Original Article

Immunomodulatory Functions of Mesenchymal Stem Cells in Tissue Engineering

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ABSTRACT

Mesenchymal stem cells (MSCs) have been demonstrated to exhibit immunomodulatory properties, thereby modulating the immune response and facilitating tissue regeneration. These properties include the ability to suppress T cell proliferation, modulate macrophage polarization, and promote regulatory T cell differentiation. It has been demonstrated that natural chemoattraction pathways can attract MSCs. These cells are created from around the injured tissues, creating a repair/regenerative microenvironment for this study. The rate of tissue regeneration is contingent upon factors such as the patient's age, the extent of tissue damage, and the specific anatomical region affected. It has been demonstrated that the manipulation of mesenchymal stem cells can exert a substantial influence on the rate of tissue damage, tissue regeneration, and cell death. The immunosuppressive and trophic mechanisms under investigation are distinct from the mechanisms that are being led by tissue engineering to replace special mesenchymal tissues. Indeed, the capacity of tissue engineering processes to facilitate trophic interactions is evident, thereby promoting remarkable tissue regeneration and ensuring the seamless incorporation of newly generated tissue into the body. The field of MSCs has been a subject of study for over two decades, and recent advancements have begun to unlock their full potential for clinical applications. It is evident that the utilization of MSCs in tissue engineering necessitates distinct rationale when compared to their application in nutritional and immunomodulatory functions. These latter efforts now appear to apply to the clinic before tissue engineering methods become feasible. The findings of this study demonstrate that MSCs possess the capacity to differentiate into various cell types, which renders them a suitable candidate for treating a wide range of human diseases.

Keywords: Macrophage, Immunomodulation, Mesenchymal Stem Cells, Bone Marrow;Tissue Engineering.

1. Context

Mesenchymal stem cells (MSCs) comprise the adult population. It has been identified in numerous organs and has been shown to exhibit a variety of functions and phenotypes when cultivated in a laboratory setting. However, under specific physiological or experimental conditions, these cells can undergo differentiation into mesodermal lineage cells, including osteocytes, adipocytes, kondrocytes, muscle cells, tenocytes, cardiomyocytes, and hematopoietic supportive stroma (1). MSCs exhibit minimal immunogenicity and can be extracted without significant complications. MSCs have thus been proposed as dependable and reliable cell sources for stem cell treatment (2). While MSCs possess the capacity for differentiation, paracrine actions are believed to be the predominant mechanism responsible for their therapeutic benefits in pre-clinical and clinical investigations. The paracrine actions of these cells encompass a range of functions, including the promotion of angiogenesis, the inhibition of apoptosis, the reduction of inflammation, and the alteration of extracellular matrix dynamics. By modifying immune system cells, such as neutrophils and macrophages, these cells can enhance the tissue microenvironments. Following the damage to the tissues or cells, the MSCs are responsible for regulating the regeneration of the entire tissue by activating or suppressing the immune system (2). The use of mesenchymal stem cells (MSCs) has shown promising results in the treatment of various diseases, including diabetes (3), cardiovascular disease (4), graft-versus-host disease (GVHD) (5), and autoimmune diseases (6).

2. Evidence Acquisition

The objective of this review is to utilize MSCs and their nutritional and immunomodulatory functions in tissue engineering. To identify relevant research studies in this area, a comprehensive search was conducted in the PubMed and Google Scholar databases. The following keywords were utilized in the search process: The following terms must be defined: "macrophage," "immunomodulation," "mesenchymal stem cells," "bone marrow," and "tissue engineering."

3. Results

3.1. Types of MSCs & Therapeutic Application of MSCs

Mesenchymal stem cells are a multipotent progenitor cell population. MSCs were initially identified in bone marrow and have since been found in a wide range of tissues, including adipose tissue, the placenta, the umbilical cord, the endometrial tissue, and the gingiva (Figure 1) (7). MSCs have the capacity to proliferate, establish colonies that adhere to plastic, and undergo osteogenesis, kondrogenesis, and adipogenesis during in vitro development. Furthermore, these cells possess multilineage potential in vivo and have the ability to produce useful cells for use in regenerative medicines (8). MSCs have the capacity to differentiate into muscle, neural progenitor cells, cardiomyocytes, and potentially other cell types, as indicated by both in vitro and in vivo research. The support of cytokines and growth factors for hematopoiesis and embryonic stem cell expansion has also been demonstrated for MSCs (9). Some more information about each cell are mentioned below:

3.1.1. Bone Marrow-Derived MSCs (BM-MSCs)

Bone marrow-derived mesenchymal stem cells (BM-MSCs) are known for their capacity to differentiate into osteoblasts, chondrocytes, and adipocytes.

3.1.1.1. Characteristics: High proliferative capacity and immunomodulatory properties.

3.1.1.2. Applications: Used in treating bone and cartilage injuries and immune modulation therapies(10).

3.1.2. Adipose Tissue-Derived MSCs (AD-MSCs)

Adipose-derived mesenchymal stem cells (AD-MSCs) are obtained from adipose tissue and are more abundant and easily accessible than bone marrow-derived mesenchymal stem cells (BM-MSCs).

3.1.2.1.Characteristics: Similar differentiation potential as BM-MSCs, with higher yield and lower donor site morbidity.

3.1.2.2. Applications: Used in cosmetic and reconstructive surgery, wound healing, and treatment of degenerative diseases(11).

3.1.3. Umbilical Cord-Derived MSCs (UC-MSCs)

The isolation of UC-MSCs from the Wharton's jelly of the umbilical cord is a critical step in the process. It is widely accepted that these cells exhibit higher proliferation rates in comparison to adult MSCs.

