Immunomodulatory Functions of Mesenchymal Stem Cells in Tissue Engineering

Abstract

Mesenchymal stem cells (MSCs) have been shown to possess immunomodulatory properties that can regulate the immune response and promote tissue regeneration. These properties include the ability to suppress T cell proliferation, modulate macrophage polarization, and promote regulatory T cell differentiation. Suffice it to say 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 speed of regeneration of tissue damage depends on the person's age, level of tissue damage, and also depends on which part of the body is damaged. It can be seen that the manipulation of mesenchymal stem cells can have very significant effects on the rate of tissue damage, tissue regeneration, and also cell death. Immunosuppressive and trophic mechanism influences are different from the mechanisms that are being led by tissue engineering to replace the special mesenchymal tissues. In fact, it can be seen how tissue engineering processes get along with trophic to promote astonishing tissue regeneration and support the smooth integration of newly created tissue into the body. MSCs have been worked on for more than 20 years and their potential has been just realized for clinical applications. It is obvious that the usage of MSCs for tissue engineering requires quite different reasons than their usage 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 reveal that MSCs have the ability

to differentiate into various cell types, which makes them an ideal 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) constitute the adult population. It is found in many organs and exhibits multiple functions and phenotypes when cultured in vitro. Under certain physiological or experimental conditions, MSCs can differentiate in vitro into mesodermal lineage cells, particularly osteocytes, adipocytes, chondrocytes, muscle cells, tenocytes, cardiomyocytes, and hematopoietic supportive stroma (1). MSCs have minimal immunogenicity and may be extracted without serious issues. MSCs have therefore been suggested as reliable and secure cell sources for stem cell treatment (2). Although MSCs are capable of differentiating, paracrine actions are thought to be the primary mechanism behind their therapeutic benefits in pre-clinical and clinical investigations. These paracrine actions include promoting angiogenesis, inhibiting apoptosis, reducing inflammation, and altering extracellular matrix dynamics. By modifying immune system cells like neutrophils and macrophages, these cells can enhance the tissue microenvironments. After the tissues or cells are damaged, the MSCs regulate the regeneration of the entire tissue by activating or suppressing the immune system (2). Diabetes (3), cardiovascular disease (4), and both GVHD and autoimmune (5) diseases have been healed significantly with MSCs.(6)

2. Evidence Acquisition

The purpose of this review is to use MSCs and their nutritional and immunomodulatory functions in tissue engineering. To locate pertinent research studies in this regard, a thorough search was conducted on the

PubMed and Google Scholar databases. The following keywords were used in the search process: "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 multilineage-capable forebear cell community. MSCs firstly were identified in the bone marrow and are now present in almost every kind of tissue, including adipose tissue, the placenta, the umbilical cord, the endometrial, and the gingiva (Figure 1) (7). MSCs can grow in numbers, form colonies that stick to plastic, and can carry out osteogenesis, chondrogenesis, and adipogenesis when they are developed in vitro. Additionally, these cells possess multilineage potential in vivo and have the ability to produce useful cells for use in regenerative medicines (8). MSCs can develop into muscle, neural progenitor cells, cardiomyocytes, and perhaps additional cell types, according to 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;

1. **Bone Marrow-Derived MSCs (BM-MSCs)**

BM-MSCs are isolated from bone marrow and are known for their ability to differentiate into osteoblasts, chondrocytes, and adipocytes.

- **Characteristics**: High proliferative capacity and immunomodulatory properties.

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

2. **Adipose Tissue-Derived MSCs (AD-MSCs)**

AD-MSCs are obtained from adipose (fat) tissue and are abundant and easily accessible compared to BM-MSCs.

- **Characteristics**: Similar differentiation potential as BM-MSCs, with higher yield and lower donor site morbidity.
- **Applications**: Used in cosmetic and reconstructive surgery, wound healing, and treatment of degenerative diseases(11).

3. **Umbilical Cord-Derived MSCs (UC-MSCs)**

UC-MSCs are isolated from the Wharton's jelly of the umbilical cord. They are considered to have higher proliferation rates compared to adult MSCs.

- **Characteristics**: Less invasive collection process, high proliferation rates, and strong immunomodulatory properties.
- **Applications**: Used in neonatal and pediatric therapies, immune-related disorders, and tissue engineering(12).

4. **Dental Pulp-Derived MSCs (DP-MSCs)**

DP-MSCs are derived from the dental pulp of extracted teeth. They are known for their robust regenerative capabilities.

- **Characteristics**: High proliferative and differentiation potential, particularly into neural-like cells and odontoblasts.
- **Applications**: Used in dental tissue engineering, neuroregeneration, and craniofacial reconstructive therapies(13).

5. **Amniotic Fluid-Derived MSCs (AF-MSCs)**

AF-MSCs are isolated from the amniotic fluid during amniocentesis. They possess properties of both embryonic and adult stem cells.

- **Characteristics**: High plasticity and differentiation potential, immunoprivileged status, and minimal ethical concerns.
- **Applications**: Used in prenatal diagnostics, treatment of congenital anomalies, and regenerative medicine(14).

6. **Menstrual Blood-Derived MSCs (MenSCs)**

MenSCs are isolated from menstrual blood and have been found to have similar properties to other MSCs.

