

## REVIEW ARTICLE

## Comparative roles of mesenchymal stem cells and fibroblast-like synoviocytes in rheumatoid arthritis

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## Abstract

Rheumatoid arthritis (RA) is an autoimmune disease affecting a large population worldwide. A strong inflammatory response at the articulation point causes significant joint and bone destruction in RA. It progresses with aging. The prevalence of RA is higher in women and older people. It mainly affects the joint, causing pain and inflammation. Conventional methods, primarily modifying rheumatic drugs and glucocorticoids, are the main therapies, while new methods are being developed and investigated. The fibroblast-like synoviocytes (FLSs) are involved in the pathogenesis of RA. By activating immune cells, they contribute to a joint environment characterized by inflammation and tissue death. Regenerative medicine is used to restore the normal functions of the cells or body. Specifically, mesenchymal stem cells (MSCs) and MSC-derived exosomes have the potential to inhibit pathways that facilitate the erosion of tissues or cartilages, while also ameliorating the autoimmune response and promoting tissue regeneration. Owing to their ability to reduce inflammation, they can be used in the treatment of autoimmune diseases. Therefore, the immunomodulatory and anti-inflammatory properties of MSCs have made them promising candidates in preclinical and early clinical investigations for RA. In this review, the potential role of FLSs in the pathogenesis of RA and their inhibition by MSCs are discussed.

**Keywords:** Regeneration of bone; Stem cells; Autoimmune diseases; Synovitis

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## 1. Introduction

Rheumatoid arthritis (RA) is an autoimmune chronic disease characterized by pain and inflammation in the joints that may lead to bone erosion. The global prevalence of RA is 460 people/100,000 population, or about 0.1% to 2% of the world population.<sup>1</sup> The etiology of RA is not fully known, and various factors, including environmental and genetic factors, are responsible for its incidence. The environmental factors include exposure to

dust, cigarette smoke, microbiota, and hormones.<sup>2</sup> RA is an immune-mediated disease in which DNA damage leads to the malfunction of immune cells, resulting in abnormal tissue repair processes that cause organ damage. It begins with the production of autoantibodies that work against post-translationally modified proteins. Over the years, progressive remodeling of the immune system occurs, during which joint-resident macrophages fail to perform their functions due to the accumulation of T cells. In the final stage, synovitis develops as stromal cells of the synovial membrane transition into auto-aggressive effector cells.<sup>3</sup>

RA mainly affects the synovium of the joint, resulting in inflammation, destruction, and loss of function of the joint. Both the innate and adaptive immune responses, along with resident fibroblast-like synoviocytes (FLS), are involved in the pathogenesis of the disease.<sup>4</sup> FLSs produce inflammatory mediators that contribute to the inflammation of the synovium and the destruction of cartilage. The suppression of FLS could be beneficial in lowering chronic inflammation. Alternatively, studies have also shown that the effect of metabolic enzyme suppression is beneficial in inflammatory disorders such as RA by suppressing FLSs.<sup>5</sup>

RA is normally treated with pharmaceuticals, dietary adjustments, and occasionally surgery. The purpose of treatment is to improve patients' quality of life while also relieving pain, reducing inflammation, and delaying or inhibiting the progression of joint deterioration. Disease-modifying anti-rheumatic drugs are the cornerstone of RA treatment. They seek to delay or inhibit the disease's progression. The examples of such drugs include methotrexate, hydroxychloroquine, sulfasalazine, etanercept, infliximab, rituximab, adalimumab, and leflunomide. Moreover, non-steroidal anti-inflammatory drugs, including naproxen and ibuprofen, can also reduce inflammation and pain.<sup>6</sup> In the fields of immunology and regenerative medicine, mesenchymal stem cells (MSCs) have drawn much attention due to their potential to treat RA. Therefore, understanding the differences and similarities between MSCs and FLSs will help develop successful treatment options for RA. In this review, the potential role of FLSs in the pathogenesis of RA and their inhibition by MSCs are discussed.