3.1.3.1. Characteristics: Less invasive collection process, high proliferation rates, and strong immunomodulatory properties.

3.1.3.2. Applications: Used in neonatal and pediatric therapies, immune-related disorders, and tissue engineering(12).

3.1.4. Dental Pulp-Derived MSCs (DP-MSCs)

Dental pulp stem cells (DP-MSCs) are derived from the dental pulp of extracted teeth. These organisms are distinguished by their remarkable regenerative capacities.

3.1.4.1. Characteristics: High proliferative and differentiation potential, particularly into neural-like cells and odontoblasts.

3.1.4.2. Applications: Used in dental tissue engineering, neuroregeneration, and craniofacial reconstructive therapies(13).

3.1.5. Amniotic Fluid-Derived MSCs (AF-MSCs)

The isolation of amniotic fluid-derived mesenchymal stem cells (AF-MSCs) is a procedure that occurs during amniocentesis. These cells exhibit characteristics of both embryonic and adult stem cells.

3.1.5.1. Characteristics: High plasticity and differentiation potential, immunoprivileged status, and minimal ethical concerns.

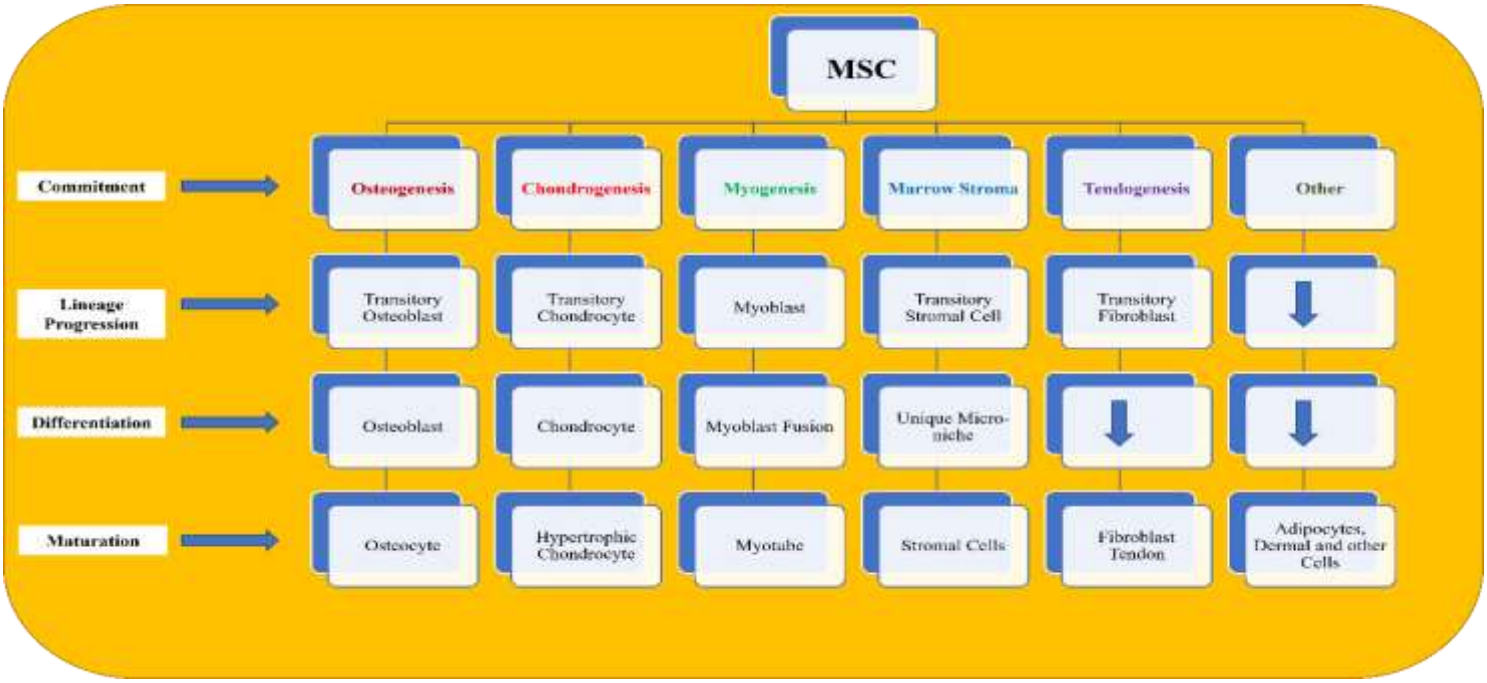

Figure 1. In a series of lineage transitions, adult mesenchymal stem cells (MSCs) can develop into muscle, tendon, marrow stroma, bone, cartilage, fat, and other connective tissues.

3.1.5.2. Applications

Used in prenatal diagnostics, treatment of congenital anomalies, and regenerative medicine(14).

3.1.6. Menstrual Blood-Derived MSCs (MenSCs)

MenSCs are isolated from menstrual blood and have been found to exhibit properties analogous to those of other MSCs.

3.1.6.1. Characteristics

Non-invasive collection, high proliferation rate, and strong regenerative potential.

