

## Mesenchymal Stem Cell-Based Therapy for Rheumatoid Arthritis – A Review

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### Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent synovial inflammation, progressive joint destruction, and immune dysregulation. Although conventional disease-modifying antirheumatic drugs (DMARDs) and biological agents have improved disease management, treatment resistance, adverse effects, and inadequate therapeutic responses remain significant challenges. Mesenchymal stromal cells (MSCs) have emerged as a promising therapeutic approach owing to their immunomodulatory, anti-inflammatory, and tissue-regenerative properties. This review discusses the immunopathogenesis of RA, focusing on the roles of B lymphocytes, T lymphocytes, autoantibodies, and pro-inflammatory cytokines in disease progression. It highlights the mechanisms through which MSCs regulate immune responses by promoting regulatory T cells (Tregs), suppressing T-helper 17 (Th17) cell responses, modulating macrophage polarization, and potentially reducing osteoclast-mediated bone destruction. The therapeutic potential of MSCs derived from different tissue sources and the emerging role of MSC-derived extracellular vesicles as cell-free therapeutic alternatives are also examined. Furthermore, current clinical evidence, translational challenges, and future research directions are explored. Preliminary clinical findings suggest potential benefits of MSC-based therapies in patients with refractory RA; however, evidence remains limited by small study populations, heterogeneous cell preparations, and insufficient long-term safety and efficacy data. Standardized manufacturing protocols, reliable potency assays, biomarker-guided patient selection, and well-designed randomized controlled trials are essential to establish their clinical utility. MSC-based therapies represent a promising investigational strategy for RA, but further research is required before their routine clinical application.

**Keywords:** Rheumatoid arthritis; mesenchymal stromal cells; immunomodulation; T lymphocytes; B lymphocytes; extracellular vesicles.

### Introduction

Rheumatoid arthritis is an autoimmune disease, that affects the bone joints, muscles and connective tissue. Approximately over 5 people for every 1000 were affecting worldwide with the age of above 55 years. The disease is most common in female than in male. However, the exact pathogenesis of disease is still unclear (1). The disease onset phase is known as pre – RA phase, which lasts for years before discovering the clinical symptoms. The presence of auto-antibodies, inflammatory cytokines and altered cell metabolism were known to circulate at the early stages of infection, the chronic inflammation is characterized with severe pain in joints that changes the patient's quality of life. The insufficient care may eventually cause joint erosion, deformities, and destruction. Over 50% of RA patients had led to disabilities and moreover had a higher risk of dying. It is essential to know the better understanding of disease pathogenesis, advancements in the treatment of RA and the effectiveness in the patient's quality of life (1).

Currently, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids and Disease modifying anti-rheumatic drugs (DMARDs) are used frequently as they have anti-inflammatory activity, reduction in pain and moreover reduces the symptoms, although these drugs reduce the inflammatory action, they also develop severe side effects and high costs (2).

### Immunology of RA

Instabilities in the inflammatory process are the hallmark of autoimmune disorders, and if required treatment is neglected, the affected bones or joints becomes dysfunctional. Joint structural problems and an imbalanced catabolic and anabolic metabolic process are linked to changes in the joint during the RA phase. These severe biochemical alterations linked to inflammatory synovitis in RA have the effect of inhibiting the joint's natural remodelling of its structures. The existence of autoantibodies prior to the disease's actual presentation is a characteristic of RA disease (3).

The presence of anti-CCP indicates the formation of immune complexes in the affected joints. During the course of RA, innate and adaptive immunity changes in the subsets of T-lymphocytes, monocytes and macrophages. In the same time of its manifestation of RA, T-reg cells gets decreased, the activation of inflamed cells increased leads to acute infection, which also stimulates the secretion of cytokines leading to chronic infection. The disease may extend as systemic infection due to the presence of pro-inflammatory cytokines IL-6 and TNF- $\alpha$  are present at the site of infection (4). The Peptidyl arginine deiminase (PADI) triggers the post translational modification process of converting arginine or glycine residues of normal proteins into citrullinated protein, that decreases the immunological tolerance in patients. These CCPs were produced by Neutrophil extracellular traps (NET) and CCP has high affinity towards the antigen binding site of human leukocyte antigen (HLA)-DR. The NET produced CCP also internalised through the Toll-like receptor 9 (TLR9) pathway, which upregulates the MHC class II expression. The increased production of NET and upregulation of MHC class II leads to inflammation of synoviocytes. The anti CCP is not only act as a biomarker for RA, but also plays a significant role in hastening inflammatory response in joints (5). The role of B cell and T cells produced by immune system plays a major role in pathogenesis of RA by kindling the inflammation on the joints. The cells may either present in synovial fluid or in peripheral blood. The proteins such as Rheumatoid factors (RF), Anti-CCP and pro-inflammatory cytokines were the inducing agents for RA produced by B cells. Simultaneously, T cells were mediated and activated by costimulatory molecules such as cytokines and chemokines of B cells. Here the main purpose of T cells is to stimulate macrophages and fibroblasts to form tissue destructive cells (Figure 1) (6) (7).