## 2. Regenerative medicine

Regenerative medicine involves the repair or replacement of damaged cells, tissues, or organs through cell transplantation, organ transplantation, or tissue engineering. The main purpose of regenerative medicine is to restore the normal functioning of cells,

tissues, and organs by promoting replacement, repair, and regeneration.<sup>7</sup> MSCs have emerged as promising candidates in regenerative medicine. First discovered in bone marrow by Alexander Friedenstein,<sup>8</sup> MSCs possess colony-forming ability, self-renewal capacity, multilineage differentiation potential, and immunomodulatory properties. They originate from the mesoderm and express cluster of differentiation (CD)73, CD90, and CD105.<sup>9</sup> Other body tissues and organs that can isolate MSCs include synovium, thymus, spleen, pancreas, amniotic fluid, umbilical cord, placenta, lung, kidney, liver, adipose tissue, dental pulp, and Wharton's jelly.<sup>10</sup> MSCs can be grown *in vitro* and directed to differentiate into various cellular phenotypes, making them attractive therapeutic agents for repairing apoptotic or necrotic connective tissues. Moreover, MSCs can differentiate into mesenchymal lineages, including chondrocytes (cells of the cartilage), osteoblasts, adipocytes, cardiomyocytes, and endothelial cells, as well as non-mesenchymal lineages, such as neuron-like cells and hepatocytes.<sup>11</sup>

MSCs are not directly involved in the engraftment of diseased cells or tissues.<sup>12</sup> Instead, they facilitate tissue repair and regeneration through alternative strategies, such as paracrine signaling with adjacent cells. Through this mode of communication, MSCs enhance cell viability, proliferation, and differentiation, while reducing fibrosis and apoptosis. These interactions also strengthen local immunity, inhibit inflammatory responses, and modulate extracellular matrix remodeling. The interaction between MSCs and adjacent cells is mediated by hormones, cytokines, chemokines, extracellular vesicles, and nanotubes.<sup>10</sup> Extracellular vesicles are lipid bilayer membrane particles of nano to microscale size secreted by host cells, playing a role in intracellular communication. Among them, MSC-derived exosomes recapitulate many of the functions of MSCs, such as tissue regeneration, through the transportation of biomolecules, including RNAs, peptides, and proteins.<sup>13</sup>

MSCs are pluripotent stem cells with plasticity. They can differentiate into cartilage, bone, cardiomyocytes, vascular cells, and ectoderm-derived glial and nerve cells.<sup>14,15</sup> Presently, MSCs are the focus of attention due to their ease of isolation from various body tissues. Their therapeutic effects include promoting wound healing, modulating the immune response, supporting nerve regeneration, enhancing angiogenesis, and exerting antiapoptotic, anti-inflammatory, and antioxidant activities. These properties, along with their potential for repairing diseased or damaged tissues, highlight their promise as a valuable cell source in the field of regenerative medicine.<sup>16</sup>

