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REVIEW

Functions of Macrophages, T Cells, and Neutrophils in the Synovial Microenvironment of Osteoarthritis

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Abstract: Previous reviews on osteoarthritis have primarily focused on inflammation caused by cartilage destruction, often overlooking the role of synovitis in the progression of osteoarthritis (OA). Macrophages, T cells, and neutrophils play critical roles in the advancement of synovitis. Therefore, this article emphasizes the functions of macrophages, T cells, and neutrophils in OA-related synovitis, aiming to provide a deeper understanding of the interactions among damage-associated molecular patterns, immune cell activation, and signaling pathways (such as NF-κB and mTOR) in OA, thereby offering new therapeutic targets. In OA, the accumulation of macrophages within inflamed synovial fluid, along with elevated levels of RANKL, tumor necrosis factor-alpha, and interleukin-1, enhances the capacity of synovial macrophages to differentiate into osteoclasts. Furthermore, synovial macrophages can polarize into either pro-inflammatory M1 or anti-inflammatory M2 phenotypes, with a predominance of the M1 phenotype promoting cartilage destruction. T cells—particularly Th17 and regulatory T cells—disrupt immune homeostasis and exacerbate inflammation. Neutrophils contribute to tissue damage by releasing elastase and reactive oxygen species, which directly injure cartilage and bone. Current OA management primarily focuses on symptomatic relief through agents such as non-steroidal anti-inflammatory drugs and corticosteroids. In contrast, emerging therapeutic strategies aim to modulate immune pathways. Promising approaches include platelet-rich plasma, mesenchymal stem cell therapy, and photobiomodulation, which have shown potential in regulating inflammation and promoting cartilage repair. A deeper understanding of the interactions among damage-associated molecular patterns, immune cell activation, and signaling pathways—such as NF-κB and mTOR—offers new therapeutic targets. Ultimately, OA management may evolve toward a precision medicine approach that integrates immune modulation with regenerative strategies to restore joint homeostasis.

Keywords: immune modulation, homeostasis, pain, osteoarthritis, synovial membrane

Introduction

Osteoarthritis (OA), a chronic, nonspecific, degenerative illness that affects 595 million individuals globally, primarily causes significant difficulties in daily living.[1] Some populations, including women, Asians, and older people, have relatively high incidence rates of OA.[2] OA is influenced by several risk factors, including joint-level variables, such as injury, dislocation, and excessive joint loading, as well as personal-level factors, such as age, sex, heredity, obesity, and food.[3,4]

The distinct pathological features of OA include articular cartilage degradation, reactive hyperplasia of the joint borders and subchondral bone, and subsequent synovial inflammation. In addition, meniscus lesions can lead to structural lesions associated with OA, such as bone marrow edema, cartilage loss, and reduced subchondral bone density. However, many meniscus lesions can cause knee joint strain, which can lead to the progression of OA.[5]

Severe joint pain can seriously affect patients' daily lives.[6,7] OA has been considered a degenerative condition that causes cartilage loss for years.[8] However, our knowledge of inflammation in OA is rapidly changing owing to ongoing advancements in molecular biology. Thus, OA may be primarily caused by inflammation.

Knee OA, is a disease of the whole joint, characterized by degeneration and pathological alterations across all articular tissues.[9] These include not only the articular cartilage, synovium, and the subchondral bone, but also menisci, ligaments, and the infrapatellar fat pad (IFP).[10] Each of these tissues undergoes distinct but interconnected degenerative changes that

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collectively drive disease progression and contribute to clinical symptoms. In addition, studies have shown that IFP becomes inflamed and fibrotic in OA and it is also involved in OA pain.[11] The IFP serves as both an active site and origin of joint inflammation, contributing significantly to the pro-inflammatory synovial environment in OA. The IFP represents a valuable reservoir of mesenchymal stem cells (MSCs), which possess immunomodulatory properties and may contribute to the regeneration of joint tissues.[11] Furthermore, all joint tissues including IFP undergo biomechanical changes.[12]

Inflammatory synovitis can result from the impact of OA on the synovial tissue of joints.[13] Although synovitis is not always present in OA, it can lead to increased discomfort, joint dysfunction, and accelerated cartilage degradation.[14] As OA worsens, the severity of synovitis increases. In individuals with OA, synovial inflammation is present in >90% of synovial tissues.[15] The thin layer of cells that makes up the synovial lining has phenotypic traits of fibroblasts and macrophages. The complex structure formed by these cells and the vascularized connective tissue matrix underneath them are significant sources of synovial fluid components that are essential for healthy cartilage and joint function.[16] The inflow of T cells and macrophages, growth of new blood vessels, and consequent release of inflammatory cytokines are typical features of synovial inflammation.[16] By promoting the synthesis of matrix metalloproteinases (MMPs), inflammatory cytokines contribute significantly to the development of OA by promoting the synthesis of MMPs.[17] Therapeutic targets for controlling the course of OA may involve understanding cellular functions in the immune response and inflammatory process, as well as how cells produce and regulate proinflammatory cytokines. Furthermore, the OA phenotype may influence the type and source of inflammatory mediators.[18] This review focuses on the biological relevance of common immune cells, such as neutrophils, T cells, and macrophages, in the OA synovium, which also suggests potential preventative and therapeutic measures.

Clinical Features and Risk Factors for OA

Clinical Features of OA

Pain

In the early stages of OA, patients experience intense and predictable pain commonly caused by mechanical injury. (Table 1) Occasionally, high-intensity activities may be restricted; however, at this point, they do not affect