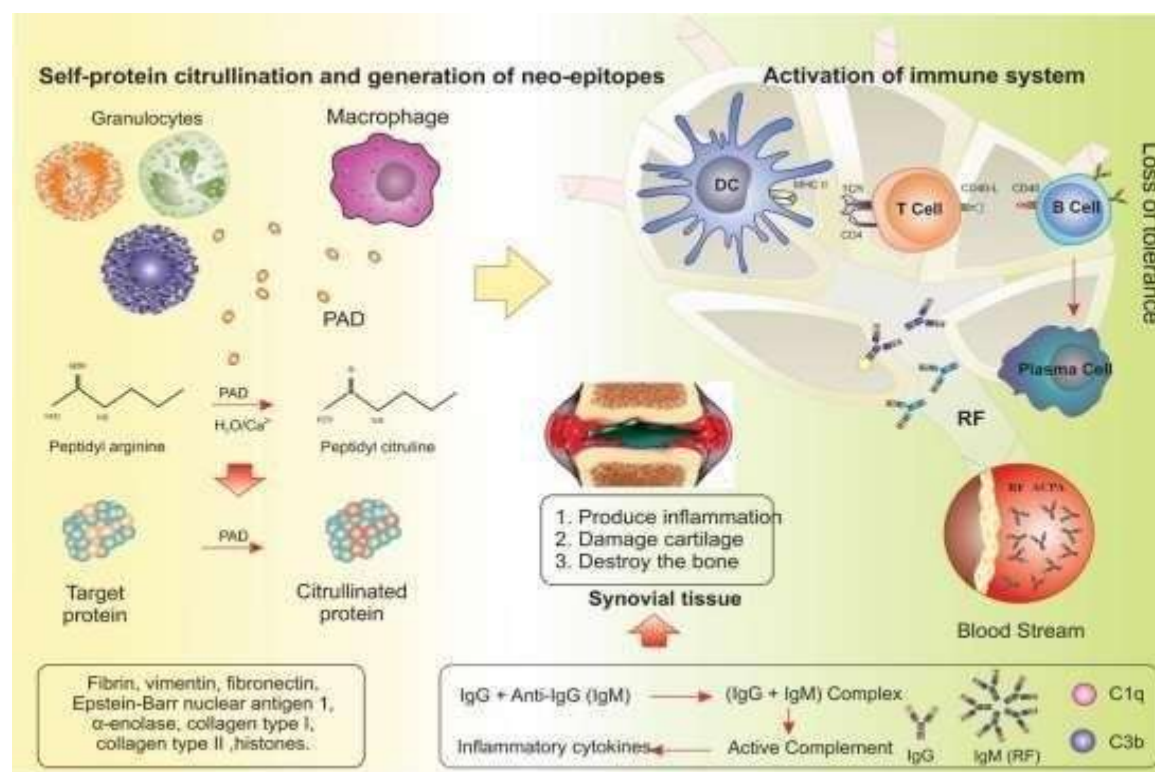


**Figure 1:** Immunology of Rheumatoid arthritis: Pathogenesis of rheumatoid arthritis: PAD-mediated citrullination generates neo-epitopes, triggering loss of immune tolerance, autoantibody production, complement activation, and inflammatory cytokine release, leading to synovial inflammation and bone destruction. (Courtesy: Babamadhi M et al., 2023)

### Role of B – Lymphocytes

The synovial tissue is also known as tertiary Lymphoid tissue (TLTs), similar to the structure of Secondary lymphoid tissue, which is correlated with the severity of inflammation based on its autoantibody titres and the presence of inflammatory cytokines (LT $\alpha$ , LT $\beta$ , CXCL13, CCL20, CCL21, and CXCL12). These cytokines especially LT $\alpha$  and LT $\beta$  were responsible for the infiltration of B cells and T cell aggregation. The TLTs also sustenance for

