylation. When nanotube formation was blocked by cytochalasin B, MSCs did not affect macrophage phagocytosis.

MSCs influence macrophage polarization, necessary for wound healing. MSCs were isolated from the dermis of BALB/c mice and co-cultured with macrophages, inducing their polarization from the M1 to M2 phenotypes, as demonstrated by a reduction and elevation in the levels of pro- and anti-inflammatory markers, respectively. In an acute skin wound model, macrophages co-cultured *in vivo* with these MSCs promoted wound healing, enhanced collagen deposition, and improved vascular regeneration. A remarkably greater expression of arginase-1 further indicated an enriched M2 macrophage environment [22]. Similar macrophage polarization was reported with adipose tissue-derived [23], nasal mucosal ectodermal [24], and bone marrow-derived MSCs on a polycaprolactone scaffold [25] [26]. MSCs influence macrophages; similarly, phagocytes significantly impact MSCs. An effective immune response to tissue damage is determined by the activation and migration of endogenous macrophages, which recruit MSCs [27].

The ability to functionally control MSCs, including their immunomodulatory effect, is of significant current interest.

The released proinflammatory molecules may alter MSC characteristics and enhance their immunosuppressive properties [17, 28]. Cyanidin-3-glucoside influences the paracrine

activity of the MSCs, modulating their secretion and the subsequent effect on immune cells, particularly macrophages and lymphocytes [29]. Prostaglandin F₂α (PGF₂α) can modify the features of lipopolysaccharide-stimulated MSCs. It promotes cell proliferation without affecting their viability and inhibits the production of IL-1β and granulocyte-macrophage colony-stimulating factor (GM-CSF) [30].

MSCs alter immune cell activity via the TNF-α-stimulated expression of *TSG-6*, which in adipose tissue-derived MSCs is regulated by high *in vitro* and *in vivo* levels of proinflammatory cytokines, including TGF-β. However, the co-treatment of MSCs with TGF-β inhibitors insufficiently modulated inflammation [31]. Co-culture of IFN-γ-pretreated MSCs with spleen mononuclear cells significantly reduced the proliferation of the latter. Pretreatment with cytokines can effectively modify the immunomodulatory impact of MSCs [28].

Genetic modifications enable MSCs to express specific proteins, which are essential for controlling therapeutic efficacy. Transfection of MSCs with plasmids that encode anti-CD3/CD20 bispecific antibodies enables the secretion of such proteins, as well as T cell recruitment, TNF-α and IFN-γ production, and isolation of exosomes with miR-15a/miR-16, which can downregulate *BCL-2*, the anti-apoptosis-related cancer gene, during adjuvant therapy [32].

Thus, MSCs inhibit T cell proliferation, increase regulatory T cell counts, while suppressing and activating the secretion of pro- and anti-inflammatory cytokines, respectively. Furthermore, they regulate other immunocompetent cells, such as B cells, neutrophils, monocytes, and macrophages. They interact with target cells via paracrine signaling or directly through cell membranes. Thus, it is possible to control the immunomodulatory effects of MSCs.

INDIVIDUAL APPLICATIONS OF MULTIPOTENT STROMAL CELL IMMUNOMODULATORY EFFECTS

Given their powerful immunomodulatory and regenerative effects, MSCs provide a promising cell therapy approach for various autoimmune and inflammatory diseases [2, 4] by suppressing the inflammatory immune responses.

In a study assessed the ability of MSCs to migrate to injured tissues; their systemic infusion dramatically suppressed contact hypersensitivity, as evidenced by the decreased inflammatory cell infiltration and proinflammatory cytokine production. Numerous MSCs migrated to injured tissues (ears) and co-localized with T cells, inhibiting their proliferation, promoting apoptosis, and suppressing the production of T cell-derived proinflammatory cytokines [13]. Intravenous injections of umbilical cord-derived MSCs during bone marrow transplantation in mice inhibited acute graft-versus-host disease and increased survival rates [2, 16].