- **Characteristics**: Non-invasive collection, high proliferation rate, and strong regenerative potential.
- **Applications**: Potential use in treating a variety of conditions, including neurodegenerative disorders, liver diseases, and cardiovascular diseases(15).

Studies have shown that mesenchymal stem/stromal cells' ability to protect against extremely provocative responses is one of their many abilities. The cells' ability to specifically target the

interleukin (IL)-1 receptor is one of their modes of function. Tumor corruption factor (TNF) and other proinflammatory cytokines from resident macrophages activate MSCs to release the multifunctional anti-inflammatory protein TNF-fortified gene/protein 6 in the second mode of activity, which is to construct a negative input circle (TSG-6). then The TSG-6 modifies the pro-inflammatory cytokine pathway by reducing atomic factor-B (NF-B) signaling inside the resident macrophages (16).

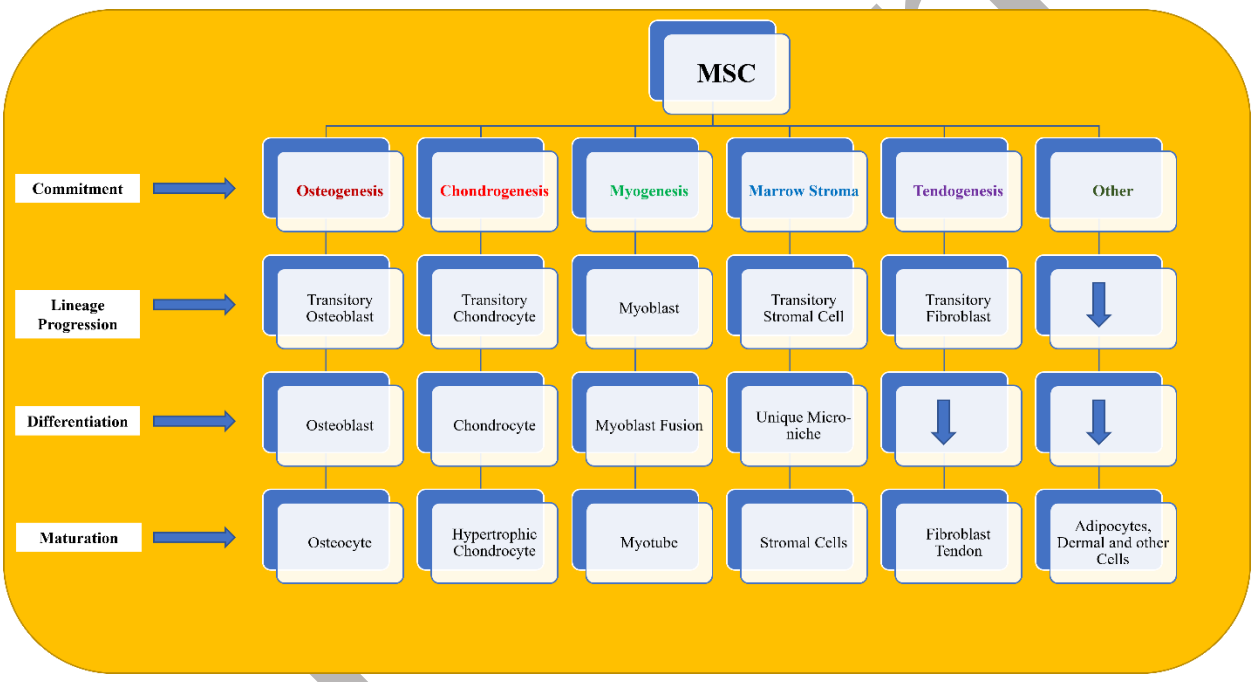


Figure 1. In a series of lineage transitions, adult mesenchymal stem cells (MSCs) can develop into muscle, tendon, marrow stroma, bone, cartilage, fat, and other connective tissues.

The desire for treating MSCs is pretty high, especially when we talk about transplant medication, sepsis, and also immune system diseases. Anyways, later discoveries show the influences of cytokine-mediated are as it were one portion of the condition as metabolically inactivated, apoptotic or the MSCs that are divided have appeared to have an immunomodulatory potential as well.

An efficient therapeutic option is provided by MSC treatment for sepsis, immune system infections, and transplant surgery (17). Be that as it may, it is still unclear exactly what makes up MSC-mediated immunomodulation at the atomic and cellular levels.

Sepsis is a clinical disorder caused by a deregulated host response to contamination. Sepsis is the foremost visit cause of death in hospitalized patients. Sepsis will stay an imperative clinical issue in the future, particularly in light of the maturing populace and rising anti-microbial resistance. In this manner, there's a dramatic requirement for unused and robotically elective treatments to treat this disorder. Based on their immunomodulatory properties, grown-up MSCs can be a novel restorative instrument to treat sepsis (18).