### 3. Synoviocytes

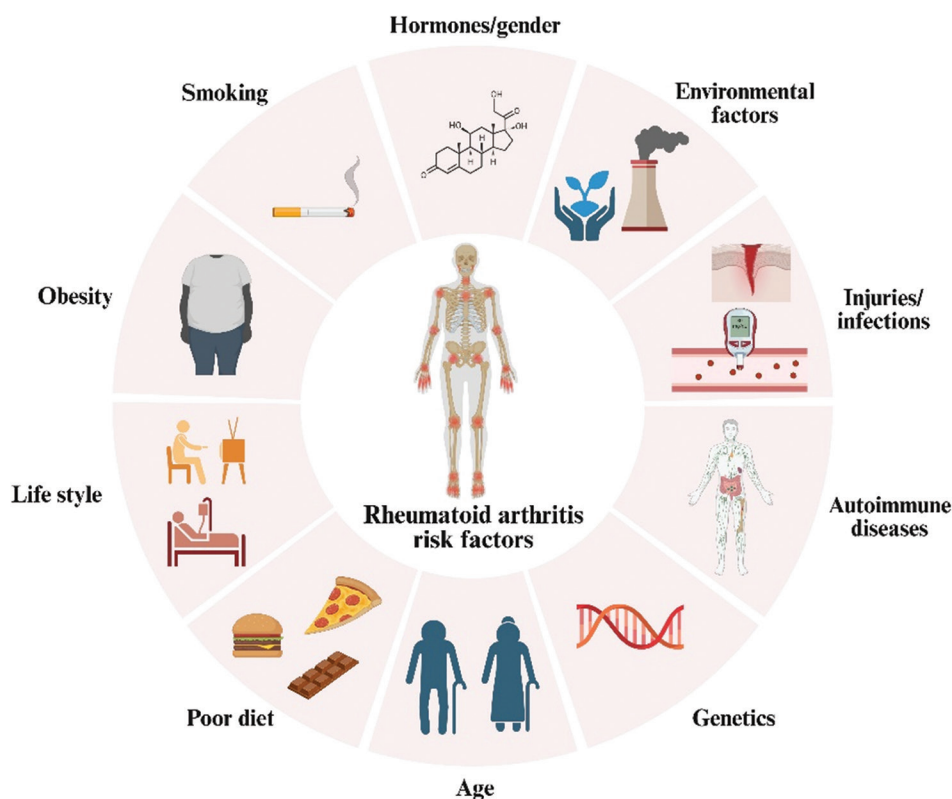
A freely moveable joint of the body, known as a synovial joint or diarthrosis, has four basic characteristic elements: a joint or fibrous capsule with a lubricated, smooth synovial membrane lining its inner surfaces, hyaline cartilage covering the articulating head surfaces, a joint cavity containing synovial fluid secreted by the synovial membrane, and extrinsic and intrinsic ligaments that hold the bones together and provide stability.<sup>17</sup>

The synovium is a thin membrane attached to the joint capsule and bones, extending from the surface of the articular cartilage. It is divided into two layers: the synovial intima and loose connective tissue. The depth of the superficial layer is one to three cells, with morphology and thickness varying by type. On the other hand, the loose connective tissue lining contains nerves, lymphatic and blood vessels, interstitial macrophages, and fibroblasts.<sup>18</sup> Together, these layers give rise to three types of synovial membranes: fibrous, adipose, and areolar. The underlying loose connective tissue and thick cellular intima make up the areolar synovial membrane. Likewise, a flat single layer of cells and adipose tissues in the underlying loose connective tissue constitutes the adipose synovial membrane, while dense collagenous tissue and thin cellular intima contribute to the fibrous synovial membrane.<sup>19,20</sup>

The synovial intima lacks epithelial and endothelial layers as well as a basement membrane. Instead, it is composed of two morphologically distinct cell types: Macrophage-like synoviocytes (type A) and FLSs (type B). Macrophage-like synoviocytes are derived from myeloid precursors in the bone marrow and have phagocytic activity, contributing to the clearance of microbes and cellular debris from the joint.<sup>21</sup> FLSs are derived from MSCs and support the synovial membrane and joint articulation by producing extracellular matrix components, lubricin, and hyaluronan.<sup>22</sup> The synovial membrane also produces synovial fluid, which reduces friction and absorbs shock. The tribological system “cartilage–synovial fluid–cartilage” provides support and redistributes forces across articulating surfaces.<sup>23</sup> Besides lubrication, synovial fluid is also enriched with nutrients required for the maintenance and growth of chondrocytes.

### 4. Pathogenesis of RA

Synovial joints are affected in RA, leading to loss of joint function and impaired articulation. The hands and feet are most often affected, and the incidence is higher in females than in males.<sup>24</sup> RA is a multifactorial disease associated with several risk factors, including the interaction of the host with the outer environment (Figure 1). Host-