3.1.6.2. Applications

Potential use in treating a variety of conditions, including neurodegenerative disorders, liver diseases, and cardiovascular diseases(15). Research has demonstrated that mesenchymal stem/stromal cells possess the capacity to mitigate responses of a highly provocative nature, representing one of their numerous functional attributes. The cells' capacity to selectively target the interleukin (IL)-1 receptor constitutes a fundamental aspect of their functionality. Tumor necrosis factor (TNF) and other proinflammatory cytokines from resident macrophages activate mesenchymal stem cells (MSCs) to release the multifunctional anti-inflammatory protein TNF-fortified gene/protein 6. In the second mode of activity, MSCs construct a negative feedback loop (TSG-6). TSG-6 modifies the pro-inflammatory cytokine pathway by reducing nuclear factor-B (NF-B) signaling inside the resident macrophages (16). The demand for MSCs is significant, particularly in the context of transplantation, sepsis, and immune system diseases. Subsequent findings have demonstrated the significance of cytokine-mediated processes as a component of the condition, as evidenced by the inactivation of metabolic processes, the induction of apoptosis, and the division of MSCs, which have been shown to possess immunomodulatory properties. The administration of mesenchymal stem cells (MSCs) has been demonstrated to be an effective therapeutic modality in the treatment of sepsis, immune system infections, and post-transplant surgery (17). Notwithstanding, the precise mechanisms underlying MSC-mediated immunomodulation at the atomic and cellular levels remain to be elucidated. Sepsis is a clinical disorder characterized by a dysregulated host response to contamination. Sepsis is the primary cause of death among hospitalized patients. Sepsis is anticipated to persist as a significant clinical concern in the future, particularly in the context of an aging population and the increasing prevalence of antimicrobial resistance. Consequently, there is a pressing need for the development of innovative and robotically driven treatments to address this disorder. According to the prevailing hypothesis, the immunomodulatory properties of adult mesenchymal stem cells (MSCs) suggest their potential as a novel therapeutic agent in the treatment of sepsis (18). The antibacterial capabilities of mesenchymal stem cells (MSCs) have already been demonstrated. The direct and indirect nature of these impacts has been demonstrated. For instance, it has been demonstrated that MSCs release antimicrobial peptides such as lipocalin-2, beta-defensins, and cathelicidin. A multitude of investigations have demonstrated that bacterial products can stimulate the production of cathelicidin LL-37 by

mesenchymal stem cells (MSCs). This finding suggests that MSCs possess the capacity to enhance antimicrobial activity in the context of infection. Furthermore, evidence has emerged that mesenchymal stem cells can enhance innate immune function through interaction with the host. For instance, research has demonstrated that exposure to MSC-secreted substances enhances the phagocytic and killing capabilities of monocytes and neutrophils. Furthermore, MSCs have been demonstrated to attenuate inflammation in sepsis-model systems. The most promising therapy for ischemia and degenerative illnesses may be stem cells because of their ability to self-renew and differentiate into multiple lineages. The most salient characteristic of these unique cells is their potential therapeutic use in regenerative medicine (19). The most extensively studied type of stem cell is the hematopoietic stem cell. Transplantation of these tissue-specific stem cells is now regarded as the gold standard of therapy for various conditions. While this constitutes the primary objective of stem cell biology research, a novel clinical application for mesenchymal stem cells as an immunotherapeutic agent has emerged. The MSC is a somatic progenitor/stem cell that can differentiate into multiple lineages. However, recent research on its immunomodulatory properties has led to an expansion in its utilization (20). As of April 2016, the National Institutes of Health (NIH) Clinical Trial Database listed approximately 500 clinical trials related to mesenchymal stem cells (MSCs) (Figure 2). MSCs have been demonstrated to possess immunomodulatory and anti-inflammatory properties in in vitro and in vivo models, exerting their effects on both innate and adaptive immune cells (21). Research has demonstrated that nitric oxide (22), indoleamine 2,3-dioxygenase (23), prostaglandin E2 (24), and hepatocyte growth factor (25) have been identified as the mediators of MSCs' inhibitory action on immune cells. Furthermore, MSCs have been investigated as a potential therapeutic agent for autoimmune encephalomyelitis. MSCs derived from embryonic stem cells were utilized in the treatment of the EAE model in cynomolgus monkeys, resulting in a reduction of clinical signs of brain lesions and neuronal demyelination (26).

3.2. MSCs and Immune Regulation

The immunological response is expected to be inhibited by a high MSC-to-lymphocyte ratio, although the proliferation of lymphocytes is increased by a low MSC-to-lymphocyte ratio. The immunomodulatory influences of MSCs on these T cell subgroups also appear to depend on the amount. MSCs have been demonstrated to induce immunosuppressive effects (27). Due to their reduced immunogenicity, mesenchymal stem cells are also recognized for their unique immunological properties. Furthermore, the presence of low quantities of human leukocyte antigen (HLA) class I in human mesenchymal stem cells has been observed, and these cells have been found to exhibit no expression of HLA-DR. The escape of HLA-DR from immune control is a critical step in the process. The presence of HLA class I is imperative for safeguarding cells against the deleterious effects of natural killer cells. Conversely, HLA is among the most significant proteins found in human cells. In the event that a cell is unable to produce the aforementioned proteins, it is susceptible to targeted elimination. A salient feature of these processes is their targeted delivery to regions of the body where inflammatory chemokines are being released. These scenarios are addressed by a variety of chemokine receptors, which facilitate their capacity to migrate and return to sites of inflammation (28). Due to their capacity to withstand immunological reactions, MSCs provide a range of therapeutic benefits, thus meriting their designation as "universal donors" (29). However, determining the security and effectiveness of these mesenchymal stem cells in allogeneic techniques is crucial for therapeutic use, as is the case with any other cell treatment. The in vitro experiments that will be discussed subsequently in this section provide substantial evidence for both the direct suppression of effector T cells by MSCs and the indirect suppression caused by MSC-induced Treg proliferation. In particular, prior to the demonstration of their immunomodulatory functions, MSCs must undergo a licensing or activation process initiated by contact with inflammatory cytokines, including IFN-γ, interleukin-1 β, and TNF-α (30, 31). The substantial number of mediators and proposed mechanisms indicate the potential for intricate interactions, which could render MSCs immunogenic or immunosuppressive. The predominant impact of MSCs on T lymphocytes appears to be contingent on the cellular microenvironment and the ratio of MSCs to T lymphocytes (31). Adult bone marrow stromal cells (BMSCs) are non-hematopoietic cells that can be identified through flow cytometry using monoclonal antibodies, such as SH-3, SH-4, and SH-2 (32). Sheep receiving intrauterine injections of human MSCs have been observed to undergo cell implantation and differentiation along a variety of mesenchymal lineages. The administration of autologous MSCs produced in vitro via intravenous injection has been demonstrated to be safe for humans. The development of hematopoietic stem cells (HSCs) can be enhanced through the co-transplantation of autologous HSCs and mesenchymal stem cells (MSCs) (33). Mesenchymal stem cells have been shown to impede T-cell production. Research has demonstrated that mesenchymal stem cells (MSCs) from both mice and humans have the capacity to impede the proliferation of activated T lymphocytes in vitro, both in autologous and allogeneic settings. The immunosuppressive effects of mesenchymal stem cells (MSCs) on autologous and allogeneic T-cell proliferation are contingent upon a high ratio of MSCs to lymphocytes and soluble components (34). Schurgers et al. demonstrated a comparable level of immunosuppressive impact of MSCs on the development of allogeneic T lymphocytes stimulated by anti-CD3. However, the immunosuppressive impacts of mesenchymal stem cells have not yet been observed in vivo (35). Prostaglandin E2, inducible nitric oxide (iNOS), and programmed death ligand-1 (PD-L1) have been