Antibacterial capabilities of mesenchymal stem cells (MSCs) have already been demonstrated. Both the direct and indirect nature of these impacts have been shown. For instance, it has been demonstrated that MSCs release antimicrobial peptides such as lipocalin-2, beta-defensins, and cathelicidin. Several investigations have demonstrated that bacterial products increase the cathelicidin LL-37 production by MSCs, indicating that MSCs can upregulate antimicrobial activity in the context of infection. Additionally, it has been demonstrated that mesenchymal stem cells can improve innate immune function by interacting with the host. For instance, studies have found that exposure to MSC-secreted substances increases the phagocytic and killing abilities of monocytes and neutrophils. MSCs have also been found to reduce 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 interesting characteristic of these unique cells is their potential therapeutic use in regenerative medicine (19). The type of stem cell that has been studied the most is the hematopoietic stem cell, and

transplantation of these tissue-specific stem cells is now thought to be the gold standard of therapy for various conditions. While this is the major objective of stem cell biology research, a surprising new clinical application for mesenchymal stem cells as an immunotherapeutic agent has arisen. The MSC is a somatic progenitor/stem cell that can differentiate into many lineages. Nevertheless, recent research on its immunomodulatory abilities has expanded its usage (20).

In fact, the NIH Clinical Trial Database listed approximately 500 clinical trials related to MSC as of April 2016 (Figure 2).

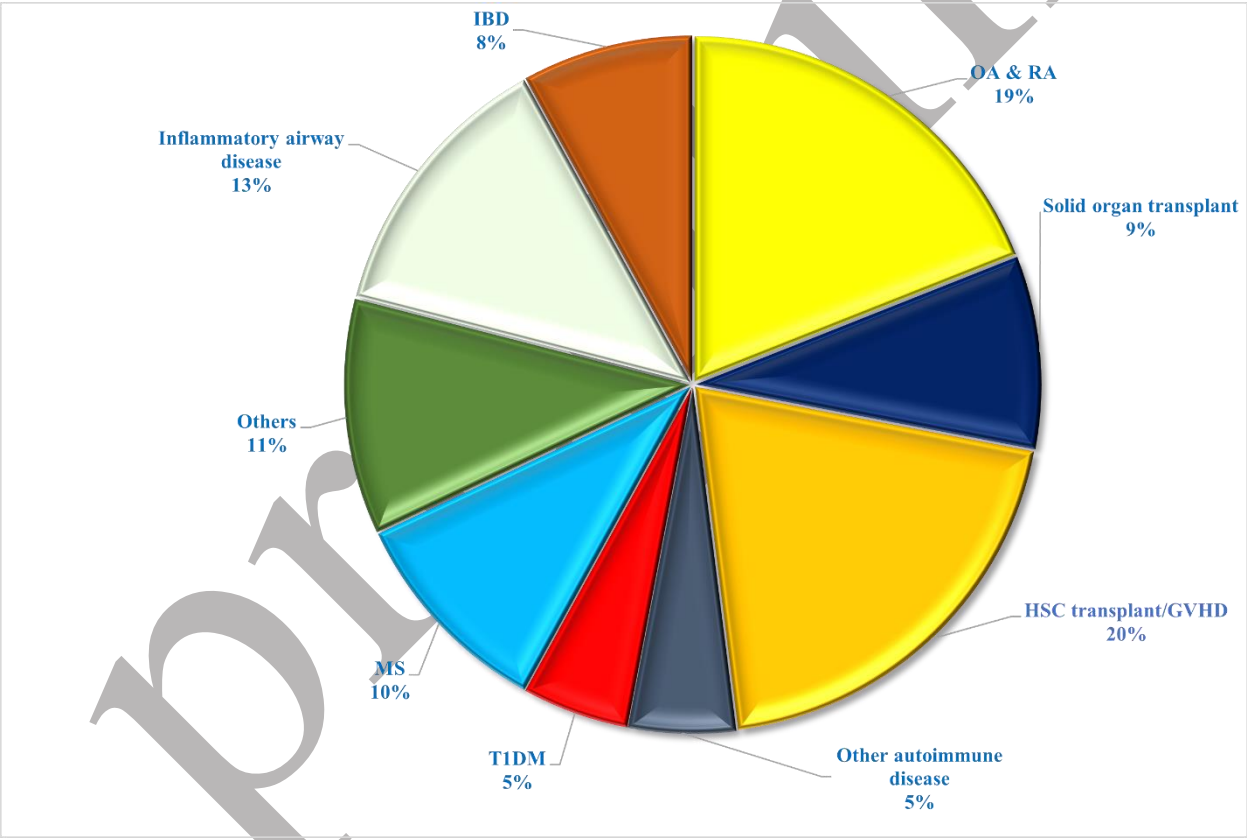


Figure 2. Clinical application of human mesenchymal stem.

MSCs have been shown in vitro and in vivo to have immunomodulatory and anti-inflammatory effects on both innate and adaptive immune cells (21). It was shown that nitric oxide (22),

indoleamine 2,3-dioxygenase (23), prostaglandin E2 (24), and hepatocyte growth factor mediate MSCs' inhibitory action on immune cells (25).

MSCs have also been investigated as a potential therapy for autoimmune encephalomyelitis. MSCs that are made from embryonic stem cells were used to treat the EAE model in cynomolgus monkeys, which decreased the 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 lead to immunosuppressive effects (27).