Allergic asthma is a chronic inflammatory disease characterized by airway hyperresponsiveness and remodeling.

MSCs can reduce inflammation and restore the immune balance, demonstrating positive outcomes, particularly in cases of steroid-resistant asthma [33].

Huntington disease is an autosomal-dominant, progressive neurodegenerative condition characterized by a selective loss of neurons in the cortex and striatum, leading to progressive motor dysfunction, cognitive decline, and behavioral symptoms. The therapy relies on immunomodulatory and/or anti-inflammatory agents, with MSCs being a promising option [34].

Multiple sclerosis is a chronic, autoimmune, inflammatory, and demyelinating disorder of the central nervous system, ultimately leading to axonal loss and permanent neurological disability. Clinical studies (completed and ongoing) support the use of MSCs to treat multiple sclerosis. Neural MSCs in the brains of adult patients and experimental animals can differentiate into oligodendrocytes and are involved in remyelination. Furthermore, MSCs can be transdifferentiated *in vitro* into oligodendrocytes. In any case, MSCs may exert beneficial effects during demyelination not only through oligodendrocyte replacement but also by immunomodulation and providing trophic support [4, 35].

Togha et al. [36] reported that the intraperitoneal injection of MSCs passed thrice can lead to immunomodulation and relieve the symptoms of experimental autoimmune encephalomyelitis induced in mice (a multiple sclerosis model). The immune effects of cell therapy were associated with inhibited lymphocyte proliferation, cytolytic activity, and IFN-γ synthesis, but enhanced IL-4 and IL-10 production by CD8⁺ cells.

Systemic sclerosis (scleroderma) is a peculiar multifaceted disease in which autoimmune phenomena, vascular abnormalities, and multi-visceral fibrosis coexist. Considering the pleiotropic effects of MSCs, displaying immunomodulatory, angiogenic, and antifibrotic capabilities, cell therapy could counteract the three main pathogenic axes of scleroderma [1].

Chua et al. [37] intraperitoneally injected four doses of (20–25) × 10⁶ cells/kg of MSCs in 16-week-old female lupus-prone MRL/lpr (Faslpr) mice. Such therapy improved survival rates and kidney function by reducing lupus nephritis activity, chronicity, and lymphocyte infiltration for over 10 weeks. Furthermore, it reduced the urinary albumin-creatinine ratio, deposition of the renal complement C3, anti-dsDNA, and the isotype antibodies: IgA, IgG1, IgG2a, IgG2b, and IgM. MSCs dampened inflammation by suppressing splenic neutrophils and monocytes/macrophages, reducing plasma levels of IL-6, IL-12, and CXCL1 but stabilizing IFN-γ and TNF-α.

Feng et al. [38] systemically infused nine patients with biopsy-confirmed lupus nephritis resistant to standard therapy with allogeneic MSCs at 2 × 10⁶ cells/kg. No side effects were reported even after 12 months of treatment. Urinary protein levels decreased dramatically within a month, followed by a gradual increase; however, they remained evidently below the baseline levels for ≤3 months. During the first three months after treatment, complete (proteinuria <0.5 g/day) and partial (proteinuria >0.5 g/day; with a decrease of >50%)

renal responses were reported in 33.3% and 44.4% of patients, respectively. Thus, a single MSC dose may be insufficient for maintaining long-term remission in refractory lupus nephritis, requiring additional treatment courses.

Immunomodulatory properties of MSCs make them a promising therapeutic option for autoimmune and inflammatory diseases, such as rheumatoid arthritis. MSCs produce a variety of soluble factors that can improve the inflammatory microenvironment in patients with rheumatoid arthritis by inhibiting T cell proliferation or inducing T cell differentiation into regulatory T cells, inhibiting B cell proliferation, differentiation, and immunoglobulin production, prompting the polarization of macrophages toward an anti-inflammatory phenotype, inhibiting neutrophil recruitment, and preventing dendritic cell maturation [39]. Intranasal administration of human adipose tissue-derived MSCs in collagen-induced experimental arthritis mouse models reduced the progression of arthritis and bone destruction [40].