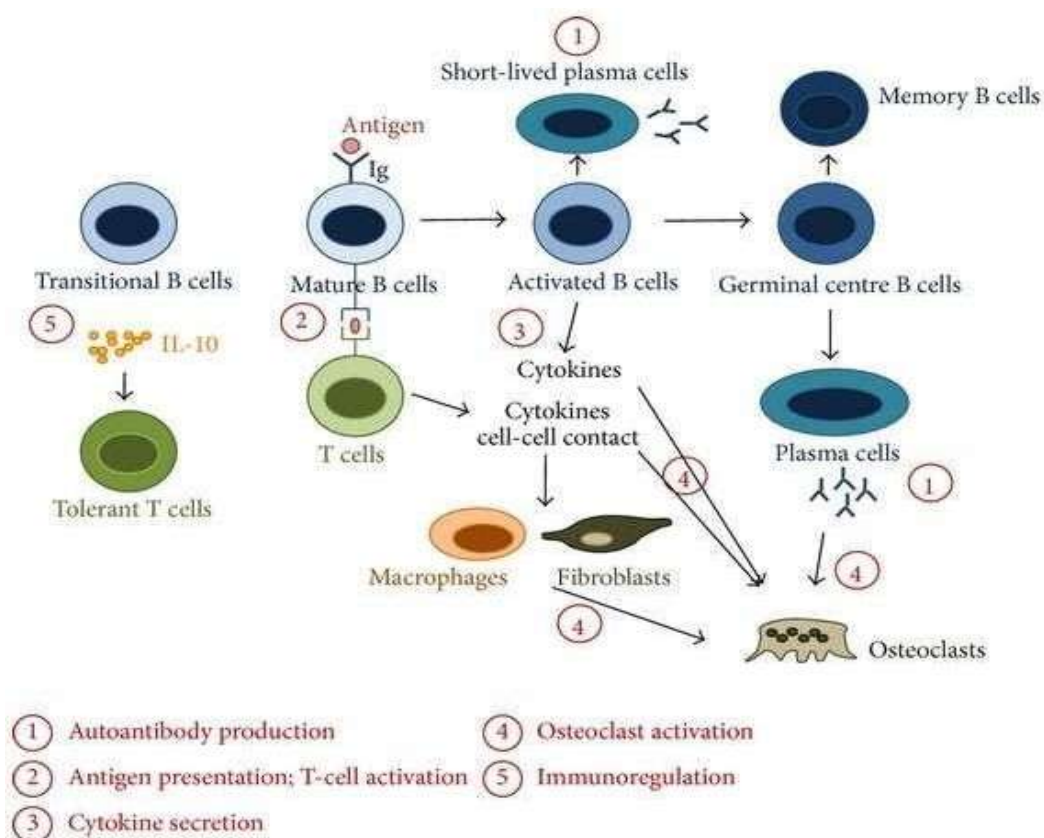


**Figure 2. Multiple roles of B cells (9).** Effector functions and differentiation pathways of B-cell subsets. Schematic representation of B-cell lineage progression and its downstream immunomodulatory and osteoclastic effects.

antigen presentation of B cell, that promotes the interaction with T- cells which leads to B cell differentiation in the affected synovial membrane. The action of the B cells also promotes the production of Anti-CCP and RA factor (8)(9). The interaction between B cell and T cell interactions were responsible for the activation and differentiation of plasma cells and its production of antibodies. The activated B cells, induce T cells to produce proinflammatory cytokines and cytokines such as interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)- $\alpha$ , and IL-17A. Activation of B cells and T cells with the help of proinflammatory cytokines and receptor activator of nuclear factor  $\kappa$ B ligand (RANKL) induces the osteoclast formation (Figure 2) (9).

### Role of T lymphocytes

The pathogenesis of RA involves the T cell activation is based on the MHC class I (CD8) and MHC class II (CD4) along with helper T cells, resulting in local inflammation. The mechanism of action also includes the environmental, genetic factor and dysregulation of immune system (11).

### Pre RA – T cells

Firstly, B cells produce IgA antibodies triggered by T cells, elevated anti CCP and RA factor are the detectable hallmark for the pre-RA disease that indicates the loss of immune tolerance which is may be an asymptomatic. Different types of T cell subsets were involved in early RA that includes CD4 T cells, Th cells and CD8 T cells (Figure 3) (10).

### CD4 T cells

CD4 T lymphocytes produce different types of T follicular helper cells and Th1, Th2 and Th17 cells, the function of these cells is to produce cytokines especially Th1 induce TNF, IFN- $\gamma$  and IL-2 which leads to bone destruction and erosion. Likewise, Th2 cell induces the production of IL-4 and IL-13 that enhances the resistance to bone resorption and osteoclasts (Figure 3) (10).