Because of their decreased immunogenicity, mesenchymal stem cells are also recognized for their privileged immunological properties. Low quantities of human leukocyte antigen class I are found in human mesenchymal stem cells and HLA-DR is not being expressed by these cells. HLA-DR is a must to escape from immune control. The existence of HLA class I is essential to protect the cell from the toxicity of natural killers. In contrast, HLA is one of the most important proteins in human cells. If any cells are not able to produce these proteins are easily targeted and get eliminated. One more key feature is that these are settled and going to those parts of the body in which inflammatory chemokines are being released. These situations are handled by multiple receptors of chemokines which support their potential to migrate and return to inflammatory locations (28). Because MSCs can tolerate immunological responses, they offer several therapeutic benefits that have earned them the term "universal donors" (29). However, determining the security

and effectiveness of these mesenchymal stem cells in allogeneic techniques is crucial for therapeutic use, just like any other cell treatment.

The in vitro experiments that are going to be discussed later in this section provide strong evidence for both the direct suppression of effector T cells by MSCs and the indirect suppression caused by MSC-induced Treg proliferation. In particular, Before MSCs exhibit their immunomodulatory functions, they must first be licensed or activated by contact with inflammatory cytokines including (30) IFN- γ, interleukin-1 β, and TNF- α (31). Interestingly, the large number of mediators and proposed mechanisms suggest complex interactions that could make MSCs immunogenic or immunosuppressive. The predominant impact appears to be dependent on the cellular microenvironment and the ratio of MSCs to T lymphocytes (31).

Adult BMSCs are non-hematopoietic cells that can be recognized by flow cytometry using antibodies that are monoclonal such as SH-3, SH-4, and SH- 2 (32). Sheep receiving intrauterine injections of human MSCs experience cell implantation and differentiation along a variety of mesenchymal lineages. Autologous MSCs produced in vitro may be administered intravenously to people without causing any harm. HSC development can be improved by co-transplanting autologous hematopoietic stem cells and mesenchymal stem cells (33).

Mesenchymal stem cells block T-cell production. It has been demonstrated that MSCs from both mice and humans may stop the growth of activated T lymphocytes in vitro in autologous and allogeneic environments. The immunosuppressive effects of mesenchymal stem cells on autologous and allogeneic T-cell proliferation depend on a high ratio of MSCs to lymphocytes and soluble components (34). Schurgers et al. showed a comparable amount of the drug 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

appeared in vivo (35). Prostaglandin E2, inducible nitric oxide (iNOS), and programmed death ligand-1 (PD-L1) have been proven to be involved in the suppression of T cells in vitro, although indoleamine A's participation in -2,3 dioxygenase (IDO) has not been demonstrated (35). The mechanism of immune cell regulation is presented below (Figure 3).