Myasthenia gravis (MG) with anti-acetylcholine receptor antibodies is an autoimmune disease characterized by severe defects in immune regulation and thymic inflammation. Sudres et al. [41] reported that naive MSCs significantly improved the course of experimental MG in mice, reducing serum anti-acetylcholine receptor antibody levels and restoring muscle receptors. Additionally, the underlying mechanisms involved in inhibiting immunocompetent cell proliferation and B cell-related and costimulatory molecules, but activating the complement regulator DAF/CD55.

MSCs are effective in the treatment of type 1 diabetes mellitus, a prevalent autoimmune disease characterized by the absence of insulin due to irreversible damage caused to islet β -cells. Experimental MSC transplantation with or without pancreatic islet cells is effective because of their multipotency and the ability to produce cytokines, angiogenic factors, and immunomodulatory molecules. MSCs can prevent the autoimmune destruction of β -cells, preserve the surviving islet cells, promote endogenous regeneration, restore specific immune unresponsiveness of β -cells, and reverse hyperglycemia [4, 42, 43].

Allogeneic islet transplantation can be an ideal alternative therapy for type 1 diabetes mellitus. The immunomodulatory and protective effects of MSCs may improve the outcomes of highly immunogenic transplantation. Mohammadi Ayenehdeh et al. [44] intraperitoneally transplanted allograft islets and syngenic adipose tissue-derived MSCs embedded within a hydrogel composite in streptozotocin-induced diabetic C57BL/6 mice. During the 32-day post-transplant period, blood glucose was monitored, decreasing from >400 mg/dL to <150 mg/dL. Graft histopathology after 32 days demonstrated that MSCs significantly reduced leukocytic infiltration. Analyses of the mononuclear cells isolated from the mesenteric lymph nodes (MLNs) and spleen showed that MSCs co-transplanted with allograft islets decreased proinflammatory and increased regulatory cytokine levels (MLNs and spleen) and regulatory T cell counts (only MLNs).

Corradi-Perini et al. [45] found MSCs to have the potential to mitigate early graft losses by regulating the associated inflammation. They investigated the effects of co-transplantation of xenogeneic bone marrow-derived MSCs and pancreatic islets obtained from Wistar rats in preventing rejection in diabetic mice. Compared to the islets only, islets + MSCs lowered the expression of inflammatory markers (TNF- α , MCP-1, and IL-1 β) and enhanced that of immune tolerance markers (IL-4, IL-10, and FOXP3).

Bone marrow-derived MSCs at 1×10^6 labeled with the chloromethyl derivatives of fluorescein diacetate were administered via the tail vein 24 h before the hydrodynamic injection of hepatitis B virus DNA. MSCs accumulated in the affected liver, decreasing immune-mediated viral infection-associated liver injury, as evidenced by reduced alanine aminotransferase levels, proinflammatory cytokine production, and inflammatory cells infiltration. MSCs inhibited the expression of NKG2D receptors on natural killer cells, activating them in the livers of mice infected with the hepatitis B virus. Furthermore, MSCs suppressed the *in vitro* cytotoxicity of these cells. They also mitigated immune-mediated liver injury associated with acute hepatitis B virus infection by inhibiting the activity of the natural killer cells [46].

Immune imbalance is crucial for tuberculosis pathogenesis and may be modulated by MSCs. Yang et al. [47] co-cultured human umbilical cord-derived MSCs with tuberculosis-infected THP-1 macrophages, a well-known model for assessing monocyte and macrophage immune responses. They found that MSCs can enhance the immune response in macrophages against *Mycobacterium tuberculosis* by activating immune receptors and inflammation-related signaling pathways.

Vitiligo is a chronic autoimmune disorder that involves skin depigmentation. Multiple combinatorial factors are involved in disease development, among which cytotoxic T, CD8⁺, and regulatory T cells are implicated in melanocyte destruction, with adaptive immunity playing a prominent role. MSCs regulate cytokine secretion and T-cell subset homeostasis, which makes them a promising cell-based treatment option for vitiligo [48].

