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# The role of the immune system in the progression of osteoarthritis

**Majid Negari***

Independent Researcher, Wetzikon, Switzerland

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***Correspondence:**
Dr. Majid Negari,
E-mail: padzadro@yahoo.com



## ABSTRACT

Osteoarthritis (OA) is traditionally viewed as a mechanical wear-and-tear disease. While mechanical loading remains a fundamental factor in joint degeneration, it does not fully explain why post-traumatic osteoarthritis (PTOA) progresses so aggressively. We propose a novel biological hypothesis suggesting that a secondary, parallel immunomediated mechanism coexists alongside this mechanical pathway. Articular cartilage normally acts similarly to immune-privileged sites, sequestering internal auto-antigens. However, joint injury breaches this barrier, exposing hidden cartilage proteins to the systemic immune system. This exposure triggers an autoimmune reaction driven by synovial macrophages and T-cells, creating a self-amplifying vicious cycle of immune recruitment and tissue destruction. This parallel cascade prevents joint healing and accelerates degeneration. To validate this model, we outline a pragmatic approach using ELISA to track phase-specific cytokines and animal models to observe progression after immunomodulation. Integrating this immunomediated continuum with classical mechanical theories shifts the therapeutic paradigm of PTOA toward targeted immunomodulatory interventions, offering a dual pathway to halt disease progression.

**Keywords:** Osteoarthritis, Post-traumatic osteoarthritis, ELISA

## INTRODUCTION

Osteoarthritis (OA) is one of the most common musculoskeletal disorders worldwide and is strongly associated with factors such as aging, obesity, nutritional deficiencies, and excessive mechanical loading of joints.[1-3] Despite its high prevalence and substantial clinical burden, the underlying mechanisms responsible for the initiation and progression of OA have not been fully elucidated.[1,4] For example, the reasons why OA frequently develops more rapidly and progresses more aggressively following joint injury remain incompletely understood.[3] Moreover, despite considerable advances in biomedical research, no disease-modifying treatment capable of effectively preventing or halting OA progression is currently available.[1,4]

Traditionally, OA has been regarded primarily as a degenerative disorder resulting from mechanical wear and tear of the articular cartilage. However, this perspective alone does not adequately explain several important clinical observations associated with the disease.[5] One such observation is the tendency of OA to gradually involve multiple joints over time, including those anatomically distant from the site of the initial pathology. In certain cases, this pattern may be partially explained by alterations in biomechanics and weight distribution. For instance, OA affecting one knee may increase the load on the contralateral knee, thereby accelerating degenerative changes in that joint. However, such biomechanical explanations appear insufficient to account for all clinical manifestations of the disease. Specifically, they do not fully explain how OA may subsequently develop in anatomically unrelated regions, such as the finger joints or cervical spine, following an initial knee injury.

The hypothesis proposed in this series of articles examines the possibility that the immune system, particularly autoimmune mechanisms, contributes to the progression and dissemination of OA.[6,11] From a mechanistic

standpoint, this framework may provide a plausible explanation for several of the aforementioned observations and help clarify the relationship between the pathological changes occurring in different joints throughout the body. It is important to emphasize that the concepts discussed are derived from previously published scientific evidence, observations, and experimental findings.[6,7] The objective was to critically analyze, integrate, and synthesize existing data into a coherent theoretical model. However, despite being grounded in the available scientific literature, the proposed framework should be considered a hypothesis rather than an established fact. Its validity must be assessed through rigorous experimental and well-designed clinical studies.

The primary purpose of this perspective is to introduce an alternative conceptual framework and encourage further research into the potential role of immune-mediated processes in the initiation and progression of OA.[6] A deeper understanding of these mechanisms may provide valuable insights into disease pathogenesis and ultimately contribute to the development of more effective therapeutic approaches for patients with OA.[4,6]

## THE HYPOTHESIS

The hypothesis presented in this article is based on a series of scientific observations and experimental findings that, when considered collectively, suggest a possible role for immune-mediated mechanisms in the progression of OA.[6,8] A review of these findings provides the conceptual foundation on which the proposed framework is built.