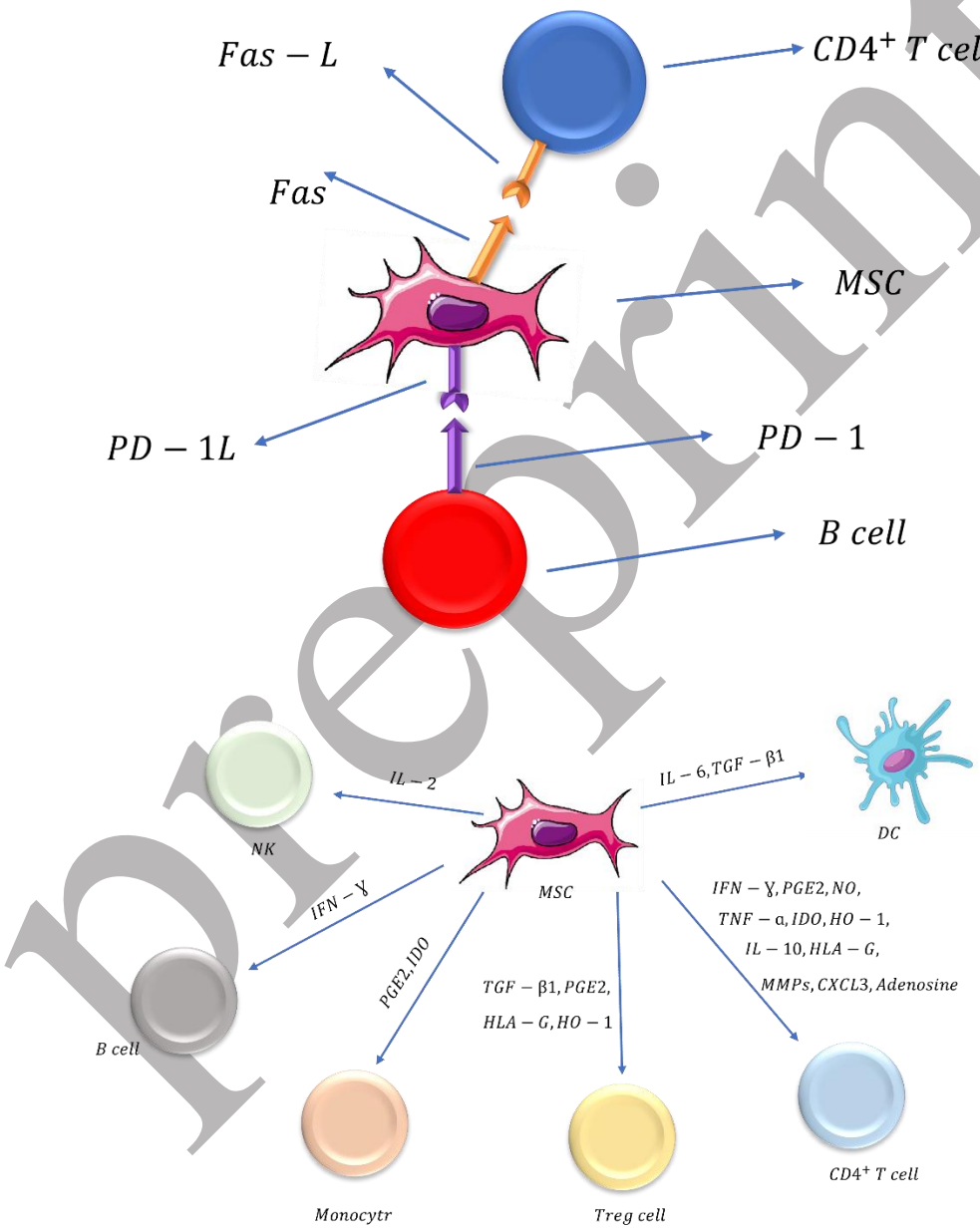


Figure 3. Mechanism of MSC-mediated immune cell regulation. (a) Direct cell-cell contact, (b) interactions between soluble components.

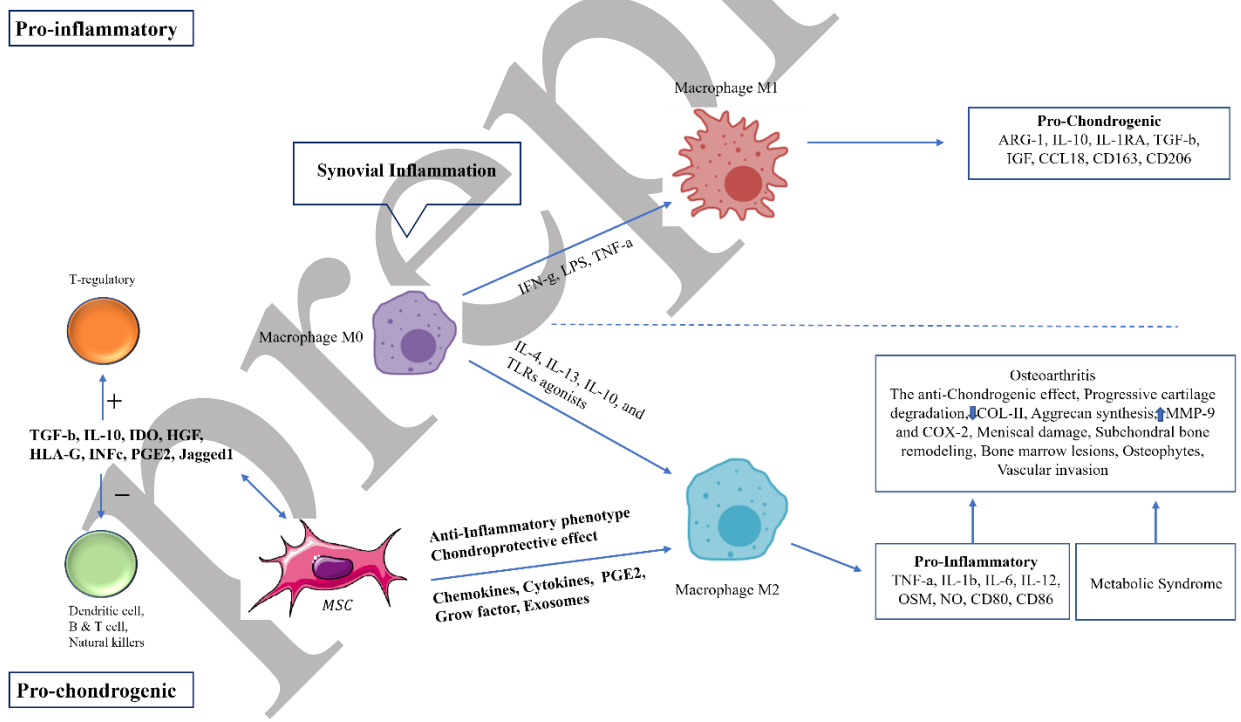
3. 3. The effect of modulating stem cell immunity on repairing tissue and organ injuries

In the world of medicine, cartilage damage is a complex illness. Cartilage damage occurs mainly at joint sites, and damage to articular cartilage limits the ability of cartilage tissue to regenerate. The immunological milieu in tissue regeneration has been the subject of much research in recent years, and this research has led us to consider that the recovery of cartilage can be improved by establishing a suitable milieu. Pluripotent stem cells that may develop into a variety of cell types, such as adipocytes, bone, and cartilage, include mesoderm-derived mesenchymal stem cells, which are generated from perivascular tissues (36).