Upon myocardial damage, protein release induces a strong antibody-mediated immune response, which can lead to adverse cardiac remodeling and eventually heart failure. MSC therapy benefits cardiac function despite low engraftment. MSCs robustly inhibit lymphocyte proliferation and antibody production *in vitro*, which is crucial considering the increase in IgG3a secretion by plasma cells in patients with end-stage heart failure [49].

Stromal cells can reduce chronic and autoimmune, as well as acute, inflammation.

Injections of human adipose tissue-derived MSCs at 5×10^5 along with the conditioned media had an anti-inflammatory effect in the paws of mice with acute inflammation induced by carrageenan. Even a single injection could eliminate inflammation-associated symptoms within 24 h, as evidenced by a reduction in paw volume and IL-6 levels [11].

Traumatic brain injury (TBI) is one of the leading causes of death and disability worldwide. A growing body of evidence suggests a link between TBI-induced neuroinflammation and neurodegenerative post-traumatic disorders. Repeated intravenous treatment with MSCs may significantly impede post-TBI neuroinflammation and improve neurological status [50].

MSCs have improved survival, enhanced bacterial clearance, and alleviated inflammation in pre-clinical acute respiratory distress syndrome (ARDS) and sepsis models. These diseases are characterized by uncontrolled inflammation, which is often underpinned by bacterial infection [21, 51]. The therapeutic effects of primed MSCs, modified to augment specific functionalities, were assessed in mice with lipopolysaccharide-induced ARDS. MSCs primed with IFN- γ and IL-1 β suppressed the activity of T cells more prominently than that of naive MSCs, concurrently inhibiting TNF- α while increasing IL-10 production in macrophages. Combined treatment with IFN- γ and IL-1 β markedly upregulated the synthesis of immune and inflammation-regulating factors. Primed MSCs suppressed the infiltration of lung tissues by inflammatory cells, modulated immunity- and inflammation-associated responses, and enhanced elastin fiber formation. In early-phase ARDS, these primed MSCs displayed enhanced homing capabilities, improved lung function, and reduced inflammation [52].

Microvesicles derived from human MSCs decrease the severity of pneumonia, with the levels of the keratinocyte growth factor mRNA partly involved in the therapeutic effect. Furthermore, these exosomes contain a substantial quantity of angiopoietin-1, which plays an essential role in vascular stabilization and inflammation resolution [53].

Exacerbations of chronic obstructive pulmonary disease (COPD) are associated with a significant decline in both the quality of life and survivability. MSCs can be a potential additional therapy for COPD. Patients who received an MSC secretome along with standard care showed lower IL-6, TNF- α , and procalcitonin levels than the control group that received standard care alone [54].

Interstitial lung diseases are a heterogeneous group of pulmonary disorders characterized by variable degrees of inflammation, interstitial thickening, and fibrosis, which distort the pulmonary architecture and impair gas exchange. Antifibrotic drugs such as pirfenidone and nintedanib limit fibrosis progression, but do not reverse lung damage. MSC-based cell therapy prevents fibrosis and promotes physiological regeneration, restoring alveolar structure and functions [55].

Human bone marrow-derived MSCs exhibited not only immunomodulatory, but also neuroprotective and anti-inflammatory effects in a Hartley guinea pig model of 2,4,6-trinitrobenzene-sulfonate (TNBS)-induced colitis. The animals received TNBS or sham treatment intrarectally, with MSCs administered 3 h later. MSCs at 1×10^6 or 3×10^6 decreased immune infiltration and prevented loss and changes in neuronal subpopulations [56].