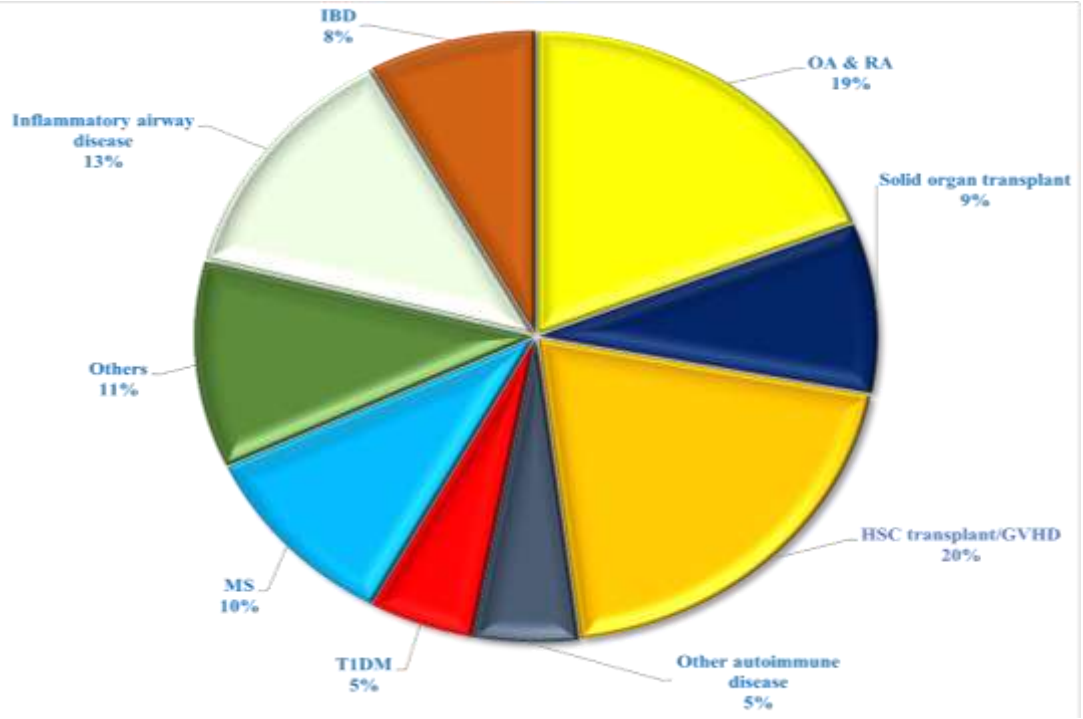

Figure 2. Clinical application of human mesenchymal stem.

demonstrated to play a role in the suppression of T cells in vitro, although the involvement of indoleamine A's participation in -2,3 dioxygenase (IDO) has not been substantiated (35). The following section will present a detailed overview of the mechanisms that regulate immune cells (Figure 3).