Table 1 Clinical Features and Risk Factors for OA

Category	Feature/Factor	Description
Clinical Features	Pain	- Early Stage: Intense, predictable pain, often caused by mechanical injury; does not affect function. - Middle Stage: Pain becomes more frequent and unpredictable; affects daily life. - Advanced Stage: Constant throbbing pain with erratic bouts of intense agony; function is severely hampered.
	Joint Stiffness	A common symptom manifesting as reduced joint flexibility, causing discomfort or movement difficulty.
	Bone Enlargement & Swelling	Both small (eg, interphalangeal) and large (eg, knee) joints may experience enlargement and swelling.
Risk Factors	Personal-Level Factors	- Age: A primary risk factor, potentially due to oxidative damage, cartilage thinning, muscular weakening, and impaired proprioception. - Sex: OA is more common in women, especially post-menopause, suggesting hormonal involvement. - Genetics: Accounts for 60% of hand/hip OA and 40% of knee OA cases. Multiple genes are likely involved. - Obesity: A major risk factor via complex biomechanical, metabolic, and inflammatory interactions.
	Joint-Level Factors	Joint Injury: Fractures accompanied by cartilage, subchondral bone, ligament, or meniscal injury lead to knee OA in 21%–40% of cases
	Obesity-Related Mechanisms	- Adipokines: Receptors are present on joint cells, potentially contributing directly to synovitis, cartilage damage, and bone remodeling. - Infrapatellar Fat Pad (IFP): Produces cytokines, lipokines, growth factors, and lipid derivatives that affect disease progression.
	Diet & Nutrition	- Vitamin D: Extensively studied, but evidence remains inconsistent. - Other Diets: Higher intake of dietary fiber, soy milk, and adherence to a Mediterranean diet show promising effects.

function. As the disease progresses, pain in the middle stage becomes more common, and stiffness becomes unpredictable Daily life is affected by pain. In advanced stages, function is severely hampered by constant throbbing pain punctuated by brief, erratic bouts of intense agony. Specific mechanical reasons for pain include meniscal injury, ligament damage, subchondral microfractures, periosteal straining, osteophyte growth, increased intraosseous pressure, synovitis, and shrinking of the joint space.[19,20] Although the biological mechanisms underlying pain remain unclear, local inflammation may play an important role.[21] For example, increased IFP signal intensity on MRI, which indicates inflammation, was positively correlated with pain in osteoarthritic knees.[22,23]

Joint Stiffness

A common symptom of OA is joint stiffness, which can manifest as a lack of flexibility in the joints and cause discomfort or difficulty in movement. (Table 1) One of the main causes of joint stiffness is a lack of synovial surface-active phospholipids.[24] Although joint stiffness is most noticeable in the morning, it can also occur later in the day, particularly after being inactive for a while.[25] Studies have found that knee joint exercise affects IFP stiffness, and an increase in stiffness has been observed in patients with knee OA.[26,27] In severe knee OA, the knee fat pad is stiffer, and greater stiffness is associated with more severe symptoms.[27]

Bone Hyperplasia and Swelling

Both small (such as the interphalangeal joints) and large (such as the knee joints) joints may experience bone enlargement and swelling owing to OA. It is caused by various pathologies, such as blocked blood, soft tissue edema, damaged chondrocytes, circulation, increased bone density, and cystic degeneration.[28]

Risk Factors for OA

Personal-level variables, such as heredity, age, obesity, sex, and diet, and joint-level variables, such as injury, joint dislocation, and aberrant joint loading are among the many postulated risk factors for OA.[29] (Table 1) Although the probable mechanism underlying joint destruction remains unknown, age may be a primary risk factor for OA at the individual level. This could be attributable to several factors such as oxidative damage, cartilage thinning, muscular weakening, and impaired proprioception.[30] OA of the hands, knees, and hips is more common in women than in men, and its frequency increases with menopause.[31] Hormones are likely involved in the development of OA, which has led researchers to speculate on this phenomenon.[32] Other factors may explain why men and women differ in terms of reduced cartilage volume, bone loss, and muscle strength deficiency.[32] Genetic factors account for 60% of hand and hip OA cases and 40% of knee OA cases. Several genes may be involved in OA onset and development.[33]

Knee OA is more prevalent when the fracture is accompanied by cartilage injury, subchondral bone injury, lateral ligament injury, or meniscal injury, in 21%–40% of cases.[34] Although cartilage loss and damage are inevitable consequences of aging, not all individuals develop OA. Obesity is another major risk factor for OA. The complex interplay between metabolic, biomechanical, and inflammatory factors caused by obesity affects OA.[35,36] Studies have revealed a strong link between the pathophysiology of OA and adipose tissue growth.[37,38] Fat factor receptors are present in almost all cells within the joint; thus, they may directly contribute to OA through synovitis, cartilage damage, and bone remodeling.[39] In addition, IFP produces many factors that may affect disease progression through paracrine mechanisms, including cytokines, lipokines, growth factors, and fatty acid and lipid derivatives.[40] In contrast to the elevated secretion of arachidonic acid (which promotes PGE2 production and exacerbates cartilage inflammation), the IFP of OA patients also released higher levels of docosahexaenoic acid (DHA), a polyunsaturated fatty acid that suppresses key inflammatory mediators including proinflammatory cytokines, cartilage-degrading enzymes, and COX-2.[38] The role of specific vitamins and diet in OA is an active area of research. Among these, research on vitamin D is the most extensive, although the results are inconsistent.[41,42] In addition to the studies on specific vitamins, other studies have explored the relationship between various diets and OA. For example, a higher intake of dietary fiber and soy milk and adherence to the Mediterranean diet have positive effects on various outcomes of OA. However, further research is needed to confirm these findings.[43]

The Immune Mechanism of OA

Inflammation is considered a major pathophysiological mechanism of OA, which is a chronic condition.[44] Numerous cell and tissue types, both inside and outside the joints, are involved in the complicated pathophysiological phenomena of OA-related inflammation.[45] Genetic predispositions and changes in gene expression caused by variations in mechanical stress encountered by chondrocytes in articular cartilage are two of the many interrelated variables contributing to the complicated pathophysiology of OA.[46] A spatially and temporally confined inflammatory response is not only beneficial but essential for tissue healing and the restoration of homeostasis.[47] For instance, at the initial stage of fracture healing, known as the inflammatory phase, resident and recruited macrophages along with other immune cells at the fracture site release various cytokines in response to injury. This early inflammatory response initiates the recruitment, proliferation, and differentiation of MSCs, promotes the synthesis of extracellular matrix proteins, stimulates angiogenesis, and ultimately leads to tissue remodeling.[48] However, when inflammation becomes dysregulated and fails to resolve, it can progress into a chronic state.[49] A growing body of evidence implicates such persistent, low-grade inflammation—often linked to metabolic syndrome and innate immunity—as a key driver in the pathophysiology of OA.[7] One of the main elements in the pathophysiology of OA is the role of the immune system in its onset and progression.[50]