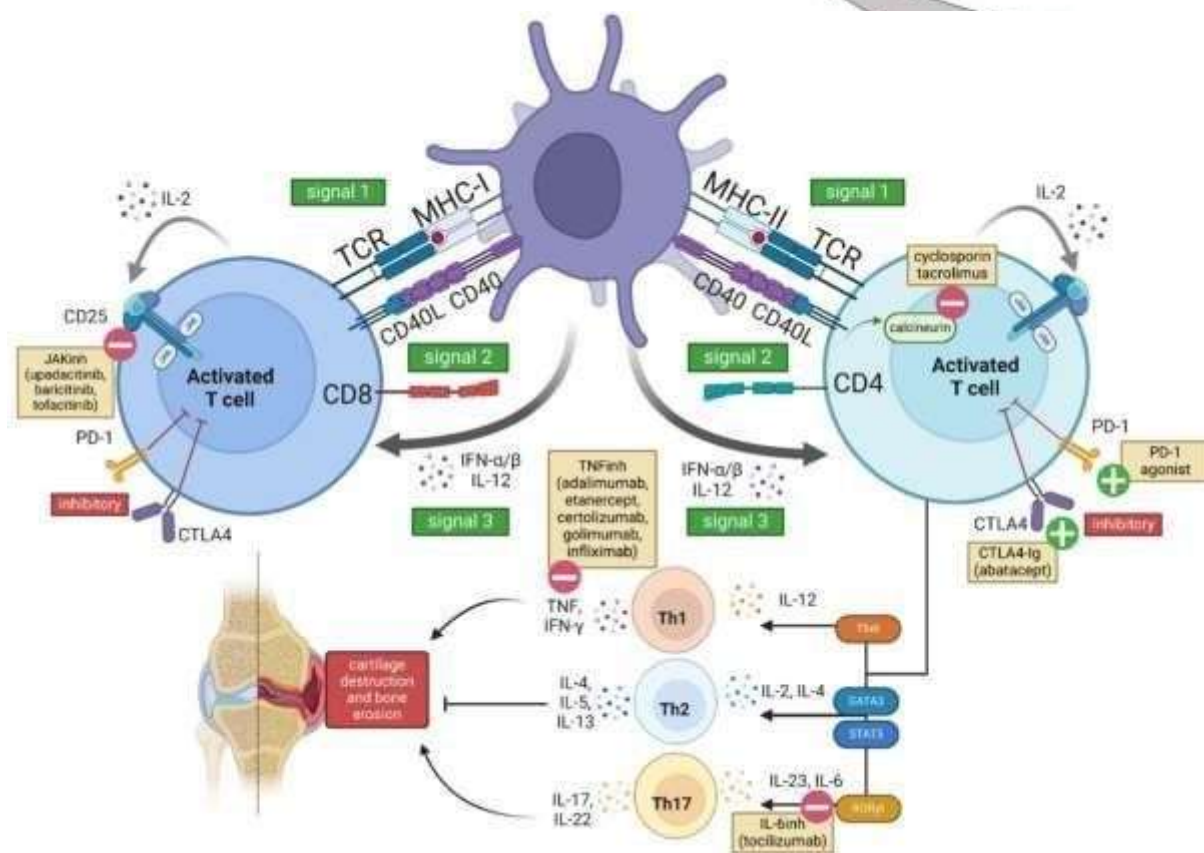


**Figure 3: Role of T lymphocytes (10).** T-cell activation, differentiation, and therapeutic targets in joint pathology. T-cell activation involves MHC/TCR recognition, co-stimulation, and cytokine-mediated polarization. CD4+ T cells differentiate into Th1, Th2, and Th17 subsets, regulated by T-bet, GATA3/STAT5, and RORγt, respectively. Th1/Th17 cytokines promote joint inflammation and destruction, whereas therapeutic targeting of JAK, calcineurin, CTLA4, IL-6, and TNF pathways can suppress pathogenic T-cell responses.

### CD8 T cells

The link between MHC class I alleles and rheumatoid arthritis shows the significant role of CD8 T cells. In Anti CCP-positive patients, CD8<sup>+</sup> T cells recognizing citrullinated antigens that shows the clonal expansion of cells expressing the genes such as GZMK and GZMB, that are particularly enriched in the synovial tissue of RA patients (11).

### Current therapies

The main target of therapy is to reduce the rate of disease progression by decreasing inflammation. The current drugs used in the treatment are Glucocorticoids (GCs), Disease modifying anti-rheumatic drugs (DMARDs), and non-steroidal anti-inflammatory drugs (NSAIDs). The combination of these drugs were also used to reduce the pain and to increase the anti-inflammatory effects (1). Methotrexate (MTX) a synthetic DMARD with anti-proliferative effect, that inhibits amino acid synthesis and platelet apoptosis. While in clinical practice as monotherapy, it is observed that there is an impairment in bone marrow pulmonological and haematological side effects. Patients with severe or moderate infections can also be treated with combination therapy of methotrexate with sulfasalazine and hydroxychloroquine (1)(12). To overcome the severity of disease progression, Methotrexate can be administered with the combination of Glucocorticoids (GCs). The effect of GCs includes apoptosis of immature CD4 and CD8 cells and Dendritic cells to tolerogenic state of DCs. Moreover, the GCs exhibit more side effects than any other drugs such as weight gain, cushingoid features, parchment-like skin, leg oedema, sleep disturbance and immunosuppression (13).

About 30-50% of population develop resistant to drugs that are exposed for years, hence the biologic DMARDs such as etanercept, infliximab and adalimumab can be added such as TNF inhibitors, IL-6 inhibitors and B-cell depleting drugs (1).

These TNF inhibitors block cytokine signalling, decrease the IL-6 expression leads to slow bone destruction. Though these drugs also exhibit severe side effects such as neurologic disorder and lymphoma (14). Similarly, NSAIDs can be divided into 2 groups based on their chemical structure and selectivity such as non-selective NSAID that inhibits Cyclooxygenase-1 (COX-1) and COX-2 and selective COX-2 inhibitor. Some of NSAIDs were ibuprofen, naproxen and etodolac. The effect of these drugs was comparatively lower than DMARDs and GCs. Although they also have some side effects like nausea, abdominal pain and gastric ulcers (15).

### Mesenchymal stem cells therapy

Mesenchymal stem cells are fibroblast-like structures with immunomodulatory effect. The differentiation of these MSCs were based on their origin of tissue sites such as bone marrow (BM), gingiva, synovium, periosteum, adipose tissue (AT), dental pulp, umbilical cord (UC) and umbilical cord blood (UCB). Different types of MSCs were osteoblasts, chondrocytes and adipocytes (Figure 4) (2). MSCs also possesses low immunogenicity, anti-inflammatory, pro-angiogenic and anti-apoptotic properties (16).