3.3. The effect of Modulating Stem Cell Immunity on Repairing Tissue and Organ Injuries

Cartilage damage is a complex illness in the field of medicine. Cartilage damage manifests primarily in joint regions, and impairment to articular cartilage curtails the capacity of cartilage tissue to regenerate. The immunological milieu in tissue regeneration has been the subject of much research in recent years. This research has led us to consider the hypothesis that the recovery of cartilage can be improved by establishing a suitable milieu. Pluripotent stem cells possess the capacity to differentiate into a range of cell types, including adipocytes, bone, and cartilage. These cells are derived from mesoderm and are characterized by their mesenchymal nature. They are generated from perivascular tissues, as outlined in reference (36). MSC-based cartilage has been demonstrated to promote polarization of macrophages to an M2 phenotype, in which macrophages upregulate CD206, exhibit reduced IL-1β release, increased IL-10 production, and decreased expression of M1 to M2-associated genes. It has been demonstrated that this substance exhibits anti-inflammatory properties, including transitions. Research indicates that MSC-based tissue engineering constructions can enhance inflammation brought on by adherence and cartilage repair by M2-polarized macrophages (37). Bone marrow stromal cell-based genetically engineered cartilage has been demonstrated to suppress inflammation in vivo by increasing M2 polarization of macrophages, resulting in improved survival when compared to the use of kondrocytes as germ cells. However, with regard to the immunosuppressive properties of mesenchymal stem cells, there is a paucity of research on the immunogenicity of kondrogenic cells, which has led to conflicting conclusions (38). A study on MSC-mediated cartilage injury repair demonstrated that the secretion of exosome by her MSCs to enhance tissue regeneration was also implicated in regulating the immunological reaction. Macrophages exhibit a high degree of flexibility and perform critical functions in the context of innate immunity. A similar behavioral pattern has been observed among resident macrophages, including CD11b, CD14, CD16, and CD68 (39), as well as synovial macrophages. Furthermore, the study demonstrated that macrophages and mesenchymal stem cells exhibit a closer geographical proximity in normal and pre-OA knees compared to OA patients. Additionally, synovial macrophages were found to be diminished in pre-OA joints relative to normal knees (40). As demonstrated in the extant literature, the presence of synovial M1 macrophages has been shown to increase the production of proteolytic enzymes that cause articular degeneration. These enzymes include MMP3, matrix metalloproteinase-1, MMP9 aggrecanase, cyclooxygenase-2, and MMP13 (41). It has been demonstrated that the process of kondrogenesis in MSCs is subject to adverse influence

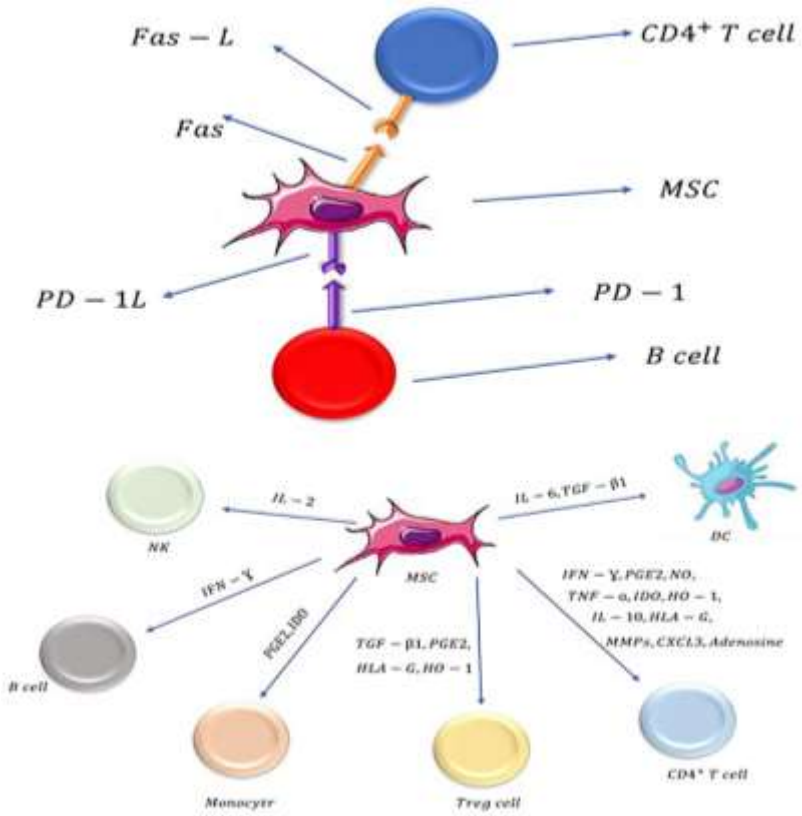

Figure 3. Mechanism of MSC-mediated immune cell regulation. (a) Direct cell-cell contact, (b) interactions between soluble components.

from monocyte-derived pro-inflammatory and synovial macrophages (Figure 4) (42).

3. 4. MSCs and GvHD

The initial reports of graft-versus-host disease (GVHD) were contributed by Barnes, Loutit, and Micklem, and Billingham provided the foundational definition of the condition as the result of immunocompetent donor cells detecting and attacking host tissues in immunocompromised allogeneic recipients. Chronic GVHD has been shown to exhibit numerous fibrotic and autoimmune characteristics, while acute GVHD is characterized by a substantial inflammatory response (Figure 5). Acute GVHD and chronic GVHD involve different pathological mechanisms (Figure 6) (43). The biological characteristics and functional mechanisms of mesenchymal stem cells are the focus of fundamental research and are a target for several possible therapeutic applications. These cells possess notable immunosuppressive properties that are evident in both in vitro and in vivo settings, constituting a distinguishing characteristic. These findings laid the foundation for the therapeutic use of MSC in the treatment of GVHD. In 2004, the initial successful case of severe steroid-resistant GVHD treated with mesenchymal stem cells was documented (17). A total of 183 patients were treated in the course of the study, as documented in fourteen publications. The response rates observed ranged from 0 to 100 percent, and estimates were derived related to the initial impact and overall survival (OS). In summary, the available data regarding the clinical efficacy of MSC infusion for aGVHD is encouraging, although it is inconsistent and remains unproven. MSCs have emerged as a promising therapeutic option for managing acute graft-versus-host disease (aGVHD), owing to their inherent immunosuppressive properties. However, it should be noted that the therapeutic effects of these devices are not always achieved (44). The diminished impact of MSCs on graft versus leukemia is a salient concern in the context of their utilization. The stimulation of regulatory cells and immunosuppression brought on by MSCs is a significant problem for patients with hematologic malignancies. MSCs have been demonstrated to support the tumor microenvironment, thereby promoting tumor development, as evidenced by several preclinical studies (45). In a clinical trial employing patients with hematologic malignancies, MSCs demonstrated efficacy in mitigating the development of GVHD, thereby averting the onset of this adverse event. However, the recurrence rate observed among patients receiving MSCs was higher than that of the control group (46). A comparison of the two groups revealed that, while three of 15 patients in the non-MSC group experienced tumor recurrence, six of 10 patients in the MSC group did so. The heightened probability of recurrence observed in the MSC group may suggest that the GVL effect is diminished by the infusion of MSCs. However, the study's limited sample size precludes the drawing of definitive