Synovium and Synovitis

Synovial inflammation, often known as synovitis, is a common symptom of OA. However, during joint illnesses, additional tissues, such as the articular cartilage, meniscus, and subchondral bone, also participate in inflammatory interactions.[51] In 1982, Goldenberg et al conducted a histopathological assessment of synovial tissues of patients with OA. They reported that nearly 90% of synovial tissues exhibited synovitis.[52] Tissue analysis and sensitivity imaging have demonstrated an extremely high incidence of synovial inflammation across all OA phases. Among patients with KL grades 2–3, the prevalence of synovitis was high. Among patients in the most severe stage (KL grade 4), up to 83% have synovitis.[53] Joint swelling, discomfort, and effusion are only a few clinical symptoms and indicators of OA directly caused by synovitis, which also represent the structural development of the disease.[54,55]

Synovial membranes are soft tissues present in the bursae, tendon sheaths, and joints. The intima is the inner layer of the continuous cellular layer, whereas the sub-intima is the outer layer. Macrophages and fibroblasts are present in the intimal layer, whereas blood, lymphatics, and fibroblasts are found in the subintimal layer.[56] As the primary barrier to molecular exchange between the articular cartilage and plasma, the synovium is essential for preserving the health of both the articular cartilage and joint. The synovial interstitium, which inhibits the diffusion of small molecules and the microvascular endothelium, which limits the transport of proteins, are dual-barrier structures that form the blood-synovial barrier.[57] In addition, Eymard et al found that IFP has a potential role in the induction of synovial inflammation in patients with severe knee OA. Furthermore, secretion of PGE2 by the IFP may be involved in the OA inflammatory process.[58]

In the case of synovial inflammation, the influx of macrophages and T cells, formation of new blood vessels, and secretion of proinflammatory cytokines are typical characteristics.[13] Comparing the main immunohistological features of inflammation in early and late OA, Benito et al have reported that synovitis severely influences disease progression.[54] Synovial tissue samples with evident hyperplasia of the synovium were immunohistochemically stained with obvious positive markers indicative of inflammatory cell infiltration (CD4+ and CD68+) and angiogenesis and were highly expressed in both early and late OA. Vascular endothelial growth factor (VEGF), intercellular adhesion molecule 1 (ICAM-1), proinflammatory cytokines, tumor necrosis factor α (TNF-α), and interleukin (IL)-1β are increased, and their expression is increased in early OA.[54] Sohn et al have reported that the synovial fluid of patients with OA exhibits higher proinflammatory cytokine levels (TNF-α, IL-6, and VEGF) than those of healthy individuals.[59]

Cellular and Molecular Mechanisms of OA Synovial Inflammation

Damage-associated molecular patterns (DAMPs), which are produced by the extracellular matrix (ECM) during cartilage degradation in the joint cavity, are key causes of both acute and chronic inflammation through the activation of the immune system in the synovium.[60–62] DAMPs are endogenous stimulants produced by dead cells or the ECM.[63] The

biological activities of DAMPs are mediated through pattern recognition receptors (PRRs).[64] The presence of these receptors in immune cells, osteoblasts, chondrocytes, and synovial cells has been previously confirmed. When DAMPs bind to these receptors, they initiate signalling pathways that trigger the activation of various transcription factors. This activation leads to the release of multiple components, such as the complement cascade, cytokines [including IL-1β, IL-6, and TNF-α], chemokines [such as CC motif chemokine ligands-2, −5, −7, and −8], catabolic factors [such as MMP-1, −3, −9, and −13], and cathepsins (B, K, and L)[65] (Figure 1).

In summary, stimulants introduced into the synovial cavity trigger the synovial cells to generate and release inflammatory mediators into the synovial fluid. These mediators subsequently stimulate chondrocytes to produce MMPs, creating a detrimental feedback loop between the synovium and the cartilage.[66] Inflammatory mediators, including cytokines, transcription factors, proteases, and ECM proteins, are linked to the definite roles of epigenetic changes and synovial inflammation in OA.[67,68] Moreover, excessive production of inflammatory mediators can result in the progressive degradation of tissues, and the origins and categories of these mediators may differ based on the OA phenotype. Given the intricate cellular and molecular mechanisms described above, we identified DAMPs as crucial in the development of OA synovitis. Targeting the activity of DAMPs and their receptors in immunotherapeutic approaches represents a promising avenue for OA treatment. Elucidating DAMPs, their receptors, and associated pathological pathways is essential to address degenerative joint conditions, including OA.

The infiltration of inflammatory cells (eg, mast cells, T cells, macrophages) into the infrapatellar fat pad (IPFP) and synovium is a hallmark of progressive osteoarthritis (KOA), leading to the secretion of various inflammatory mediators.[40] Among these, prostaglandin E2 (PGE2) plays a critical role in the crosstalk between the IPFP and synovium by stimulating the inflammatory response in fibroblast-like synovial cells.[58] In addition, leptin released by IPF can induce IL-8 expression via leptin receptor, IRS-1, PI3K, Akt cascade and promotion of NF-κB/p300 binding in human synovial fibroblasts.[69]

Immune Cells in OA Synovial Inflammation

Numerous immune cells from the innate and adaptive immune systems have been identified in the synovial tissues of patients with OA. According to Lindblad et al, inflammation in the synovium close to the cartilage may cause a more