One of the distinctive biological features of articular cartilage is its avascular and alymphatic nature. Unlike most tissues, healthy cartilage lacks blood and lymphatic vessels, limiting its direct interaction with immune cells under physiological conditions.[21] Consequently, many cartilage-specific antigens remain largely inaccessible to routine immune surveillance throughout human lifespan. In this respect, articular cartilage may be considered a relatively immune-isolated tissue, whose internal components are normally protected from direct recognition by the adaptive immune system.[21]

Histopathological studies of osteoarthritic joints have provided additional observations of potential relevance. Examination of damaged joint tissues has consistently demonstrated the accumulation of macrophages and fibroblast-like cells on the surface of degenerating cartilage.[7,14] At the same time, microscopic fragments generated during cartilage breakdown have been detected within the synovial fluid.[19] These cellular populations contribute to ongoing tissue degradation by producing matrix-degrading enzymes, including collagenases and other proteolytic mediators that can disrupt the extracellular matrix.[14,21]

Several studies have reported the presence of numerous cartilage-derived particles suspended within the synovial fluid of patients with OA. This observation has been referred to in some reports as the “golf ball phenomenon,” reflecting the abundance of microscopic cartilage fragments released during the degenerative process.[19] The detection of these particles indicates that the products of cartilage destruction are not confined to the damaged tissue but can disseminate throughout the joint cavity, where they may interact with resident immune and inflammatory cells.[18,19]

Further evidence supporting a potential immune contribution comes from studies demonstrating the presence of antibodies directed against type II collagen, one of the principal structural proteins of articular cartilage. In a subset of patients with OA, these antibodies have been identified in either synovial fluid or peripheral blood samples.[16,17] Their presence suggests that, at least in certain individuals and at particular stages of disease progression, cartilage-derived antigens become accessible to the adaptive immune system and elicit a specific immune response.[11,16]

Recent investigations have highlighted the dynamic role of synovial fibroblasts in OA. Under pathological conditions, these cells may adopt a more activated and aggressive phenotype.[20] Beyond their role in clearing tissue debris, activated fibroblasts secrete cytokines and signaling molecules that promote macrophage recruitment and polarization toward proinflammatory states.[14,20] Through these interactions, inflammatory pathways may become self-sustaining, generating a cycle of tissue damage and immune activation that contributes to the progressive deterioration of the joints.[6,8]

Another noteworthy aspect of cartilage biology is the highly organized extracellular matrix structure. In addition to the lack of vascular and lymphatic networks, healthy cartilage contains a dense matrix that physically restricts the penetration of many immune cells, including lymphocytes and dendritic cells (DCs).[21] Consequently, numerous cartilage components remain effectively concealed from immune recognition under normal conditions. However, when cartilage integrity is disrupted, these previously sequestered molecules may be released into the joint environment, potentially exposing the immune system to antigens that it has not encountered previously.[21]

Similar mechanisms have been documented in other tissues that exhibit varying degrees of immune privilege. The human eye is one of the most extensively studied examples.[22,23] Under normal circumstances, structures such as the retina are shielded from direct immune surveillance by the blood-retinal barrier (BRB). Following severe ocular injury and disruption of protective barriers, previously hidden antigens may be exposed to the immune system, triggering an immune response.[22,23] In certain cases, this response extends beyond the injured eye and affects the contralateral healthy eye, resulting in a condition known as sympathetic ophthalmia.[22,25]

A comparable phenomenon has been described in the testes, where spermatogenic tissues are partially protected from immune recognition by specialized anatomical barriers.[24] Damage to these barriers may expose sperm-associated antigens to the immune system and lead to the development of immune responses that can affect both injured and uninjured tissues.[24]

Taken together, these observations indicate that the disruption of protective barriers surrounding immune-isolated tissues can expose previously concealed antigens, thereby facilitating the development of novel immune responses and, in some cases, autoimmune reactions.[23,24]

Within this context, an important question emerges: could the progressive destruction of articular cartilage and subsequent release of cartilage-derived antigens initiate a similar process in OA? This possibility forms the central premise of the hypothesis proposed in this study.