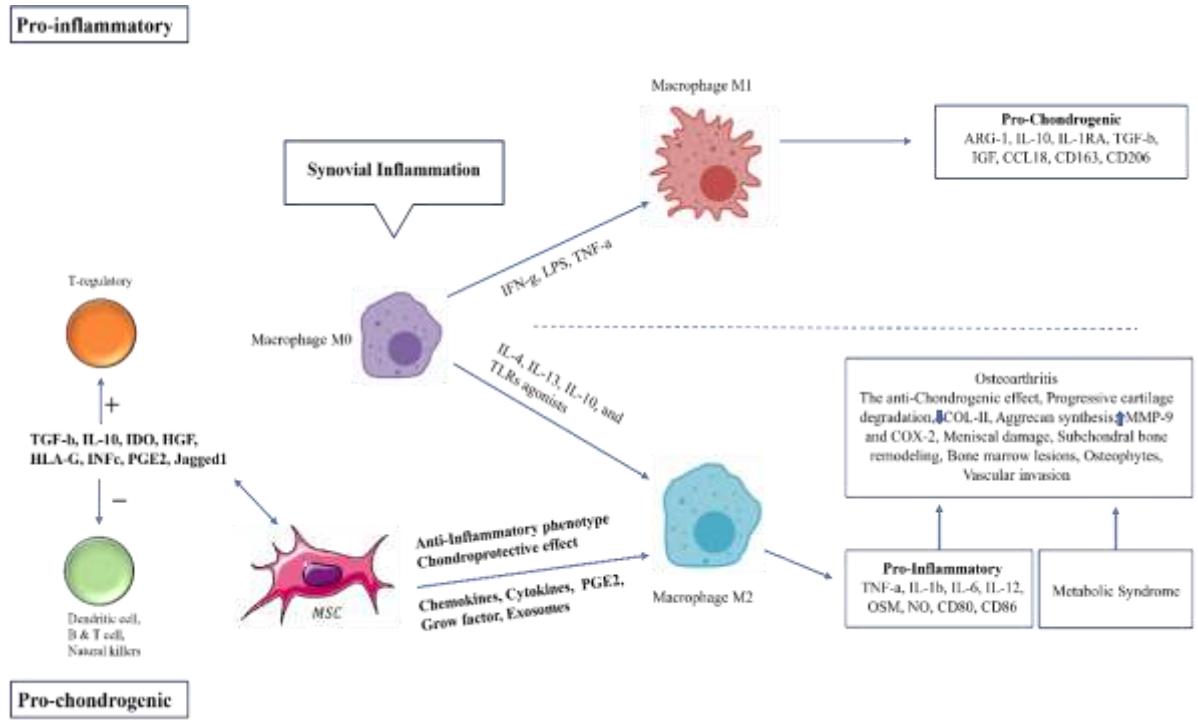

Figure 4. Macrophage pathways that are pro-chondrogenic and pro-inflammatory in cartilage damage and healing.

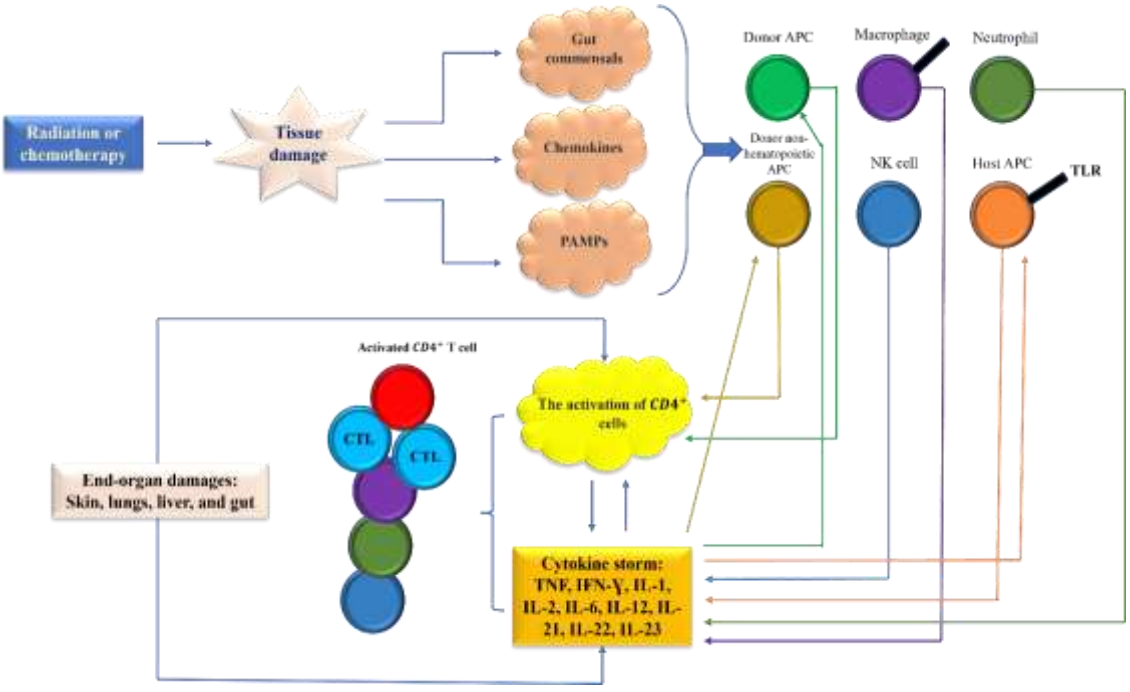

Figure 5. The whole GVHD acute cascade. The initiation and maintenance of acute graft-versus-host disease (GVHD) have been characterized as having four phases, each of which contains a positive feedback loop that keeps the process going.