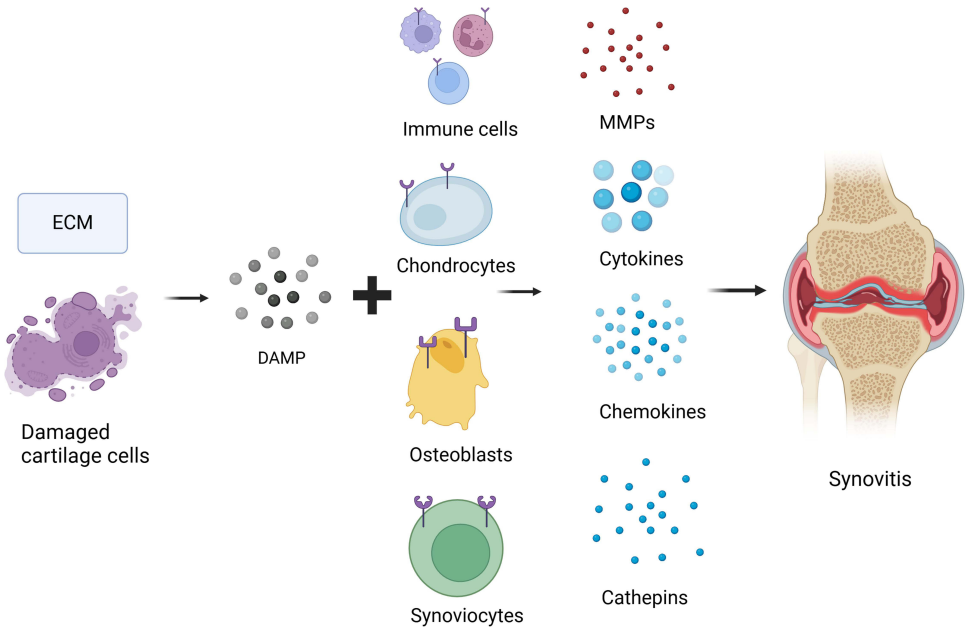

Figure 1 Cellular and molecular mechanisms in osteoarthritis synovial inflammation.Immune system activation is initiated and driven by chondrocyte death, triggering damage-associated molecular patterns (DAMPs). The biological activity of DAMPs is mediated by pattern recognition receptors, which are present on the surfaces of immune cells, chondrocytes, osteoblasts, and synovial cells. The binding of DAMPs to these receptors initiates downstream signaling cascades, leading to the activation of multiple transcription factors. Figure created in BioRender. Luo, P. (2025) https://BioRender.com/n10z021.

https://doi.org/10.2147/JIR.S563253

intense inflammatory response, which is characterized by T cells surrounded by B and plasma cells.[70] Compared with the synovium of healthy individuals, the synovium of patients with OA has fewer anti-inflammatory regulatory T cells and more proinflammatory immune cells, such as M1 macrophages, Th1 cells, and Th17 cells.[71–73] When synovial samples from patients with knee OA were examined, cells lining the joint were highly immunoreactive and phagocytic. Synovial fluid from end-stage osteoarthritic knees during total arthroplasty showed significant enrichment of macrophages, T cells, and neutrophils.[74]

To initiate tissue healing, different inflammatory cells are drawn to the site of damage and release proinflammatory and catabolic mediators.[75] To facilitate tissue healing, macrophages first move to the inflammatory site and then undergo phenotypic changes under the pathological conditions of OA. Furthermore, pathogens or DAMPs may be released by injured tissues and cells, which can trigger macrophage inflammatory signalling pathways, produce various cytokines, and attract additional inflammatory cells, such as T cells, neutrophils, and lymphocytes.[76] Researchers discovered that T-cells and macrophages account for 22% and 65% of the synovial tissue in patients with OA, respectively.[77] The neutrophil population was the smallest. The functions of neutrophils, T cells, and macrophages in OA are discussed in detail below.

Role of Macrophages in the Synovium in OA

As a basic defense system acquired by humans from invertebrates, the innate immune system recognizes infections using germline-encoded proteins.[78] Innate immune cells either directly destroy pathogens or trigger a cascade of events that activate the adaptive immune system. Natural killer (NK) cells, dendritic cells, and macrophages are cells of the innate immune system.[79] Innate immune cells called macrophages exist in nearly every tissue and affect homeostasis, wound healing, and immune response.[80] "Synovial macrophages" usually refer to tissue-resident macrophages located in the synovial membrane and subintima membrane.[81] The synovial membrane consists of two different cell types: synovial macrophages (type A synovial cells) and fibroblast-like synovial cells (type B synovial cells).[78] Their propensity for phagocytic behavior is their most distinctive trait. However, they also perform several other tasks, including producing and secreting many secretory chemicals and starting and controlling hormones and cellular immunity.[82] Synovial macrophages differentiate into osteoclasts with the ability to resorb lacunar material, although this process requires the involvement of M-CSF or TNF-α/IL-1 in addition to RANKL.[83] Macrophages also play a significant role in the production of MMPs, which are enzymes that break down all ECM proteins. In OA and other joint disorders, macrophage infiltration in the IFP has been observed to increase.[84] Studies have identified the presence of both M1-like (CD11c+) and M2-like (CD206+) macrophage markers in this tissue.[85,86] According to Wei et al, macrophages isolated from the IPFP of affected joints suppress the chondrogenic differentiation of MSCs,[86] indicating a potentially adverse effect of these macrophages on cartilage repair. Nonetheless, the exact roles and origins of macrophages within the IPFP require further investigation.

The inflammatory response necessary for musculoskeletal tissue healing is primarily mediated by macrophages.[87] Macrophages are the most prevalent invading cells and important mediators of inflammation, making them important players in OA. The microenvironment determines whether macrophages are typically activated (M1-type macrophages) or alternatively activated (M2-type macrophages).[88] Induced by proinflammatory mediators such as interferon-γ and lipopolysaccharide, M1-type macrophages secrete cytokines and contribute significantly to the host's defence against infection. In response to IL-4 and IL-13, M2-type macrophages secrete anti-inflammatory IL-10, the IL-1 decoy receptor, and arginase, further inhibiting the action of IL-1β and inducible Nitric Oxide Synthase (iNOS), and are associated with tissue remodeling. Along with fibroblasts, macrophages often remain dormant in healthy synovial joints. However, they can polarize into proinflammatory M1-type macrophages when OA stimulates inflammation.[89] In OA synovial fluid, M1-polarized macrophages release growth factors, cytokines, MMPs, TIMs, and other substances that cause inflammation and cartilage deterioration[90] (Figure 2). Furthermore, the ability of M1 and M2 macrophages to dynamically adjust their polarization in response to changes in the microenvironment suggests that macrophage polarization is plastic.[91] Thus, targeting macrophage polarization may prove to be a successful treatment strategy during the onset of OA, as it may decrease the production of detrimental inflammatory cues to chondrocytes by converting proinflammatory M1 macrophages into anti-inflammatory M2 macrophages. The direct in vivo involvement of macrophages in human OA was validated in another study.[92] Thus, inflammation and macrophages are intimately linked to joint symptoms and the radiological severity of OA in the knee.