MSC-based cartilage promotes polarization of macrophages to an M2 phenotype, in which macrophages upregulate CD206, Reduced IL-1β release, increased IL-10 production, and decreased expression of M1 to M2-associated genes. Allows demonstrating anti-inflammatory properties, including transitions. According to some research, 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 can suppress inflammation in vivo by increasing M2 polarization of macrophages, resulting in improved survival compared to using chondrocytes as germ cells. However, regarding the immunosuppressive features of mesenchymal stem cells, Observations for chondrogenic cells have been published with disagreement (38).

A study on MSC-mediated cartilage injury repair showed that the secretion of exosomes by her MSCs to increase tissue regeneration was also implicated in regulating the immunological reaction.

٢٢٥ Macrophages have a great degree of flexibility and perform important functions in innate
٢٢٦ immunity. Similar behaviors are shared by resident macrophages such as CD11b, CD14, CD16,
٢٢٧ and CD68 (39), as well as synovial macrophages. Additionally, they showed that macrophages
٢٢٨ and mesenchymal stem cells are geographically closer to one another in normal and pre-OA knees
٢٢٩ than in OA patients and that synovial macrophages are reduced in pre-OA joints compared to
٢٣٠ normal knees (40). It has also been demonstrated that synovial M1 macrophages increase the
٢٣١ production of proteolytic enzymes that cause articular degeneration, including MMP3, matrix
٢٣٢ metalloproteinase-1, MMP9 aggrecanase, cyclooxygenase-2, and MMP13 (41). It was shown that
٢٣٣ the chondrogenesis of MSCs was adversely impacted by monocyte-derived pro-inflammatory and
٢٣٤ synovial macrophages (Figure 4) (42).



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٢٣٦ **Figure 4.** macrophage pathways that are pro-chondrogenic and pro-inflammatory in cartilage damage and
٢٣٧ healing.

٢٣٨ **3. 4. MSCs and GvHD**

Barnes, Loutit, and Micklem were the first to report GVHD, and Billingham established the basic definition as a condition in which immunocompetent donor cells detect and assault host tissues in immunocompromised allogeneic receivers. Chronic GVHD has many fibrotic and autoimmune traits, but acute GVHD contains a high amount of inflammatory elements (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 topic of fundamental study and are a target for several possible therapeutic applications. These cells have strong immunosuppressive qualities that are discernible both in vitro and in vivo, which is one of their most notable traits. These results served as the foundation for the therapeutic use of MSC to treat GVHD. In 2004, the primary successful instance of severe steroid-resistant GVHD treated with mesenchymal stem cells was announced (17).

183 patients were treated in total over fourteen publications, with response rates ranging from 0 to 100 percent and estimates related to the first impact and overall survival (OS). In conclusion, the data on the clinical efficacy of MSC infusion for aGVHD is encouraging although inconsistent and unproven.

MSCs are a very promising treatment for aGVHD due to their immunosuppressive function. However, the therapeutic effects are not always achieved (44).