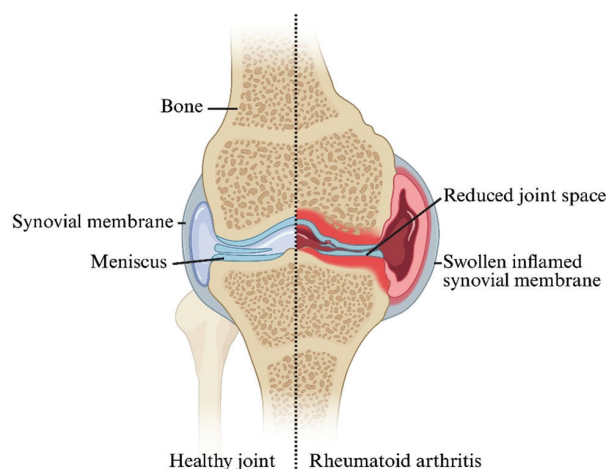


**Figure 1.** Risk factors of rheumatoid arthritis (Created in BioRender. Shakoor, A. (2025) <https://BioRender.com/lyviftg>)

associated factors include reproductive, hormonal, genetic, epigenetic, neuroendocrine, and comorbid conditions, while environmental factors encompass infectious agents, microbiota, airborne exposures, smoking, socioeconomic factors, and diet.<sup>25,26</sup>

The changes in synovium are the characteristic feature of RA, characterized by the accumulation of inflammatory cells in affected joints, facilitating the inflammatory process and contributing to the destruction of bone and articular cartilage (Figure 2).<sup>27</sup> Other changes include neutrophil infiltration into the synovial fluid and the presence of B cells, T cells, plasma cells, macrophages, and mast cells in the synovial sublining.<sup>28</sup> Elevated extracellular matrix production, enhanced synovial fibroblast proliferation, and increased angiogenesis facilitate the process of infiltration. Moreover, the hyperplasia of the synovial membrane causes the thickening of the layer from its normal 1–3 cell layers to as many as 15 layers.<sup>22</sup>

Both innate and adaptive immune responses are involved in the pathogenesis of RA. The upregulation of the cytokine network, involving interleukin-1 (IL-1), IL-6, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), indicates the role of innate immune response in disease development.<sup>29,30</sup> Similarly, B cells and T cells also have a role in RA pathogenesis, while autoantibodies directed against the Fc region of immunoglobulin G drive arthritis development.<sup>31</sup> Besides immune cells, joint-resident cells—the main focus of this review—are also critically involved. Under physiological conditions, osteoblasts, FLSs, osteoclasts, and chondrocytes maintain joint homeostasis. However, their functions are altered in RA, resulting in joint destruction. For example, FLSs promote cartilage degradation, while osteoclasts mediate bone resorption.<sup>32,33</sup>



**Figure 2.** Comparative demonstration of a healthy (left) and a rheumatoid arthritis-affected joint (right) (Created in BioRender. Shakoor, A. (2025) <https://BioRender.com/2l590ku>)

In RA, FLSs play a crucial role in driving inflammation and cartilage degradation. Under physiological conditions, FLSs organize the structure and maintain the function of the synovial membrane through cadherin-11, a transmembrane glycoprotein that facilitates cell-to-cell adhesion. Loss of cadherin-11 function leads to hypoplastic synovium, characterized by reduced extracellular matrix and a lower number of cells in the synovial intima.<sup>34</sup> Experimental studies in cadherin-11-deficient mice showed that FLSs are important mediators for the erosion of cartilage and inflammation, suggesting that targeting FLS in RA may provide therapeutic benefit.<sup>34</sup>

In RA, the normal functions of FLSs are overridden, and they shift from homeostatic roles to pathogenic ones, promoting inflammation and joint destruction through inflammatory mediators and cell surface interactions.<sup>22</sup> This shift is driven by diverse factors, including extracellular matrix components, membrane-associated and soluble growth factors, chemokines, cytokines, infiltrating leukocytes, and bioactive lipids. Among these, macrophages secrete cytokines IL-1 $\beta$  and TNF- $\alpha$ , T cells produce IL-17 and IFN- $\gamma$ , while FLSs release IL-6 and transforming growth factor-beta (TGF- $\beta$ ).<sup>35–37</sup>