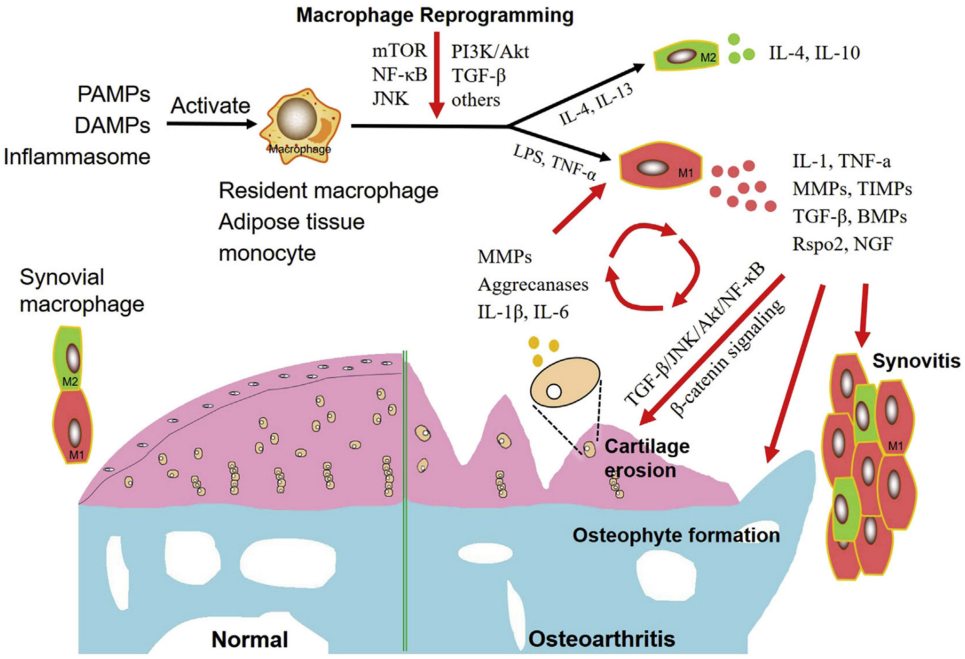

Figure 2 Mechanism of macrophages in osteoarthritis progression.Pathogen-associated molecular patterns, damage-associated molecular patterns (DAMPs), and inflammasomes are microenvironmental stimuli that promote the activation and polarization of synovial macrophages. This process is also regulated by signaling pathways, such as mammalian target of rapamycin, nuclear factor-κB (NF-κB), c-Jun N-terminal kinase (JNK), and phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt). The increased number of M1-polarized macrophages in the synovium of osteoarthritis secretes various factors, including cytokines, growth factors, matrix metalloproteinases, and tissue inhibitors of metalloproteinases, thereby triggering inflammation and subsequent cartilage degeneration and osteophyte formation. Besides autocrine interactions, polarized macrophages alter intracellular signaling pathways in chondrocytes, including transforming growth factor-β, JNK, Akt, NF-κB, and β-catenin signaling pathways, promoting the degradation of extracellular matrix components. As a DAMP, the ECM further stimulates the activation and polarization of macrophages, forming a vicious cycle of inflammation and cartilage degeneration. Polarized synovial macrophages and macrophage reprogramming may be suitable targets for the prevention and early treatment of osteoarthritis. Copyright 2020. Reproduced from Zhang H, Cai D, Bai X. Macrophages regulate the progression of Osteoarthritis. Osteoarthritis and cartilage. May 2020;28(5):555–561. doi:10.1016/j.joca.2020.01.007.[90]

The presence of active macrophages in the periarticular tissues of the knee joint and their correlation with OA symptoms suggest that inflammation caused by macrophages is frequent and might be the root cause or exacerbating factor of OA symptoms in other joints throughout the body.[93]

Role of T Cells in the Synovium in OA

T cells, including memory T cells, cytotoxic T cells, and helper T cells, play a key role in OA pathophysiology. T lymphocytes are the primary cause of synovial infiltration in patients with OA.[94] T cell infiltration in synovial tissue is dominated by CD4+ T cells, and patients with OA have more CD4+ T cells in the lower layer of the synovium than healthy individuals.[94] The CD4 antibody is a cytokine present in the surface of CD4+ T cells, which are crucial immunological cells in the human immune system. According to the enzyme-linked immunosorbent assay (ELISA) data, patients with OA had higher blood levels of soluble CD4 antibodies, according to ELISA controls. These findings suggest a role for peripheral T helper (Th) cells in the pathophysiology of OA.[77] Furthermore, T lymphocytes expressing HLA antigen D-related (DR) were found in the synovium of patients with OA, according to immunohistochemical investigations.[95] These results corroborated the observation that activated T cells are present in the synovium of patients with OA; nearly all T cells in the synovium of patients with OA expressed the activation markers HLA-DR and CD69.[96]

The interleukin-2 receptor (IL-2R) alpha chain CD25 is expressed mostly on the surface of immune-related cells such as B cells, NK cells, and activated T cells.[35] After interacting with its ligand IL-2, CD25 forms a high-affinity heterotrimeric receptor with β and γ chains and participates in a range of immunological responses.[97,98] According to the findings of an MR investigation by Luo et al, hip OA is causally associated with seven CD25-related characteristics.[99] The development of inflammation in hip OA can be reduced by either increasing the number of T lymphocytes expressing CD25 or increasing the expression level of CD25. A greater abundance of CD25, which competitively intercepts IL-2, a crucial component necessary

for the survival of nearby activated T cells, is responsible for this effect.[99] Overall, substantial alterations in T cell profiles have been observed in the synovial fluid, peripheral blood, and synovium of patients with OA.[95] Thus, T cells may be associated with OA etiology.

Numerous elements are important determinants of T cell destiny, including intracellular signal transduction [such as mechanistic Target Of Rapamycin (mTOR) complex 1 (mTORC1)], external stimuli (such as antigens), and cellular metabolism (such as amino acid metabolism).[100] For example, mTORC1 controls Th17 differentiation and IL-17 production via a number of pathways, including Signal Transducer and Activator of Transcription 3 (STAT3), Hypoxia-Inducible Factor-1-αlpha subunit (HIF-1α), Ribosomal protein S6 kinase 1 (S6K1), and Ribosomal protein S6 kinase 2 (S6K2), which suggests that mTORC1 signalling may be used to modify the pathophysiology of OA.[101] Furthermore, the activation and differentiation of T cells, particularly Th1 and Th17 cells, are significantly affected by amino acid metabolism and transport, suggesting that amino acid metabolism influences OA pathophysiology. Additionally, the balance between Th17 and Treg cells is disrupted throughout the degenerative phase of OA, resulting in inflammatory reactions and articular cartilage degeneration.[102] Patients can experience pain relief and improved joint function by regulating the Th17/Treg balance to reduce the inflammatory response. Therefore, controlling the Th17/Treg cell imbalance is a key target for the treatment of OA (Figure 3). Many levels of intervention, such as the modulation of different transcriptional regulators, cytokines, and epigenetic changes, can influence the activation and function of Th17/Treg cells. These interventions can reduce OA symptoms by altering the symptoms of OA. These targets should be considered promising novel therapeutic approaches for treating OA.