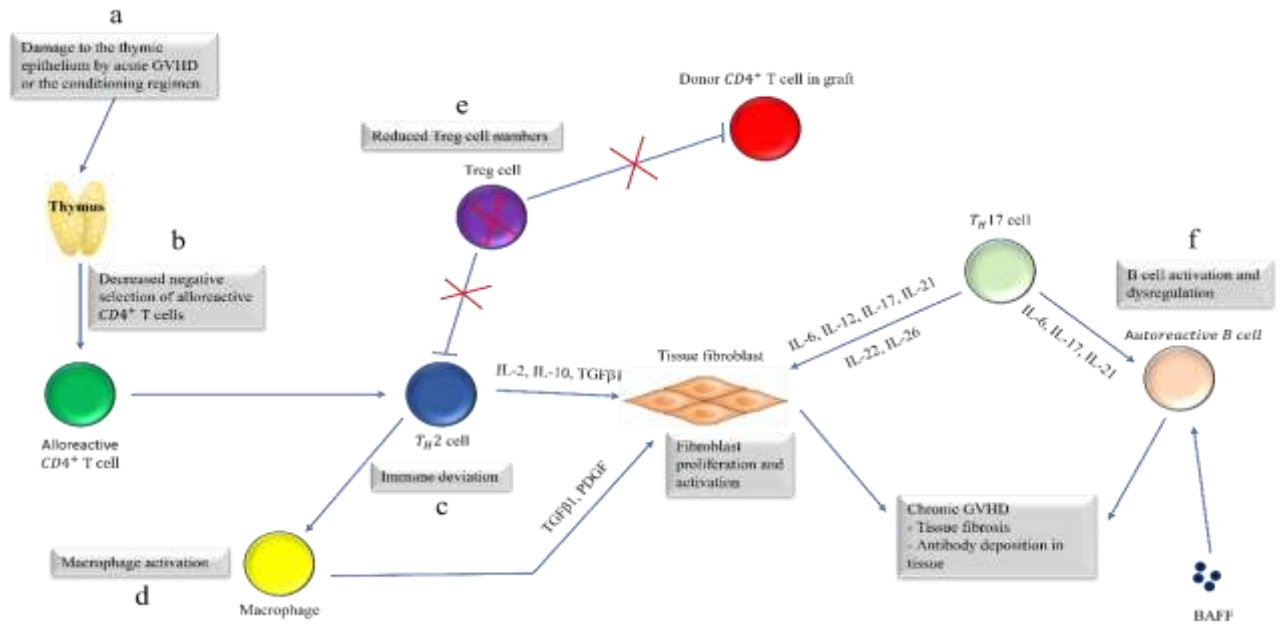

Figure 6. Key factors in the development of chronic GVHD. Six characteristics are specific to this illness, although the pathogenesis of chronic GVHD mostly relies on the polarization of CD4+ T cells into TH2 cells.

conclusions. Conversely, a clinical experiment has demonstrated that the administration of MSCs can halt GVHD without addressing the consequences of GVL. In a trial conducted prior to the advent of nonmyeloablative HSCT, mesenchymal stem cells (MSCs) were implanted in patients diagnosed with hematologic malignancies. The results indicated a reduction in graft rejection and acute graft-versus-host disease (aGVHD) incidence rates, attributable to the infusion of MSCs. However, the relapse rate remained comparable to the historical control group that did not receive MSCs (47).

3.5. Immunoregulatory Effects of MSCs in TE

The liver, heart, and skeletal systems have extensively utilized stem cell-integrated tissue engineering. The utilization of stem cell tissue engineering in orthopedic systems for connective tissue, such as the meniscus and cartilage, exhibits considerable potential for advancement (48, 49). In the progression of TE, the immunomodulatory properties of stem cells are of particular significance. The elevated levels of IL-1 and other pro-inflammatory cytokines present in the synovial fluid of joints in OA play a pivotal role in the progression of arthritis. The adaptive and innate immunological reactions are collectively influenced by the capacity of MSCs to modulate the immune system. The lymphocyte-dominated adaptive immune response exerts a substantial influence on the rate of fracture repair (50).

3.6. Bladder

Currently, the fabrication of replacement or replacement-type bladders frequently involves the use of components from the gastrointestinal tract. However, it is important to note that stomach tissues are specialized for the absorption of certain solutes, while bladder tissue is designed for the expulsion of solutes. A considerable body of research has been dedicated to the exploration of alternative substances and tissues for the purposes of regeneration and replacement, owing to the constraints associated with the utilization of digestive system segments. The effective utilization of donor tissue and the creation of optimal conditions for long-term survival, differentiation, and development are paramount to the success of cell transplantation procedures employed for bladder restoration. Expanded muscle and urothelial cells can be seeded onto polymer scaffolds and allowed to adhere to one another to generate sheets of cells (51). From an autologous bladder biopsy specimen, urothelial and muscle cells were independently cultivated and seeded onto a bladder-shaped biodegradable polymer scaffold. The findings of this study demonstrated that normal-appearing, anatomically, and physiologically functioning bladders can be created by tissue engineering (52).