Sources of MSCs were isolated from stroma of various tissues such as bone marrow and mostly in the subcutaneous fat of any preferred tissues. To identify the preferred MSC therapies, a committee named the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy established in 2006 the minimal identifying characteristics for human MSCs is formed to follow some criteria i.e (a) plastic-adherent cells when maintained in standard culture conditions; (b) expression of CD105, CD73 and CD90, and lack expression of CD45, CD34, CD14 or CD11b, CD79a or CD19 and HLA-DR surface molecules and (c) capacity to differentiate into osteoblasts, adipocytes and chondroblasts in vitro (17).

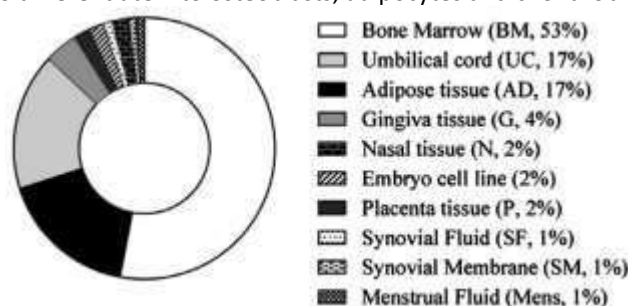


**Figure 4. Various sources of MSCs based on the previously reported clinical studies (2).**

Bone marrow was the predominant source (53%), followed by umbilical cord and adipose tissue (17% each). Other sources contributed smaller proportions, including gingiva (4%), nasal tissue, embryo cell lines, and placenta (2% each), while synovial fluid, synovial membrane, and menstrual fluid each accounted for 1%.

Mesenchymal stem cells produce extracellular vesicles (EVs) contains and releases various tropical molecules that promotes tissue repair or regeneration, that decreases the cytotoxic activity by NK cells and develops the antigen presenting cells (APC) thereby inhibits the innate immunity. They also suppress the Th cells to inhibit the proliferation and induces the Tregs (16). MSCs also have the ability to inhibit the proliferation of memory T cells to cease the production of proinflammatory cytokines. This mechanism was driven by the COX-2 inhibitor released from MSCs (1). Generally, MSCs have the ability to adopt either modulating innate or acquired immunity by increasing the pro-inflammatory cytokines and decreasing the production of NK cells, B cells and T cells. Depending on the pathogenesis of RA, the MSCs can undergo either pro-inflammatory (MSC 1) or anti-inflammatory effect (MSC 2) (2). MSCs has the property to suppress the immune response by regulating the immunomodulatory effect by inducing the macrophage transition and by inhibiting the T cell activation and proliferation. MSC migrates to the damaged region and induces their therapeutic effect by angiogenesis and immunoregulation. The high levels of cytokines in RA induces various other cytokines such as hepatocyte growth factor (HGF) and transforming growth factor-beta (TGF- $\beta$ ), soluble factors like PGE2, indoleamine-2,3-dioxygenase (IDO), and nitric oxide (NO) that exerts their therapeutic action by inhibiting the effector T cells and boost Tregs (18).

MSCs polarises the macrophages, based on its function macrophages can be distinguished into M1 and M2. M1 macrophage produces pro-inflammatory cytokines that stimulates the osteoclast and bone deterioration, whereas, the M2 macrophage produces anti-inflammatory molecules which produces Tregs and stimulate the COX-2 and modifies the phenotype of secretory EVs (19). Additionally, MSCs have the capacity to regenerate into various types of cells that possess anti-fibrotic activity, enhance angiogenesis and tissue regeneration activity. Since the MSCs have the capacity to develop multipotency that differentiate into several types of tissues such as In vitro, chondrogenic tissue differentiation of MSCs by cultivating them in the presence of TGF- $\beta$ 1 or TGF- $\beta$ 3, insulin-like growth factor-1 (IGF-1), fibroblast growth factor 2 (FGF-2), or bone morphogenetic protein 2 (BMP-2) (19). MSCs can undergo osteogenic differentiation when stimulated by vitamin D3,  $\beta$ -glycerophosphate, ascorbic acid, and bone morphogenetic proteins such as BMP-2, BMP-4, BMP-6, and BMP-7.

### Role of MSC in RA

Mesenchymal stem cells (MSCs) can interact with various immune cells—such as dendritic cells (DCs), T and B lymphocytes, and natural killer (NK) cells—to regulate cytokine release, their use in RA therapy is considered a promising approach, as they can modulate the pathological processes underlying this autoimmune condition. Beyond tissue repair, MSCs perform several vital functions, including modulation of the microenvironment, activation of resident progenitor cells through cell-to-cell interactions, and secretion of bioactive molecules. The cytokines and growth factors produced by MSCs play a key role in tissue regeneration and reconstruction. Owing to these properties, MSCs have emerged as a potential therapeutic option for RA (20) (Figure 5).