Role of Neutrophils in the Synovium of Patients with OA

A subset of polymorphonuclear leukocytes and neutrophils may be the first white blood cells drawn to the site of inflammation, serving as the first line of defense against invasive microbes.[103] Neutrophils participate in cytokine and chemokine cascades linked to inflammation and utilize intercellular interactions to regulate immune responses.[104] Neutrophils have the greatest potential for cytotoxicity among cells associated with OA because they produce reactive oxygen species and degrade enzymes.[105] Neutrophils comprise 8% of cells in synovial fluid.[106] In OA, neutrophils are

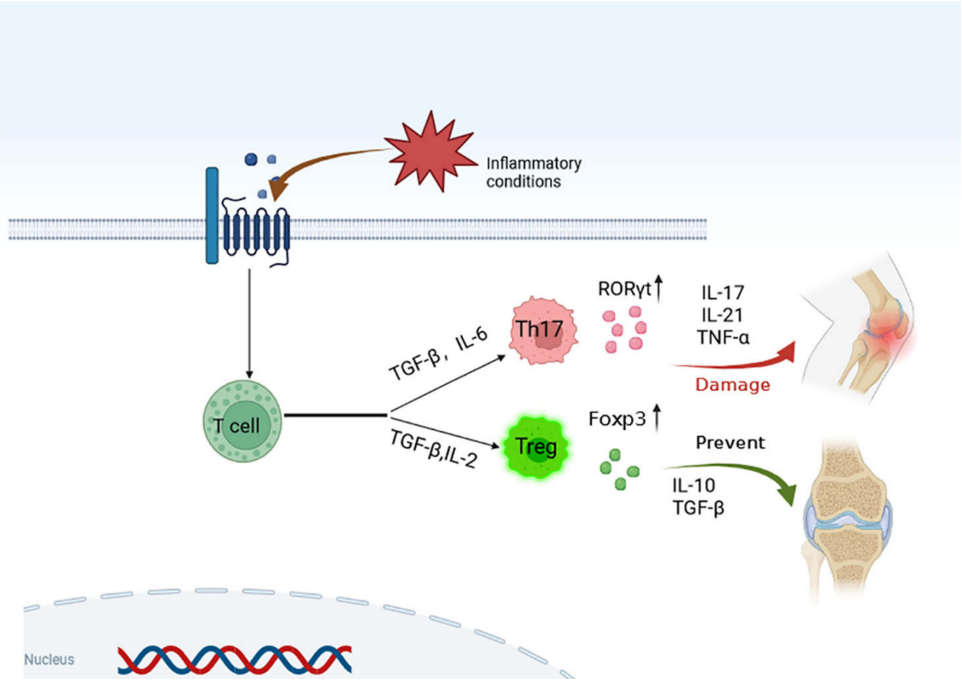

Figure 3 Imbalance of Th17/Treg cells is an important mechanism for OA occurrence.Th17 cells promote inflammatory responses. Meanwhile, Tregs inhibit inflammatory responses and antagonize the effects of Th17 cells. An imbalance in the Th17/Treg cell ratio is involved in the pathophysiology of OA. Copyright 2024, Reproduced from Wen Z, Qiu L, Ye Z et al. The role of Th/Treg immune cells in osteoarthritis. Frontiers in immunology. 2024;15:1393418. doi:10.3389/fimmu.2024.1393418.[102]

among the first immune cells to enter the synovium. They also contribute to many chemokines and cytokines released by the immune cells into the synovial fluid[107] (Figure 4). The synovium and synovial fluid of patients with OA contain chemokines that recruit immune cells and activate signaling cascades that accelerate the progression of OA. In synovial fluid, neutrophils form complexes with neutrophil gelatinase-associated lipocalin and MMP-9, which accelerates cartilage degradation.[74] VEGF is present in neutrophils, and a significant amount of VEGF is present in the supernatant following vesicle release upon stimulation.[108] VEGF exacerbates OA pain, increases vascular density, and promotes endothelial cell proliferation within the OA synovium.[109]

On the one hand, degradative elastase is strongly related to the severity of OA, with neutrophils being the primary source.[74] Chondrocyte enlargement and compensatory synthesis throughout the ECM occur naturally during endochondral ossification, but are inappropriately stimulated at the onset of OA. Moreover, in advanced OA, chondrocyte differentiation, proliferation, and hypertrophy are unrestrained, leading to subchondral bone calcification and hardening, accompanied by articular surface fibrosis.[110,111] Hypertrophic chondrocytes die and stop growing as OA progresses. Apoptosis-induced cavity emptying causes articular cartilage degradation, eventually leading to osteophytes.[74] Neutrophil elastase (NE) can drive neutrophils and other immune cell types to move through the ECM, thereby increasing inflammation. In vitro studies have demonstrated that NE, even at low doses, can rapidly destroy cartilage collagen.[112] Overactivation of MMP-13 may be the medium that cause permanent cartilage degradation in patients with OA.[113] Neutrophils release NE, which activates latent pro-MMP-13. Pro-MMP-13 is a critical regulatory node between maintaining cartilage homeostasis and triggering pathological destruction. In the study of OA pathogenesis, detecting the level of pro-MMP-13 is often used as a biomarker for the activity of tissue remodeling, particularly cartilage degradation.[114] In vitro, NE directly and robustly activated pro-MMP-13, and N-terminal sequencing identified cleavage close to the cysteine switch at[70] MKKPR, ultimately resulting in the fully active form with the neo-N terminus of[83] YNVFP, which is closely related to cartilage collagen destruction in OA patients with synovitis.[112]