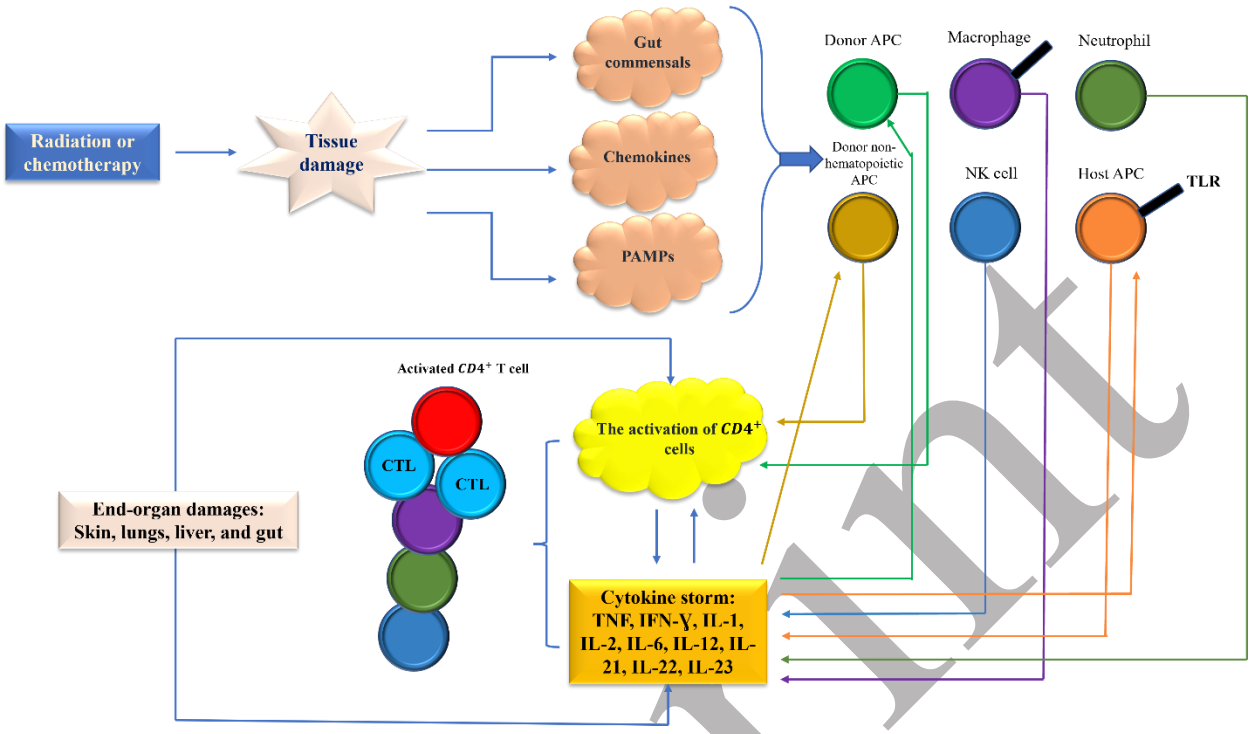

Figure 5. The whole GVHD acute cascade. The initiation and maintenance of acute graft-versus-host disease (GVHD) have been characterized as having four phases, each of which contains a positive feedback loop that keeps the process going.

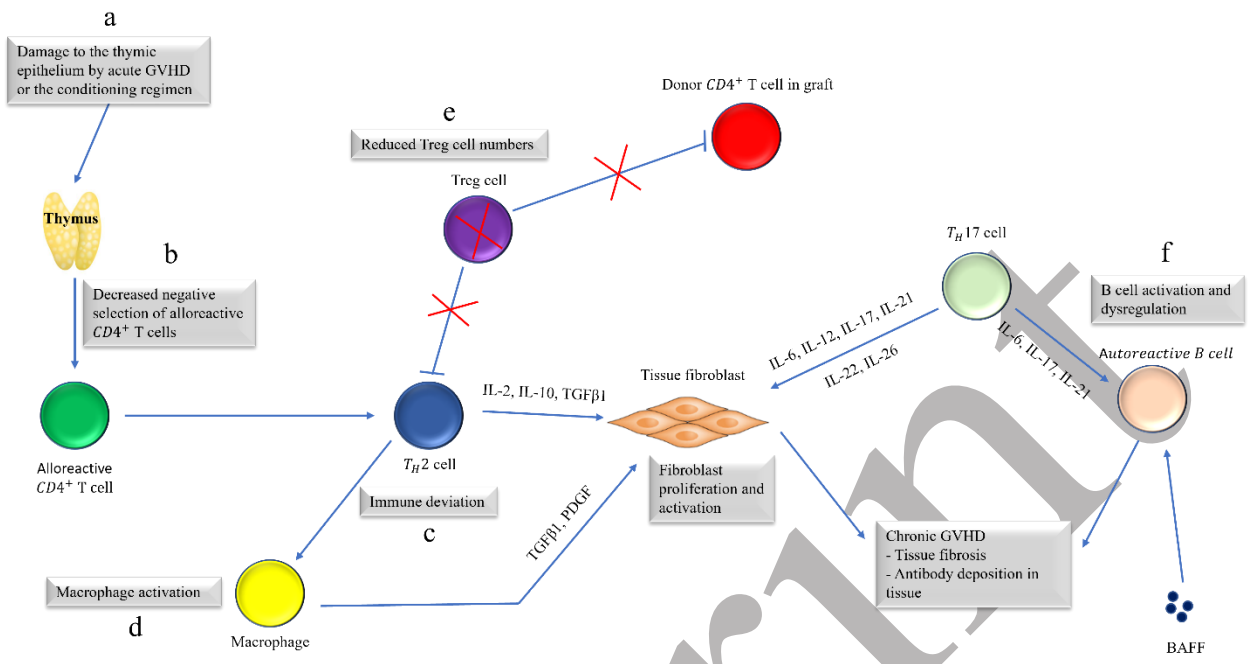

Figure 6. key factors in the development of chronic GVHD. Six characteristics are specific to this illness, although the pathogenesis of chronic GVHD mostly relies on the polarization of CD4+ T cells into TH2 cells.

The weakened graft-versus leukemia impact is the main issue with the usage of MSCs. The stimulation of regulatory cells and immunosuppression brought on by MSCs is a significant problem for patients with hematologic malignancies. MSCs support the tumor microenvironment, which promotes tumor development, as demonstrated by some preclinical studies (45).

MSCs decreased the development of GVHD in a clinical trial utilizing patients with hematologic malignancies to avoid GVHD, however, the recurrence rate among patients was greater than that of the control group (46).

Compared to 3 of 15 patients in the non-MSC group, 6 of 10 patients in the MSC group had tumor recurrence. The much greater risk of relapse in the MSC group may indicate that the GVL effect is lessened by the infusion of MSCs, although this study's sample size is too tiny to make any clear

conclusions. On the other hand, a clinical experiment also demonstrates that the administration of MSCs can stop GVHD without removing the consequences of GVL. Before nonmyeloablative HSCT , MSCs were implanted in patients with hematologic malignancies in this trial while the graft rejection and aGVHD incidence rates were decreased by MSCs, the relapse rate remained comparable to the previous group that did not receive MSCs (47).

3.5. Immunoregulatory effects of MSCs in TE

The liver, heart, and skeletal systems have extensively used stem cell-integrated tissue engineering. The use of stem cell tissue engineering in orthopedic systems for connective tissue like meniscus and cartilage still has a lot of potential for progress(48, 49).