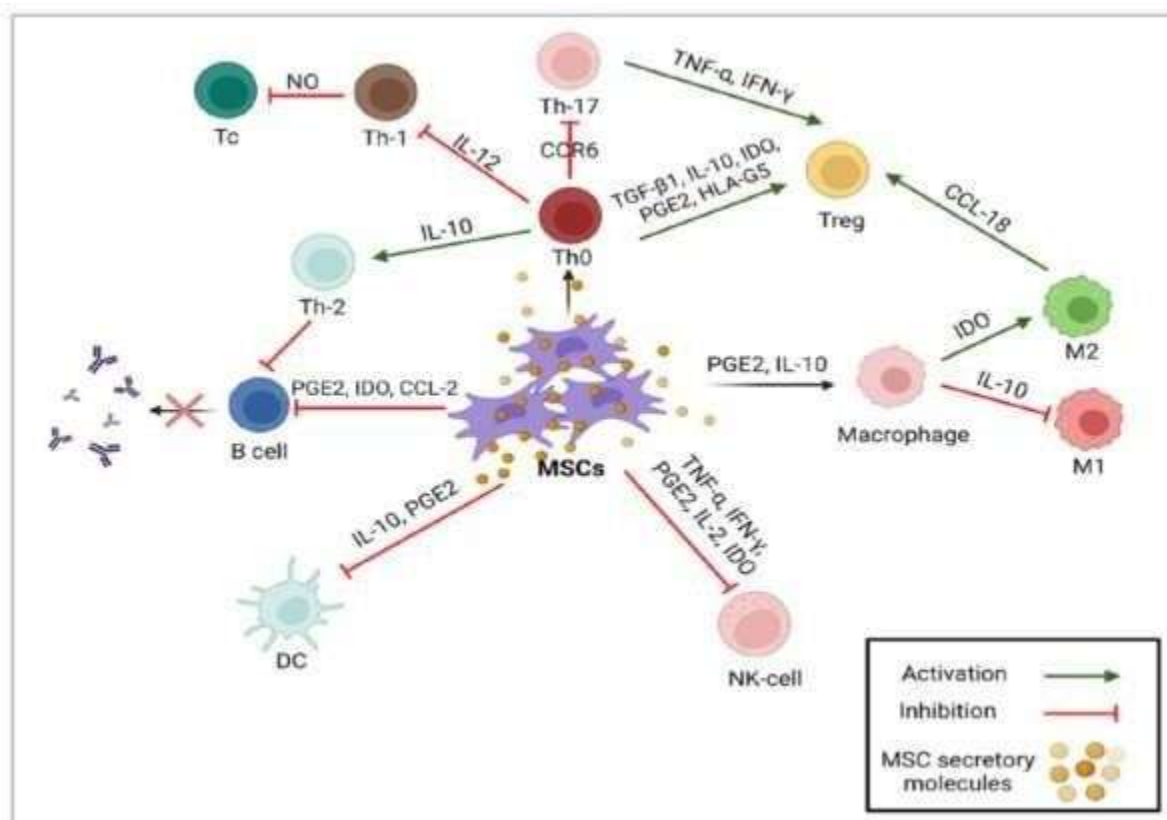


**Figure 5: Role of MSCs in RA.** Immunomodulatory mechanisms of mesenchymal stem cells (MSCs). MSCs modulate T-cell polarization, promoting Th2/Treg while suppressing Th1/Th17 responses. They promote anti-inflammatory M2 macrophage polarization and suppress B-cell and dendritic-cell activity. MSC-derived factors also inhibit NK-cell activation, collectively reducing immune-mediated inflammation.

## MSC-mediated immunomodulation in the RA microenvironment

The therapeutic potential of mesenchymal stromal cells (MSCs) in rheumatoid arthritis (RA) is primarily attributed to their ability to restore immune homeostasis within the inflammatory synovial microenvironment. In response to inflammatory signals, including interferon- $\gamma$  (IFN- $\gamma$ ), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interleukin-1 $\beta$  (IL-1 $\beta$ ), MSCs exert immunoregulatory effects through the secretion of soluble mediators such as prostaglandin E2 (PGE2), indoleamine-2,3-dioxygenase (IDO), nitric oxide (NO), transforming growth factor- $\beta$  (TGF- $\beta$ ), hepatocyte growth factor (HGF), and tumor necrosis factor-stimulated gene-6 (TSG-6). In RA, these immunoregulatory actions may help correct key pathogenic immune disturbances, particularly the imbalance between pro-inflammatory Th17 cells and regulatory T cells (Tregs), as well as the predominance of pro-inflammatory M1 macrophages. By promoting regulatory immune phenotypes and limiting excessive inflammatory responses, MSCs may reduce synovial inflammation and the production of inflammatory mediators involved in joint damage. Consequently, MSC-mediated immunomodulation may indirectly limit RANKL-associated osteoclast activation and contribute to the protection of cartilage and bone. (Table 1) (21, 22).