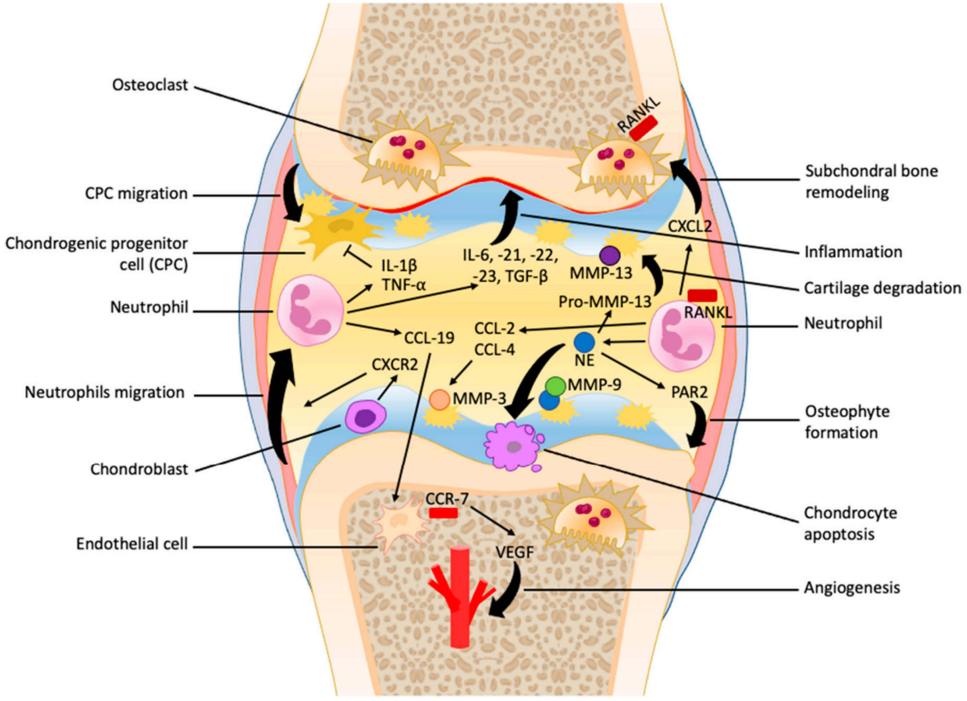

Figure 4 Role of neutrophils in the osteoarthritis progression. Neutrophils are recruited to the synovial bursa and promote the secretion of numerous cytokines and chemokines in the synovial fluid, which facilitate inflammatory responses and vascular infiltration, and inhibit the migration of chondroprogenitor cells. Neutrophil elastase formation exacerbates cartilage degradation, chondrocyte apoptosis, imbalance of subchondral bone remodeling, and osteophyte formation. Copyright 2022. Reproduced from Chaney S, Vergara R, Qiryaqoz Z, Suggs K, Akkouch A. The Involvement of Neutrophils in the Pathophysiology and Treatment of Osteoarthritis. Biomedicines. Jul 6 2022;10(7)doi:10.3390/biomedicines10071604.[107]

Treatment for Synovitis in OA

Current Treatment Methods

Currently, the cause of OA remains unresolved. Controlling symptoms, slowing disease progression, and improving the quality of life are the goals of all OA treatments. Currently, OA is treated with medication, surgery, physical therapy, exercise therapy, and weight loss (if applicable).

Most patients with OA take various medications, including glucocorticoids, opioids, nonsteroidal anti-inflammatory drugs, and cytokine inhibitors, which can reduce inflammation to some degree.[115,116] Intra-articular injection of corticosteroids effectively relieves OA pain, although its effect is short-lived.[117] Intra-articular injection of the corticosteroid FX006 has short-term efficacy. Researchers have examined the long-term effects of a triamcinolone acetonide (TA) extended-release formulation prepared using microsphere technology in patients with knee OA. According to several randomized, double-blind, controlled dose optimization studies, TA-ER can considerably improve the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) ratings for physical function, pain, and stiffness. Compared to the placebo, it also improved knee injury and OA outcome scores, particularly the Knee Osteoarthritis Outcome Scale - Quality Of Life (KOOS-QOL) score. Thus, it has been authorized by the Food and Drug Administration to treat OA-related knee discomfort. An additional benefit of the TA-ER mode of action is that systemic exposure is lower than that of rapid-release triamcinolone acetonide because of its slower intra-articular release rate.[118] Currently, intramuscular and intra-articular steroid injections offer temporary relief from OA symptoms. In the United States, sustained-release formulations for intra-articular steroid injections have recently been approved.

In cases where all therapeutic and pharmacological intrusions have proven ineffective, clinical procedures, including arthroscopic lavage, debridement, bone microfracture, and abrasion arthroplasty of the worn joint, may be necessary.[119] The most common physical therapies for patients with OA are electrotherapy, acupuncture, ultrasound, and cold and heat therapy.[120] Exercise therapy can improve changes in pain scores in patients with OA, increase muscle strength, and increase the stability of the affected joint; however, no difference in inflammatory activity has been observed.[121]

Potential Treatment Methods

Drugs have long been injected intra-articularly to treat patients with OA, and this method works well because it produces short-term analgesic and anti-inflammatory benefits.[122] Extended and frequent injections can cause cartilage deterioration or damage to the other joint components. Consequently, investigating the biological regulatory factors that can stimulate cartilage regeneration and maintain joint homeostasis is crucial and beneficial for advancing novel intra-articular therapeutic approaches. Further investigation of the molecular mechanisms that trigger and maintain synovial inflammation is required. A deeper understanding of these pathways might reveal novel therapeutic targets. Macrophage polarization offers valuable insights for the development of novel interventions against OA. Clinical studies have demonstrated that the intra-articular administration of cells and their derivatives is promising for promoting the polarization of synovial macrophages within osteoarthritic joints. The use of platelet-rich plasma (PRP) is a strategy that is becoming increasingly popular in therapeutic settings. (Table 2) PRP, which is made from a patient's blood, stimulates tissue-building processes, reduces inflammation, and relieves pain to maintain joint health.[123] Preclinical studies have shown that PRP increases M2 macrophage polarization and suppresses M1 macrophage polarization in OA. PRP has anti-inflammatory properties by altering the canonical NF-κB signalling pathway in various cell types, including chondrocytes, synovial cells, and macrophages.[124] Adipose tissue-derived mesenchymal stem cells (ADMSCs) are a promising cell source.