Takeyama et al. [57] systemically administered adipose tissue-derived MSCs intraperitoneally in mice with dextran sulfate sodium-induced acute colitis. It significantly reduced the clinical and histopathological severity of colitis. MSCs were distributed throughout the lymphatic system in the mesenteric lymph nodes and spleen. Following tissue injections, some MSCs were located in the regional lymph nodes [58, 59]. Post-intravenous infusion, a few MSCs had also migrated to the lymph nodes, increasing the levels of specific, regulatory immunocompetent cells. Such a finding highlighted that the migration of MSCs to the lymph nodes is vital to the execution of their immunomodulatory effects. Luciferase + adipose tissue-derived MSCs were identified to preferentially migrate toward the intestines when infused through the inguinal lymph nodes in mice with colitis. MSCs protected 58% of the mice against induced colitis. The response to MSC therapy remarkably correlated with the enhanced accumulation of MSCs in the popliteal, parathymic, parathyroid, and mesenteric lymph nodes [10].

Given their immunomodulatory properties, MSCs are a promising therapeutic option in immune-mediated acute liver failure. A single intravenous injection of MSCs reduced the severity of CCl₄- and α -galactoceramide-induced acute hepatitis, as well as the hepatotoxicity of natural killer cells, via paracrine signaling. The serum levels of the proinflammatory IL-17 decreased, and those of the immunosuppressive IL-10 increased, with associated changes in the number of natural killer cells secreting these interleukins. The MSCs did not significantly alter the total counts of IL-17-producing neutrophils, as well as the CD4⁺ and CD8⁺ T cells in the affected liver. Furthermore, MSCs demonstrated modulatory properties in an *ex vivo* co-culture system with liver slices in which inflammation was induced with CCl₄ [5].

Notably, Maiborodin et al. [60] could not detect any differentiation in MSCs transfected with GFP and cell membranes stained with Vybrant[®] CM-Dil after injecting them into the affected liver. Thus, they concluded that the use of MSCs is ineffective for the rapid restoration of liver resection, since the injected cells do not differentiate *in vivo* into hepatocytes, epithelial cells of the bile capillaries, endotheliocytes and pericytes of the vascular membranes, fibroblasts of scar tissue or other connective tissue structures, or any other cell types present in the liver. However, MSCs can improve parenchymal neutrophil counts and facilitate the resolution of necroses and hemorrhages.

Arzi et al. [61] used allogeneic adipose tissue-derived MSCs (2×10^7 cells) to treat chronic gingivostomatitis (a fungal infection) in seven domestic cats. The MSCs were administered intravenously; each animal received two injections one month apart. Of the seven cats, four responded to treatment: complete clinical remission or a substantial clinical improvement (each $n = 2$). Clinical remission lasted up to 20 months, and no relapses were reported. Most animals had increased pre-therapy levels of circulating CD8⁺ T cells and a decreased CD4/CD8 ratio; however, clinical resolution was

not associated with any improvement in these parameters. Nonresponders showed a more severe systemic inflammation (neutrophilia, hyperglobulinemia, and increased IFN- γ and TNF- α levels) before MSC therapy.

Intrauterine adhesions are a prevalent condition characterized by poor regeneration of the damaged endometrium. Maiborodin [62, 63] demonstrated that autologous bone marrow-derived MSCs improve the patency of uterine horns with cicatrices. Xin et al. [64] reported comparable findings on endometrial regeneration and fertility restoration using MSC-derived apoptotic bodies. Kononkov et al. [65] assessed the effects of bone marrow-derived MSCs and their products secreted into the conditioned medium on the microcirculatory bed within the broad ligament of the uterus in Wistar rats with chronic genital inflammation. Contrasting changes in microcirculation and lymphatic drainage parameters were observed in the broad ligament after administration via different routes. This observation is crucial while devising cell-based therapy for inflammatory and degenerative processes in the pelvic organs.

Thicker endometria, increased gland numbers, and fewer fibrotic areas were found in female Sprague Dawley rats with a mechanically injured endometrium that received human amniotic MSCs. MSC transplantation significantly reduced the mRNA levels of proinflammatory cytokines (TNF- α and IL-1 β) and increased those of the anti-inflammatory cytokines (FGF-2 and IL-6). It can be concluded that MSC transplantation promotes endometrial regeneration after injury in rat models, possibly owing to their immunomodulatory properties [66].