| Pathway Category                              | Specific Factors Involved                                                                                                                                                     | Effect / Action of MSCs                                            | Functional Outcome                                          |
|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|-------------------------------------------------------------|
| Anti-Inflammatory & Immunosuppressive Factors | <ul style="list-style-type: none"> <li>• IL-10</li> <li>• TGF-<math>\beta</math></li> <li>• IDO</li> <li>• PGE<sub>2</sub></li> <li>• TSG-6</li> <li>• HGF</li> </ul>         | Upregulated / Secreted by MSCs into the synovial microenvironment. | Suppresses the overactive immune response in the joint.     |
| Pro-Inflammatory & Bone-Destructive Factors   | <ul style="list-style-type: none"> <li>• TNF-<math>\alpha</math></li> <li>• IFN-<math>\gamma</math></li> <li>• IL-17</li> <li>• NO (Nitric Oxide)</li> <li>• RANKL</li> </ul> | Downregulated / Inhibited by MSC actions.                          | Halts joint inflammation and tissue destruction.            |
| Cellular Regulation                           | <ul style="list-style-type: none"> <li>• Tregs (Regulatory T cells)</li> </ul>                                                                                                | Promoted / Increased by MSCs.                                      | Restores immune tolerance in the synovial microenvironment. |

**Table 1:** MSC-mediated immunomodulation in the rheumatoid arthritis microenvironment. In response to inflammatory cytokines (IFN- $\gamma$ , TNF- $\alpha$ , and IL-1 $\beta$ ), MSCs release immunoregulatory mediators that promote Treg responses and suppress Th17 cells and macrophage activation, potentially reducing inflammation, osteoclastogenesis, and joint tissue damage. **Abbreviations:** MSCs, mesenchymal stromal cells; RA, rheumatoid arthritis; IFN- $\gamma$ , interferon- $\gamma$ ; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; IL-1 $\beta$ , interleukin-1 $\beta$ ; PGE2, prostaglandin E2; IDO, indoleamine-2,3-dioxygenase; NO, nitric oxide; TGF- $\beta$ , transforming growth factor- $\beta$ ; HGF, hepatocyte growth factor; TSG-6, tumor necrosis factor-stimulated gene-6; Th17, T helper 17 cells; Tregs, regulatory T cells.

## Clinical evidence of MSC therapy in rheumatoid arthritis

Clinical evaluation of MSC-based therapy in rheumatoid arthritis (RA) remains limited, with available evidence derived mainly from small early-phase clinical studies. Initial human investigations of autologous bone marrow-derived MSCs in patients with refractory RA reported reductions in disease activity and clinical symptoms following intravenous administration, suggesting potential therapeutic benefit in patients with inadequate responses to conventional treatment. More recent studies evaluating allogeneic bone marrow-derived clonal MSCs have similarly reported acceptable short-term tolerability, with preliminary improvements in pain, disease-related symptoms, and quality-of-life measures. However, these findings remain difficult to interpret because of the small sample sizes and substantial heterogeneity among studies, including differences in MSC source, cell dose, manufacturing procedures, administration route, concomitant antirheumatic medications, and patient populations. Importantly, the durability of clinical responses and long-term safety of MSC therapy in RA remain insufficiently established. Thus, although early clinical findings support the feasibility and potential therapeutic

value of MSC-based interventions, current evidence is not yet sufficient to support their routine use in RA. Well-designed randomized controlled trials using standardized MSC preparations, clinically meaningful predefined endpoints, appropriate comparator groups, and long-term follow-up are needed to establish their efficacy, safety, and therapeutic position in RA management (23–25).

### Translational challenges and future directions

Despite encouraging clinical findings, several translational barriers continue to limit the development of MSC-based therapy for RA. A major challenge is the biological and manufacturing heterogeneity of MSC products, as their functional properties can be influenced by tissue source, donor characteristics, culture conditions, passage history, and cryopreservation. Establishing clinically meaningful potency assays and reproducible manufacturing protocols is therefore essential for ensuring consistency between batches and across clinical studies. In addition, better understanding of the determinants of MSC persistence and therapeutic activity in the inflamed joint may help explain interindividual variability and facilitate patient selection. An emerging approach is the development of MSC-derived extracellular vesicles (MSC-EVs) as cell-free therapeutic agents. MSC-EVs contain bioactive proteins, lipids, and regulatory RNAs and may retain important therapeutic properties of MSCs while potentially reducing some of the practical limitations associated with administration of living cells. Their relatively defined biological composition also creates opportunities for improved characterization, storage, quality control, and therapeutic engineering. However, MSC-EV research remains predominantly preclinical, and substantial challenges related to isolation, characterization, dosing, potency assessment, and large-scale GMP-compatible production must be resolved before clinical translation. Future research should therefore prioritize standardized manufacturing and quality-control frameworks, validated potency measures, biomarker-guided patient selection, and rigorous evaluation of treatment durability and safety. Optimization of MSC priming or engineering and investigation of MSC-EVs, particularly in combination with established disease-modifying antirheumatic drugs (DMARDs), may further improve therapeutic precision. Collectively, these approaches could facilitate the development of more reproducible and clinically applicable cell-based and cell-free therapies for patients with refractory RA. (Figure 6) (26–28).