These cells display substantial immunomodulatory and anti-inflammatory properties via the prostaglandin E2 (PGE2)/cyclooxygenase 2 (COX) 2 pathway.[125] (Table 2) ADMSCs reduce NF-κB1 and NF-κBIA (NF-κB signal inhibitors) and therefore may primarily activate the NF-κB pathway to suppress macrophages.[126] Furthermore, Ma et al engineered groundbreaking artificial M2 macrophages, which have remarkable therapeutic potential as M2 macrophages in OA treatment.[127] Macrophage membranes make up the "shell", whereas the "yolk" consists of nanogels that are responsive to inflammation. This construct showed targeted delivery and prolonged retention in inflammatory areas while suppressing macrophage immune activity and has potential as a future intra-articular treatment for OA. Photobiomodulation therapy

Table 2 Summary of Novel Therapeutic Strategies for Osteoarthritis (OA)

Therapeutic Strategy	Mechanism of Action / Characteristics	Research Stage / Findings	References
Conventional Intra-articular Injections	Provides short-term analgesic and anti-inflammatory effects.	Clinically applied, but frequent injections may cause joint damage.	[122]
Platelet-Rich Plasma (PRP)	Derived from patient's blood, stimulates tissue repair and reduces inflammation; promotes polarization of macrophages toward the anti-inflammatory M2 phenotype and suppresses the pro-inflammatory M1 phenotype in preclinical studies, exerting anti-inflammatory effects via the NF-κB pathway.	Increasingly popular in clinical settings; effective in preclinical studies.	[123,124]
Adipose Tissue-Derived Mesenchymal Stem Cells (ADMSCs)	Exhibit significant immunomodulatory and anti-inflammatory properties, primarily via the PGE2/COX-2 pathway; may suppress macrophage activity by modulating the NF-κB pathway.	A promising cell source.	[125,126]
Artificial M2 Macrophages	Innovative biomimetic structure (macrophage membrane "shell" encapsulating an inflammation-responsive nanogel "core"), enabling targeted delivery to inflammatory sites and suppression of immune activity.	Preclinical research, shows great potential as a future intra-articular therapy.	[127]
Photobiomodulation Therapy (PBMT)	Low-level laser therapy that reduces pain and levels of inflammatory cytokines; first demonstrated to shift synovial macrophage polarization from M1 to M2 phenotype in OA models, improving synovitis and cartilage degradation.	An emerging therapeutic strategy, effective in animal models.	[128,129]
MMP-13 Inhibitor (CL82198)	Matrix Metalloproteinase-13 (MMP-13) is a key enzyme degrading cartilage ECM and a important therapeutic target. CL82198 inhibits its activity.	Significantly alleviated OA progression in a preclinical model, but no clinical studies have been conducted.	[130]
Targeting Inflammatory Cytokines (TNF, IL-1)	These two key pro-inflammatory cytokines can initiate an intra-articular inflammatory cascade, directly leading to the release of matrix-degrading enzymes such as MMPs, which subsequently break down cartilage.	Suggests potential therapeutic targets.	[131,132]

Abbreviations: ECM, extracellular matrix; PGE2, prostaglandin E2; COX-2, cyclooxygenase-2; OA, osteoarthritis.

(PBMT), also known as low-level laser therapy, is an emerging therapeutic strategy. PBMT has been shown in vivo to reduce pain, decrease the levels of inflammatory mediators (eg, TNF-α, IL-1β, and IL-6) and decrease joint swelling in various animal models of OA.[128] Zhang et al showed for the first time that PBMT can alter synovial macrophage polarization in collagenase-induced mouse knee OA.[129] For example, we exposed the right knees of OA mice to a 630-nm LED device at different power densities for 4 weeks, and histological and immunostaining analyses revealed significant improvements in synovitis, cartilage degradation, and osteophyte formation. The transition of synovial macrophage polarization from M1 to M2 phenotype may partially contribute to therapeutic outcomes.[129]

Two important proinflammatory cytokines that can initiate the synthesis of inflammatory mediators in the joint microenvironment are TNF and IL-1.[131,133] Broadly expressed MMPs and other matrix-degrading enzymes are released directly leading to cartilage degradation.[132] A family of zinc-dependent proteolytic enzymes known as MMPs is essential for the breakdown of ECM components. Among them, MMP-13 has emerged as a promising therapeutic target. Wang et al examined the effect of an MMP-13 inhibitor, CL82198, on MMP-13 activity in a preclinical OA model.[130] Beginning on the first postoperative day, the surgically generated OA model mice received either CL82198 or saline control via daily intraperitoneal injection.[130] After CL82198 treatment, OA progression was significantly alleviated. However, no clinical studies have investigated this compound.[130]

Outlook

The novelty of our review lies in its systematic construction of the "immune-inflammation-destruction" vicious cycle network model in OA, which advances beyond the traditional mechanical wear paradigm. It highlights the paradigm shift towards immune-targeted therapies over symptomatic treatment and prospectively outlines an evolving path toward precision medicine, thereby providing a new theoretical framework and therapeutic strategy for OA research. The future paradigm of OA treatment is expected to shift toward precision medicine based on immune subtyping, achieving joint homeostasis restoration through chronological interventions (eg, early-stage immunomodulation combined with late-stage regenerative strategies).

Currently, the broad consensus is that OA is a complex condition influenced by multiple factors and that synovitis and immune cells are key contributors to its progression. Investigating the role of immune cells in OA pathogenesis can help preserve joint homeostasis and mitigate pathological damage. Consequently, novel targeted therapies are gaining increasing attention. Additionally, many emerging treatment strategies focus on slowing the degeneration of articular cartilage; however, the capacity to restore joint structure is deemed essential for individuals with advanced OA.[134] Regenerative medicine, a field that leverages cell and gene therapy, along with tissue engineering, has emerged as one of the most promising areas in biotechnology. It offers significant potential for researchers, healthcare professionals, and patients.[135] Moreover, regenerative medicine holds the potential for personalized therapy and for addressing complex, multifactorial conditions, including OA.

Data Sharing Statement

Data availability is not applicable as no data was generated for this paper.

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Author Contributions

PW - Conceptualization, Formal Analysis, Writing - Original draft; LL - Methodology, Investigation, Formal Analysis, Writing – Original draft. All authors took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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