Toll-like receptors (TLRs) activate FLSs. These receptors stimulate an innate immune response by recognizing pathogen-associated molecules. In addition, factors such as necrotic cells or heat shock proteins can also activate TLRs, thereby sustaining chronic immune responses.<sup>38,39</sup> In the RA synovium, several TLRs, including TLR2, TLR3, and TLR4, are expressed on FLSs, contributing to disease pathogenesis by increasing chemokines and cytokines expression.<sup>40,41</sup> Chronic inflammation further amplifies the inflammation process, as tissue damage provides signals that stimulate FLSs. Furthermore, toll-like ligands and membrane-bound vesicles released by immune cells also enhance FLS activation. During inflammation, proteins such as hyaluronan and lubricin in the synovial fluid are degraded. These proteins normally regulate FLS activity and protect cartilage from erosion induced by FLS-derived proinflammatory mediators.<sup>42,43</sup>

The interaction of leukocytes with cell surface receptors plays a role in the activation of FLS. Once stimulated, FLSs increase the expression of adhesion molecule receptors on their surface, promoting inflammatory cells to attach to FLSs.<sup>44</sup> Meanwhile, inflammation causes hypoxia, leading to the activation of FLS factors that drive cartilage degradation. Collectively, all the above-mentioned mechanisms induce proinflammatory cytokine synthesis, leading to inflammation and tissue damage.



#### 4.1. Cellular pathways in the pathogenesis of RA

FLSs are important factors in the development of RA, contributing to chronic joint inflammation, cartilage degradation, and bone erosion. Cytokines such as TNF- $\alpha$ , IL-1, and IL-6 activate FLSs, leading to the release of additional cytokines, chemokines, and matrix metalloproteinases<sup>3</sup> that degrade the extracellular matrix and accelerate cartilage destruction. In addition, integrins and selectins, two types of adhesion molecules, promote FLS migration into the synovial area, where they interact with immune cells to exacerbate inflammation.

Autoantibodies such as rheumatoid factor and anti-citrullinated protein antibodies further stimulate FLSs to produce cytokines, exacerbating the inflammatory response. In addition, FLSs' TLRs recognize endogenous ligands and initiate inflammatory pathways, such as nuclear factor-kappa B, Janus kinase, and signal transducer and activator of transcription, thereby intensifying the inflammatory cascade. FLSs also activate nuclear factor kappa B ligand to promote the development of osteoclasts and bone resorption.<sup>45</sup> Moreover, they support synovial angiogenesis, ensuring the persistence of the inflammatory microenvironment.

#### 4.2. Pathways involved in the suppression of synoviocytes by MSCs

RA is an autoimmune disease in which local joint reactions stimulate the immune system, leading to chronic joint damage. FLSs play a dual role: they contribute to tissue destruction while activating the immune response. By promoting the influx, differentiation, and survival of immune cells in the synovial membrane, FLSs drive the progression of disease through tissue damage and inflammation. Therefore, inhibiting FLS activity is critical for limiting RA pathogenesis and inflammation.<sup>46</sup>

In RA, FLSs produce angiogenic factors, such as vascular endothelial growth factors, which enhance angiogenesis. The persistence of angiogenesis can lead to synovial

composition changes by enhancing the transport of inflammatory factors, nutrients, and proteases.<sup>47</sup> Exosomes act as a vehicle for the transportation of therapeutic agents. MSC-derived exosomes prevent the destruction of tissues by inhibiting angiogenesis and hyperplasia in the joint.<sup>48</sup>

Single-stranded non-coding RNAs, such as microRNA, are involved in the regulation of a variety of gene expressions. They have a role in cellular physiological activities, such as apoptosis, proliferation, and differentiation. In addition, they mediate the responses of inflammation in non-immune and immune cells. It has been reported that MSC-derived miR-320a levels were significantly lower in the synovial tissue of RA patients compared with those of healthy individuals. This downregulation suggests that restoring miR-320a expression could provide therapeutic benefit. Indeed, a study has shown that the upregulation of miR-320a inhibited the proliferation and promoted the apoptosis of RA-induced FLSs by inactivating the mitogen-activated protein kinase-extracellular signal-regulated kinase 1/2 signaling pathway.<sup>49</sup>