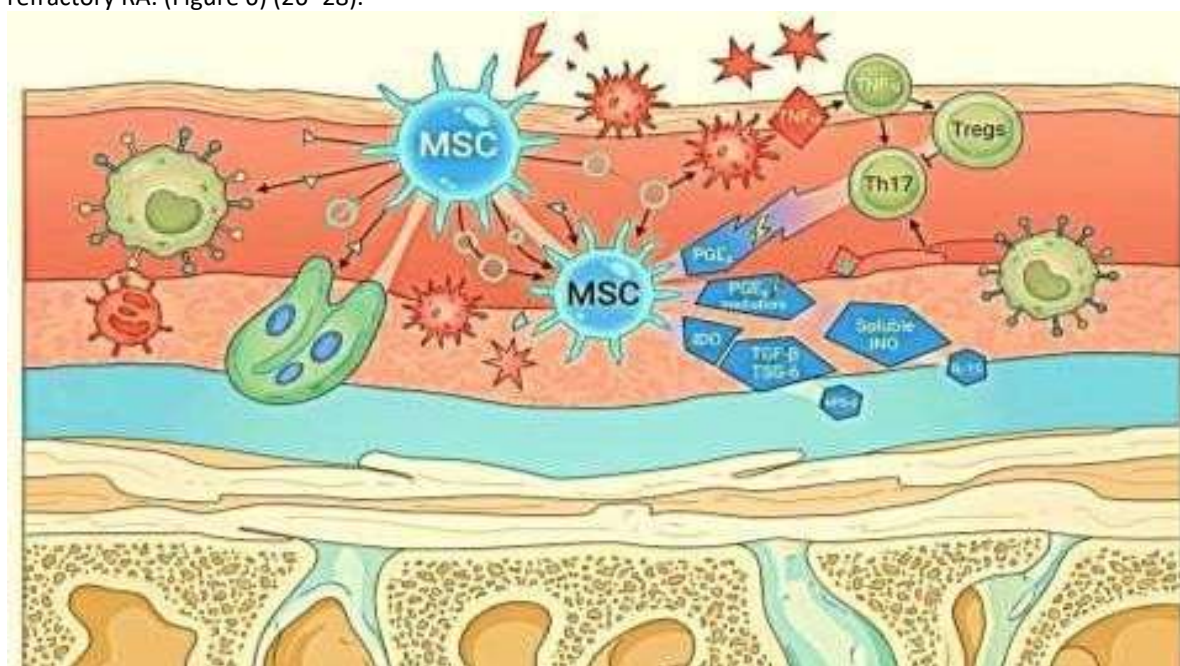


**Figure 6: MSC-mediated immunomodulation in the rheumatoid arthritis synovial microenvironment.** Schematic representation of MSC-mediated regulation of the inflammatory RA synovial microenvironment. In response to TNF-α and IFN-γ, MSCs release immunoregulatory mediators, including PGE<sub>2</sub>, IDO, TGF-β, IL-10, HGF, TSG-6, and NO, promoting Treg responses while suppressing Th17 cells, macrophage activation, and inflammatory signaling. These effects may reduce RANKL-associated osteoclastogenesis and subsequent bone and cartilage damage. **(A)** Pro-inflammatory phase; **(B)** MSC-mediated immunoregulatory phase.

**Abbreviations:** MSCs, mesenchymal stromal cells; RA, rheumatoid arthritis; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; IFN- $\gamma$ , interferon- $\gamma$ ; Tregs, regulatory T cells; Th17, T helper 17 cells; PGE<sub>2</sub>, prostaglandin E<sub>2</sub>; IDO, indoleamine 2,3-dioxygenase; TGF- $\beta$ , transforming growth factor- $\beta$ ; IL-10, interleukin-10; HGF, hepatocyte growth factor; TSG-6, tumor necrosis factor-stimulated gene-6; RANKL, receptor activator of nuclear factor- $\kappa$ B ligand.

### Conclusion And Future Perspectives

Rheumatoid arthritis (RA) is a complex autoimmune disease characterized by persistent synovial inflammation, progressive joint damage, and variable responses to existing therapies. Although conventional disease-modifying antirheumatic drugs (DMARDs) and biologic agents have substantially improved disease control, a proportion of patients continue to experience inadequate responses, treatment intolerance, or refractory disease. These unmet clinical needs have encouraged investigation of MSC-based approaches as potential regenerative and immunomodulatory therapies. The evidence reviewed in this article indicates that MSCs have considerable therapeutic potential in RA, with preclinical studies demonstrating biological activity and early clinical investigations suggesting possible improvements in disease-related outcomes. However, clinical evidence remains limited and heterogeneous, and important questions regarding treatment durability, optimal cell products, patient selection, and long-term safety remain unresolved. Consequently, MSC therapy should currently be regarded as an investigational approach rather than an established alternative to standard RA treatment.

Future progress will depend on improving the reproducibility and clinical translation of MSC products through standardized manufacturing, reliable potency assessment, and identification of biomarkers that can predict therapeutic response. Cell-free approaches based on MSC-derived extracellular vesicles and combination strategies with established DMARDs may provide additional opportunities for developing more precise and scalable therapies. Well-designed randomized clinical trials with standardized products, clinically meaningful endpoints, and long-term follow-up will ultimately determine whether MSC-based interventions can become a safe and effective therapeutic option for patients with refractory RA.

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