Numerous researchers have suggested that the immunomodulatory effects of MSCs allow their application in the effective treatment of hyperactive acute inflammation and reducing the severity of chronic immune inflammation and graft-versus-host disease. MSCs effectively suppress the rejection of transplanted cells, organs, and tissues. Furthermore, they can be used to treat autoimmune diseases such as Huntington's disease, scleroderma, multiple sclerosis, autoimmune encephalomyelitis, rheumatoid arthritis, MG, autoimmune type 1 diabetes mellitus, hepatitis, and others.

SPECIFICS OF MULTIPOTENT STROMAL CELL THERAPY

MSC therapy requires constant quality control, with a focus on immunosuppressive mechanisms before use in clinical practice [9].

For an effective MSC therapy, Culture-induced changes in gene expression levels must be considered. Adipose tissue-derived MSCs cultured in a conventional medium showed a gradual decrease in the expression of pluripotency markers (epithelial-mesenchymal transition proteins and genes). Therefore, early-passage MSCs may be a better therapeutic choice for injured tissues [6]. Furthermore, *in vitro* human MSC cultures demonstrated lower therapeutic efficacy against MG than the naive MSCs [56].

The use of MSCs largely depends on their source and *in vivo* functions. MSCs derived from bone marrow and amniotic fluid of healthy donors exhibit different immunomodulatory properties [67]. MSCs displayed decreasing adipogenic capacity in the following order: adipose tissue-derived MSCs > bone marrow-derived MSCs > umbilical cord-derived MSCs. No morphological or immunophenotypical differences were observed [8]. The clinical efficacy of allogeneic MSCs was lower than fresh autologous ones. Furthermore, the mechanisms of action of autologous and allogeneic MSCs may vary [14, 61].

The functional capabilities of MSCs decrease with age, a phenomenon that is insufficiently studied, whereas cell senescence-related mechanisms are well understood. Furthermore, the successful clinical application of MSCs requires a general understanding of their aging process. Senescent MSCs are highly heterogeneous and may not always express the characteristic phenotypic markers; moreover, the genes and molecules regulating MSC senescence are still unknown. However, understanding the molecular mechanisms behind MSC aging and senescence-associated alterations in their microenvironment is essential for detecting senescence-related dysfunctions [68].

Progressive senescence may be associated with increased MSC proliferation, reducing their ability to inhibit T cells [9]. In contrast, bone marrow-derived MSCs isolated from young mice exhibited a greater proliferative and osteodifferentiation potential and a more potent immunomodulatory effect than those isolated from aged mice [69].

Despite numerous publications supporting the therapeutic efficacy of MSCs against various medical conditions and diseases, specific rules must be followed when selecting the MSC source and preparing them for administration. Interspecies variations in the expression of several characteristic MSC genes must be considered. The MSCs derived from bone marrow, amniotic fluid, umbilical cord, and other organs and tissues vary. Autologous MSCs are preferable for cell therapy; if necessary, young healthy individuals with no comorbidities must be used as donors. The MSC culture before administration must be limited to three passages.

NEGATIVE IMMUNOMODULATORY EFFECTS OF MULTIPOTENT STROMAL CELLS

Along with the significant positive immunomodulatory effects of MSCs, evidence of their negative effect [70, 71] or high probability [27] also exists.

Adipose tissue-derived MSCs with immunomodulatory effects are crucial stromal cells within the tumor microenvironment. MSCs significantly inhibit the immunocompetent cells in cancer patients, promoting tumor progression and immune evasion [71].

Abdelhamid et al. [70] found that MSC therapy induces inflammation. Allogeneic MSC-stimulated peripheral blood mononuclear cells significantly reduced the levels of

anti-inflammatory cytokines (IL-10, IL-1Ra, and TGF- β 1) and increased those of the proinflammatory mediators (IL-1 β , IL-6, TNF- α , and SAA). Furthermore, they enhanced the proportion of CD14⁺ cells compared to the lipopolysaccharide-treated non-stimulated mononuclear cells.