A study has shown that the downregulation of CXCL9 in RA inhibited the activation, transfer, and invasion of FLSs, thereby suppressing the stimulation of immune factors and decreasing the severity of RA.<sup>50</sup> Bone marrow-derived MSCs exhibit potent immunomodulatory effects, while umbilical cord-derived MSCs also inhibit the proliferation of FLSs by suppressing indoleamine 2,3-dioxygenase, IL-10, and TGF- $\beta$ 1.<sup>51,52</sup>

Moreover, after homing to inflamed tissues, MSCs predominantly regulate FLS through paracrine signaling mechanisms. By secreting IL-10, TGF- $\beta$ , and other anti-inflammatory cytokines, MSCs inhibit the production of proinflammatory cytokines, such as TNF- $\alpha$  and IL-1 $\beta$ , thereby suppressing FLS activation.<sup>46</sup> In addition, FLS can internalize MSC-derived extracellular vesicles carrying microRNAs and other regulatory molecules, which downregulate inflammatory gene expression and attenuate their aggressive phenotype. Meanwhile, FLS death can be induced by MSCs through the Fas ligand/Fas receptor

**Table 1. Types of cells or molecules and their role in rheumatoid arthritis (RA)**

Type of cells/molecules	Normal functions	Role in RA	References
Macrophage-like synoviocyte (type A)	Clear microbes and cellular debris	Tissue damage and inflammation	21
Fibroblast-like synoviocyte (type B)	Protect the synovial membrane by producing extracellular matrix, lubricin, and hyaluronan	Tissue damage and inflammation	22
Mesenchymal stem cells	Promote healing of the wound, regulation of the immune system, regeneration of nerves, angiogenesis, antiapoptotic action, anti-inflammatory and antioxidant activity, and repair of diseased or damaged tissues	Protective role	16
Exoneme	Promote tissue regeneration	Protective role	13
Cadherin-11	Ameliorate erosion and protect cartilage	Protective role	52

pathway, further limiting pathogenic FLS activity. Besides, MSCs modulate the immunomodulatory activities of M2 macrophages and regulatory T cells (Tregs), which collectively suppress FLS-driven inflammation. Through these immunosuppressive and anti-inflammatory mechanisms, MSCs create a microenvironment in the synovial membrane that prevents the activation and growth of pathogenic FLS, thereby assisting in the regulation of RA development.<sup>24</sup> The comparative roles of different cell types or molecules are presented in [Table 1](#).

## 5. Conclusion

In healthy synovial tissue, MSCs and FLSs have important roles in mediating immune homeostasis and preventing inflammation. However, in RA, various factors, including direct interaction of FLS and MSCs with chemokines, cytokines, and other immune cells, disrupt their immunomodulatory functions. Proinflammatory mediators drive the abnormal proliferation of RA-associated FLS, shifting the roles of both MSCs and FLSs from immune regulation toward immune activation. A thorough understanding of FLS functions in the synovium is therefore necessary for the development of fibroblast-specific therapeutic agents. There is a vast heterogeneity in the composition of the synovium between patients and within different regions of the joint, yet only a few agents targeting the specific cells in the synovium have been identified. Therefore, identifying agent's specific to the target still requires investigation. As cells in the lining and sub-lining of the synovium have different functions, therapies must account for the microenvironment and spatial context that shape fibroblast behavior. In addition, in other autoimmune diseases, the pathogenic role of fibroblasts varies across diseases. For example, fibroblasts contribute to fibrosis in idiopathic pulmonary fibrosis and scleroderma, whereas in RA, FLSs primarily drive the destruction of tissue and inflammation. Therefore, for novel treatment strategies, a better understanding of fibroblasts in different diseases is necessary. Finally, several key questions remain unanswered for MSC-based therapies, such as the isolation site of joint-derived MSCs, as well as the appropriate dosing, delivery route, and treatment frequency.

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## Conflict of interest

Hamayun Khan is employed by Sami Pharmaceuticals. Farakh Munir is employed by Air Pharmaceuticals. The

remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Ethics approval and consent to participate

Not applicable.

## Consent for publication

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## Availability of data

Not applicable.

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