In the progression of TE, the immunomodulatory properties of stem cells are very significant. IL-1 and other pro-inflammatory cytokines that are elevated in the synovial fluid of joints in OA play a role in the progression of arthritis. The adaptive and innate immunological reactions are together impacted by MSCs' capacity to modify the immune system. The lymphocyte-dominated adaptive immune response has a substantial impact on how quickly fractures repair (50).

3.6. Bladder

Currently, tissues to replace or recreate the bladder are frequently made from parts of the gastrointestinal tract. However, Stomach tissues are designed for the absorption of certain solutes, although bladder tissue is designed for the expulsion of solutes. Numerous researchers have tried using different substances and tissues for regenerating and replacing because of the limitations of using digestive system segments.

Utilizing donor tissue effectively and creating the ideal circumstances for long-term survival, differentiation, and development are essential to the success of cell transplantation procedures used

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 sample, urothelial and muscle cells were independently grown 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 alone or in combination with cells in tissue engineering for biomedical purposes. Hydrogels can be made from natural, synthetic, or a combination of these polymers. In cartilage tissue engineering, cartilage ECM-derived biomaterials are often used to foster chondrocyte and MSC regeneration. The primary components of the cartilage extracellular matrix are HA, chondroitin sulfate (CS), and collagen (53). Other natural polymers that are commonly employed include gelatin, alginate, and chitosan. Most naturally generated polymers, on the other hand, are mechanically weak and degrade quickly. As a result, biodegradable and biocompatible synthetic polymers including poly (ethylene glycol) (PEG), polyvinyl alcohol (PVA), and poly (DL-lactic-co-glycolic acid) (PLGA) are widely employed in cartilage tissue engineering (54).

3.8. Bone

MSC modulation is a different method to influence immune cells for bone tissue engineering, taking into account that MSCs are typically utilized as repair cells for bone tissue engineering. Typically, scaffolds are seeded with MSCs before being implanted in bone defects for bone repair. According to research by Seebach et al., cultured MSCs encourage the recruitment of M1

macrophages and endothelial progenitor cells to scaffolds, enabling early maturation and vascularization (55).

Ueno et al. created scaffolds for serious bone defects using lentivirus-transduced MSCs that overexpress IL-4. They showed that modified MSCs embedded in scaffolds could encourage M2 polarization of macrophages while having no effect on M1 activity in the initial stages of inflammation. Scaffolds produced by IL-4 can stimulate bone regrowth, suggesting that using scaffolds loaded with modified MSCs may be a promising tactic (56). Thus, choosing of MSCs may be a future 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. According to Liu et al., the systemic infusion of MSCs can upregulate Tregs while downregulating inflammatory cytokines (IFN- and TNF-) at implantation sites. This method can also 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 marrow is in the spotlight for future technological advancements in tissue engineering since it is the only organ with at least two different types of stem cells (SSCs and HSCs) and the organ that contains the progenitors for many other distant tissues. Recent research suggests that the conventional barrier dividing the mesodermal and hematopoietic tissue systems and lineages is disintegrating. The marrow contains cells that may regenerate cardiac muscle, skeletal muscle, and blood vessels.

It has been suggested that both MSCs and HSCs in the bone marrow are responsible for the surprising capacity for myogenesis and cardiomyogenesis. What we have called the HSC may be

considerably more than that a true multipotent stem cell with transdermal potentials that are often committed to Hematopoiesis as a result of local signals. The benefit of conveniently harvesting and cultivating marrow cells from an adult individual is that the HSC can be separated and get purified in vitro.

These investigations shed light on how the tissue engineering landscape could change relatively soon. The occurrence of pleiotropic and heterotopic stem cells in the bone marrow has clear consequences for daily life for the future of stem cell treatment that should not be overlooked, aside from theoretical considerations and, when necessary, further experimental evidence.

5. Conclusion

Almost all types of organs and tissues in the human body are now being worked on using tissue engineering techniques. Personnel with expertise in cell culture transplantation, expansion, polymer design, and harvest is necessary for this technology to be effectively used since tissue engineering combined the domains of engineering, materials science, and cell transplantation. Engineered tissues are being developed at various phases, with some currently being used clinically, others in preclinical research, and some in the discovery phase. Recent developments show that synthetic tissues may eventually have a broader range of clinical applications since they offer a promising therapeutic alternative for patients who need tissue replacement. According to the topic that is mentioned above, it’s obvious that nowadays technology is improving in every field of study and occupation especially when we talk about biology. Tissue engineering is one of the fields which is distinguished and popular that is becoming worldwide. This review represents that tissue engineering would become one and the most useful way to cure untreatable tissue injuries which can change the world of biology and science simultaneously.

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Authors' Contribution

Study concept and design: Abdolmaleki A. and Asadollah A.

Acquisition of data: Basharzad Seddigh H. and Nahumi A.

Analysis and interpretation of data: Abdolmaleki A., Asadollah A. and Nahumi A.

Drafting of the manuscript: Ashique S., Abdolmaleki A., Asadollah A. and Nahumi A

Critical revision of the manuscript for important intellectual content: Yazdannasab N.

Ethics

We hereby declare all ethical standards have been respected in preparation of the submitted article.

Conflict of Interest

The authors declare no conflict of interest in this research.

Data Availability

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

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