## A HYPOTHETICAL MODEL OF THE ROLE OF THE IMMUNE SYSTEM IN OSTEOARTHRITIS PROGRESSION

Drawing on the scientific observations and evidence discussed above, a hypothetical model can be proposed to describe how immune-mediated mechanisms may contribute to the initiation and progression of OA.[6,11] Rather than introducing entirely new concepts, this model attempts to integrate existing findings into a unified pathogenic sequence that may help explain several unresolved aspects of the disease.

### *Phase I: Initial tissue injury and antigen exposure*

The proposed process begins with an initial insult to the articular cartilage of the knee joint. Such damage may arise from acute joint trauma, age-related degenerative changes, obesity, abnormal biomechanical loading, weakness of the surrounding musculature, or a combination of these factors.[1-3,36]

Regardless of the initiating cause, disruption of the highly organized cartilage matrix exposes structural components that are normally sequestered within the tissue, including type II collagen and other extracellular matrix molecules.[18,21]

As cartilage degeneration progresses, degradation products and microscopic cartilage fragments are released into synovial cavities.[18,19] Under normal physiological conditions, many cartilage-associated antigens remain relatively isolated from direct immune recognition because of the unique biological characteristics of articular cartilage.

However, tissue injury may alter this by exposing previously concealed molecules to the cells of the immune system residing within the joint environment.[6,16]

### *Phase II: Activation and engagement of the immune response*

The presence of tissue damage and cartilage debris may trigger innate immune system activation. Synovial macrophages, which typically contribute to tissue maintenance and repair, may undergo phenotypic changes and adopt a more pro-inflammatory profile.[13,15] Simultaneously, synovial fibroblasts may become activated and participate in both debris clearance and inflammatory signaling.[14,20] These cells may recruit additional immune cells into the joint and amplify local inflammatory responses through the production of cytokines, chemokines, and other inflammatory mediators.[26,28] Consequently, the inflammatory microenvironment gradually becomes more prominent.

Continued tissue destruction may generate sufficient quantities of cartilage-derived antigens to allow their uptake by antigen-presenting cells, particularly dendritic cells.[11,28] After processing these antigens, dendritic cells may migrate to regional lymphoid tissues and present antigenic peptides to naïve T lymphocytes via major histocompatibility complex (MHC) molecules.[11] Under appropriate immunological conditions, this interaction may stimulate the expansion of T-cell populations capable of recognizing cartilage-associated antigens, including pro-inflammatory T-helper subsets, such as TH1 and TH17 cells.[27]

Activated T-helper cells may subsequently support B cell activation through direct cellular interactions and cytokine-mediated signaling pathways.[27,28] Following antigen recognition and clonal expansion, B-lymphocytes differentiate into antibody-producing plasma cells. In this context, antibodies directed against cartilage components, particularly type II collagen, can be generated.[16,17] Notably, these antibodies have been identified in a subset of patients with OA, suggesting that adaptive immune responses against cartilage-derived antigens may occur under certain circumstances.[16]

### *Phase III: Escalation of inflammation and repair failure*

If cartilage-directed antibodies are present, they may bind to the exposed cartilage structures and form immune complexes within the joints.[29] These complexes can activate the complement system, thereby initiating additional inflammatory pathways.[29,30] Complement activation can enhance the recruitment and activation of macrophages, neutrophils, and other inflammatory cells while simultaneously promoting further tissue injury. Consequently, a positive feedback loop may develop in which inflammation accelerates tissue destruction, and tissue destruction further amplifies inflammation.[6,26,30]

Persistent inflammation may have important consequences for the biological function of chondrocytes, which are responsible for maintaining cartilage homeostasis and matrix repair.[21,37] Exposure to inflammatory cytokines and

immune mediators may impair the ability of chondrocytes to effectively synthesize and restore extracellular matrix (ECM) components. As repair mechanisms become progressively compromised, cartilage loss may occur at a rate that exceeds the limited regenerative capacity of the tissue.[3,37]

***Phase IV: The self-sustaining pathogenic cycle***

In the final stage of the proposed model, two interconnected pathological processes may operate simultaneously. The first involves ongoing mechanical damage resulting from joint loading, structural instability, and altered biomechanics.[1,5] The second is immune-mediated injury driven by chronic inflammation and potentially autoimmune responses directed against cartilage-associated antigens.[6,28] The interaction between these mechanisms may establish a self-perpetuating cycle in which cartilage degradation promotes further immune activation, and immune activation accelerates cartilage destruction.