3.7. Cartilage

Hydrogels are utilized in tissue engineering for biomedical applications, either as a standalone solution or in conjunction with cells. The composition of hydrogels can vary, with the potential to utilize natural, synthetic, or a combination of these polymers. In the domain of cartilage tissue engineering, the utilization of cartilage ECM-derived biomaterials has emerged as a pivotal strategy to promote the regeneration of bothchondrocytes and MSCs. The primary components of the cartilage extracellular matrix are hyaluronan (HA), kondroitin sulfate (CS), and collagen (53). Other natural polymers that are frequently utilized include gelatin, alginate, and chitosan. In contrast, most

naturally occurring polymers exhibit a deficiency in mechanical strength and are prone to rapid degradation. Consequently, synthetic polymers that are biodegradable and biocompatible, including poly (ethylene glycol) (PEG), polyvinyl alcohol (PVA), and poly (DL-lactic-co-glycolic acid) (PLGA), are extensively utilized in cartilage tissue engineering (54).

3.8. Bone

MSC modulation is a distinct approach to modulate immune cells for bone tissue engineering, recognizing that MSCs are predominantly employed as repair cells in bone tissue engineering. Typically, the implantation of scaffolds in bone defects for the purpose of bone repair is preceded by the seeding of said scaffolds with MSCs. Research by Seebach et al. has demonstrated that cultured MSCs encourage the recruitment of M1 macrophages and endothelial progenitor cells to scaffolds, thereby enabling early maturation and vascularization (55).

Ueno et al. developed a method for creating scaffolds for severe bone defects using lentivirus-transduced MSCs that overexpress IL-4. The findings indicated that modified MSCs integrated within scaffolds were capable of promoting M2 polarization of macrophages while exerting no influence on M1 activity during the initial phases of inflammation. Scaffolds produced by IL-4 have been observed to stimulate bone regrowth, suggesting that the use of scaffolds loaded with modified MSCs may represent a promising therapeutic strategy (56). Consequently, the selection of MSCs may emerge as a prospective priority. In addition to being directly loaded onto scaffolds to control immune cells, MSCs can also be infused into the body systemically to reduce inflammation. As posited by Liu et al., the systemic infusion of mesenchymal stem cells (MSCs) has been demonstrated to upregulate regulatory T cells (Tregs) while concomitantly downregulating pro-inflammatory cytokines, such as interferon- (IFN-) and tumor necrosis factor (TNF), at the implantation sites. This method has also been demonstrated to enhance bone regeneration in MSC-seeded scaffolds (57). Systemic MSC infusion has been demonstrated to support bone repair in animal models. Future research should, however, examine precise processes (58).

4. Future Perspective

The focus on marrow stems from its significance in the realm of future technological advancements in tissue engineering. Marrow stands as a unique organ due to its possession of at least two distinct types of stem cells, namely, stromal stem cells (SSCs) and hematopoietic stem cells (HSCs). Notably, marrow serves as the origin of progenitors that give rise to a wide array of distant tissues, underscoring its critical role in tissue regeneration and repair. Recent research suggests that the conventional barrier dividing the mesodermal and hematopoietic tissue systems and lineages is disintegrating. The marrow contains cells that have the potential to regenerate cardiac muscle, skeletal muscle, and blood vessels. It has been proposed that both myogenic stem cells (MSCs) and hematopoietic stem cells (HSCs) present in bone marrow are responsible for the remarkable capacity for myogenesis and cardiomyogenesis. The term "HSC" may in fact encompass a considerably more extensive range of properties and functions. A true multipotent stem cell possesses transdermal potentials, often undergoing differentiation into hematopoietic cells in response to local signals. The primary advantage of harvesting and cultivating marrow cells from an adult individual is that it enables the separation and purification of the hematopoietic stem cell (HSC) in a laboratory setting. These investigations illuminate the potential for imminent transformation in the domain of tissue engineering. The presence of pleiotropic and heterotopic stem cells in bone marrow has significant implications for daily life and the future of stem cell treatment. These considerations should not be overshadowed by theoretical frameworks or overlooked in favor of additional experimental evidence.

5. Conclusion

Tissue engineering techniques are now being applied to almost all types of organs and tissues in the human body. The effective utilization of this technology is contingent upon the presence of personnel with expertise in cell culture, transplantation, expansion, polymer design, and harvest. The integration of tissue engineering with the domains of engineering, materials science, and cell transplantation has resulted in a multifaceted field that necessitates the expertise of professionals with a wide range of specializations. The development of engineered tissues is currently underway, with various tissues undergoing different phases of research. Some of these tissues are already being utilized in clinical settings, while others are in preclinical research or in the preliminary discovery phase. Recent advancements in the field suggest that synthetic tissues may eventually encompass a more extensive array of clinical applications, as they present a promising therapeutic alternative for patients in need of tissue replacement. As indicated by the aforementioned topic, it is evident that contemporary technology has undergone significant advancements across diverse academic disciplines and professional domains, particularly within the field of biology. Tissue engineering is a field of study that has gained significant prominence and popularity on a global scale. This review asserts that tissue engineering has the potential to become a highly effective treatment for irreparable tissue injuries, thereby profoundly impacting the fields of biology and science.

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Authors' Contribution

Study concept and design: A. A, A. A.
Acquisition of data: B. SH, N. A.
Analysis and interpretation of data: A. A, A. A, N. A.
Drafting of the manuscript: A. S, A. A, A. A, N. A.
Critical revision of the manuscript for important intellectual content: Y. N.

Ethics

It is hereby asserted that all ethical standards have been observed in the preparation of the submitted article.

Conflict of Interest

The authors have declared no conflicts of interest in relation to this research.

Data Availability

The data that support the findings of this study are available upon request from the corresponding author.

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