In mice with experimental HBV infection, MSCs increased viral gene expression and replication *in vivo* by suppressing the activity and cytotoxicity of natural killer cells *in vivo* and *in vitro*, as well as the receptors involved in their activation in the liver. Therefore, MSCs may prolong virus clearance post-HBV infections [46].

CONCLUSION

MSCs have been extensively studied, with the focus gradually shifting from their reparative properties to immunomodulatory effects. MSCs suppress T cell proliferation, both directly and via exosomes. Furthermore, they suppress the production of proinflammatory cytokines while activating the anti-inflammatory ones. Given the immunomodulatory effect of MSCs, they are effective in treating Huntington disease, multiple sclerosis, autoimmune encephalomyelitis, scleroderma, systemic lupus erythematosus, rheumatoid arthritis, MG, and other disorders. MSCs have demonstrated therapeutic efficacy in acute respiratory distress syndrome models, suggesting that cell therapy can be used in patients with COVID-19. Therefore, MSCs are a promising therapeutic option for autoimmune and inflammatory diseases; they can be used to treat autoimmune disorders or to improve cell, tissue, and organ transplantation outcomes. Furthermore, the immunomodulatory and immunosuppressive mechanisms of MSCs have been studied insufficiently.

Potential complications of the immunomodulatory effects of MSCs, such as long-term, severe immunosuppression, prolonged inflammation during infections, and favorable conditions for tumor progression due to immune evasion, must be accounted for. Further research into the mechanisms underlying the immunomodulatory effects of MSCs, as well as indications and contraindications for the use of cell therapy in humans and animals, is needed. Moreover, the search for ways to control MSC functions under various conditions is relevant.

ADDITIONAL INFORMATION

Author contributions: I.V.M.: conceptualization, formal analysis, project administration, writing—review & editing; G.Yu.Ya.: investigation, writing—original draft; M.E.R.: investigation, writing—original draft; A.Yu.Ts.: investigation, writing—original draft; B.V.Sh.: conceptualization, project administration, writing—review & editing. All authors approved the version of the manuscript to be published and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy

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ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. И.В.М. — определение концепции, анализ данных, пересмотр и редактирование рукописи, администрирование проекта; Г.Ю.Я. — проведение исследования, написание черновика рукописи; М.Е.Р. — проведение исследования, написание черновика рукописи; А.Ю.Ц. — проведение исследования, написание черновика рукописи; Б.В.Ш. — определение концепции, пересмотр и редактирование рукописи, администрирование проекта. Все авторы одобрили рукопись (версию для публикации), а также согласились нести ответственность за все аспекты работы, гарантируя надлежащее рассмотрение и решение вопросов, связанных с точностью и добросовестностью любой её части. **Этическая экспертиза.** Одобрение этического комитета на проведение исследования не получали. Причина — рукопись представляет собой не запланированное исследование, а обзор литературы из открытых источников.

Источники финансирования. Исследование поддержано в рамках государственного задания ИХБФМ СО РАН «Фундаментальные основы сохранения здоровья нации» № FWGN-2025-0019. Финансовой поддержки со стороны компаний-производителей оборудования, реактивов и лекарственных препаратов авторы не получали.

Раскрытие интересов. Авторы заявляют об отсутствии отношений, деятельности и интересов за последние три года, связанных с третьими лицами (коммерческими и некоммерческими), интересы которых могут быть затронуты содержанием статьи.

Оригинальность. При создании настоящей работы авторы не использовали ранее опубликованные сведения (текст, иллюстрации, данные).

Доступ к данным. К настоящей работе применима редакционная политика журнала в отношении совместного использования данных, полученных в исследовании.

Генеративный искусственный интеллект. При создании настоящей статьи технологии генеративного искусственного интеллекта не использовали.

Рассмотрение и рецензирование. Настоящая работа подана в журнал в инициативном порядке, на момент подачи рецензирование не проведено.

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