Such a framework could help explain several characteristic features of OA, including its chronic and progressive nature, the limited capacity of articular cartilage for regeneration, and the tendency for disease activity to persist even after the initial mechanical insult.[2,4] It is important to emphasize that although each component of this model is supported by existing knowledge in immunology and joint biology, the integration of these elements into a single causal pathway remains hypothetical. Accordingly, the model should be viewed as a conceptual framework designed to generate testable predictions and stimulate further experimental and clinical investigations, rather than as a definitive explanation of OA pathogenesis.

## EVALUATION AND TESTING OF THE HYPOTHESIS

The proposed pathogenic model can be critically evaluated through both experimental animal studies and longitudinal clinical investigations. First, to test the validity of the autoimmune component, peripheral blood and synovial fluid samples from patients with PTOA should be analyzed longitudinally using enzyme-linked immunosorbent assays (ELISA) to track the emergence and titers of autoantibodies against type II collagen and other extracellular matrix components. These immunological profiles can then be correlated with the radiographic and symptomatic progression of the disease to determine if autoantibody levels predict more aggressive joint destruction.

Second, the hypothesized "golden window of intervention" can be evaluated using well-established in vivo animal models of joint injury (such as the anterior cruciate ligament transection model). Animals can be randomized to receive immunomodulatory interventions, such as platelet-rich plasma (PRP) or specific macrophage-modulating agents, at varying time intervals post-injury (e.g., 24 hours, 1 week, and 4 weeks). Subsequent histopathological evaluation, micro-CT imaging, and flow cytometry of synovial tissue can confirm whether early intervention successfully prevents the polarization of macrophages toward pro-inflammatory phenotypes and halts the development of the self-perpetuating autoimmune cycle compared to delayed treatment.

Finally, to verify the involvement of the adaptive immune system, regional lymph nodes from animal models can be analyzed using immunohistochemistry and ELISpot assays to detect the activation and expansion of cartilage-specific CD4+ T-helper cells (specifically TH1 and TH17 subsets) following initial cartilage trauma. If these experimental approaches fail to demonstrate distinct autoimmune activation or clinical benefits from early intervention, the central premise of this hypothesis would be challenged.

## CONCLUSION

OA has traditionally been viewed as a disease primarily driven by mechanical degeneration of the articular cartilage. While mechanical factors play a central role in disease initiation and progression, they may not fully explain several important clinical features of OA, including its chronic nature, progressive course, and continued deterioration of joint tissues following the initial injury.

The hypothesis presented in this article proposes that, in addition to mechanical and metabolic influences, immune-mediated mechanisms may contribute to the progression of OA in at least a subset of patients. According to this conceptual framework, cartilage damage may expose previously sequestered cartilage-derived antigens to the immune system, potentially initiating inflammatory and immune responses that further promote tissue destruction and impair repair processes. Therefore, the interaction between mechanical injury and immune activation may contribute to the establishment of a self-sustaining cycle of joint degeneration.

It is important to emphasize that this model does not suggest that OA should be regarded as a classical autoimmune disease. Rather, it proposes that immune and autoimmune-like processes may represent one component of a multifactorial pathogenic network that interacts with the established biomechanical, genetic, and metabolic factors of OA.

Although the proposed framework remains hypothetical, it offers a potential explanation for several observations that are not fully accounted for by current models of OA pathogenesis. More importantly, it generates several testable questions that may guide future experimental and clinical studies. Further investigation is required to determine whether immune-mediated mechanisms play a

meaningful role in disease progression and whether targeting these pathways may provide new opportunities for the prevention or treatment of OA.

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