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Inflammation in osteoarthritis: the latest progress and ongoing challenges

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Abstract

Purpose of review—The understanding of inflammation in osteoarthritis is rapidly evolving. This review highlights important basic science, mechanistic, and clinical findings since 2020 that underscore the current notion of osteoarthritis as an inflammatory disease.

Recent findings—There exists a disconnect between clinical radiographic findings and patient symptoms in osteoarthritis. Inflammation, in particular synovitis, has been put forward as a potential explanation for this disconnect. New findings have shed light on the temporal dynamics and activation states of joint-resident or systemically derived immune cell populations, notably macrophages, that participate in the inflammatory response. The intricate crosstalk in which they engage may underpin disparate pain and symptoms in patients, for instance during osteoarthritis flares. The role of biological and environmental factors such as exercise, age, and diet, have been the subject of recent studies for their protective or destructive roles in osteoarthritis inflammation. Despite these advances, no disease-modifying osteoarthritis treatments targeting inflammation have emerged.

Summary—Osteoarthritis is a debilitating chronic disease that manifests with widely varying symptomatology. Inflammation is now appreciated as a key pathophysiological process in osteoarthritis, but there remain considerable gaps in our understanding of its role in disease progression and how best to target the inflammatory response for therapeutic interventions.

Keywords

inflammation; osteoarthritis; treatment

INTRODUCTION

Inflammation was not initially held to be a feature of osteoarthritis, despite the etymological origins of the suffix ‘-itis’, meaning inflammation [1]. Once it was discovered that acute and chronic inflammation were evident in osteoarthritis, it was viewed as simply a sequela rather than a driver of disease, especially when compared with prototypical inflammatory

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conditions, such as rheumatoid or psoriatic arthritis. Indeed, clinical studies of inflammatory arthritis have conventionally utilized osteoarthritis tissue samples as ‘non-inflammatory controls’. However, recent preclinical and clinical evidence now strongly supports the notion that inflammation is a central protagonist in driving osteoarthritis disease.

Osteoarthritis inflammation is a complex pathophysiological phenomenon that encompasses multiple cell and tissues types within and beyond the joint. Spatially and temporally limited inflammation is beneficial and necessary for tissue repair and the restoration of homeostasis; however, uncontrolled, dysregulated inflammation that does not resolve is destructive and underpins chronic inflammatory conditions [2]. Synovial inflammation, termed synovitis, is a classical hallmark of arthritis; however, other tissues such as articular cartilage, meniscus, and subchondral bone also participate in inflammatory interplay during joint disease. Pioneering work in the 1960s and 1970s employed radioisotope tracing to assess joint inflammation. Dick *et al.* [3] observed greater uptake of intravenously delivered radioisotope in inflamed joints, which they ascribed to greater synovial tissue and fluid volume as a result of synovitis. In response to the paucity of clinical data on synovial pathology in osteoarthritis, in 1982, Goldenberg *et al.* [4] assessed histopathology of osteoarthritis patient synovial tissue and found almost 90% exhibited synovitis. Prior to the 21st century, biochemical and immunological assays lacked the sensitivity to properly assess inflammatory markers in osteoarthritis patients. Using a new high-sensitivity assay for C-reactive protein (CRP), Spector *et al.* [5] showed a positive correlation between serum CRP and osteoarthritis disease progression, suggesting a systemic Inflammatory profile. This was early evidence of systemic inflammation in osteoarthritis. By the turn of the century, the broad notion of inflammation as a pathological driver of osteoarthritis, rather than just a secondary symptom, started to take hold [6]. The landmark histopathological classification system for synovitis developed by Krenn *etal.*[7] in 2002 allowed for more comprehensive assessment of inflammation in arthritis. Mounting evidence in the two decades since has solidified the central role of inflammation in osteoarthritis [1,8,9]; however, there still exists many unanswered questions about its underlying mechanisms, clinical manifestations, and above all, how to effectively target inflammation for disease-modifying therapeutics.

This review synthesizes the most recent findings from 2020 onwards to assess our understanding of osteoarthritis as an inflammatory disease, to highlight the latest mechanistic insights into inflammation in osteoarthritis, and relate these findings to our progress on targeting inflammation to treat osteoarthritis.

CELLULAR AND MOLECULAR MECHANISMS OF INFLAMMATION IN OSTEOARTHRITIS

The innate inflammatory response

Accumulating findings from *in vitro* studies and preclinical animal models have shed light on acute and chronic inflammatory mechanisms in osteoarthritis. A fundamental driver of acute and persistent inflammation is the presence of endogenous intracellular or extracellular stimuli known as damage-associated molecular patterns (DAMPs), which activate innate immunity via pattern recognition receptors such as the toll-like receptor

(TLR) and nod-like receptor (NLR) families [10]. DAMPs are proposed to underlie the vicious inflammatory cycling between joint-resident cell types during various arthritides, and their temporal fluctuation may be the basis of unpredictable, sudden-onset osteoarthritis flares [11], reminiscent of those seen in rheumatoid arthritis.

Joint-resident and systemically derived immune cells play a crucial role in orchestrating the inflammatory response, via perpetuating DAMP-derived signals and interacting with other resident cell types. Recent findings from Huang *et al.* [12▪▪] in a mouse model of inflammatory arthritis have shed light on the importance of F4/80^{hi} MHC Class II^{neg} synovial resident macrophages in the timely resolution of inflammation. Resolution is achieved in part by suppressing the *in situ* differentiation of infiltrating monocytes into an F4/80^{hi} MHC Class II^{pos} macrophage phenotype, which is responsible for perpetuating chronic synovitis, and promoting monocyte differentiation into a F4/80^{hi} MHC Class II^{neg} resident-like phenotype, which is capable of suppressing chronic inflammation. Given the use of an autoimmune inflammatory arthritis model in this study, further investigation is necessary to understand whether similar resident and systemically derived macrophage subsets also regulate the onset, perpetuation, and resolution of osteoarthritis inflammation. The endocannabinoid system (ECS) has gained recent attention as an inflammatory mediator in numerous disease contexts, and in 2021, Rzeczycki *et al.* [13] demonstrated that cannabinoid receptor type II is highly expressed by F4/80^{pos} synovial macrophages, which enrich greatly in the synovium of injured mouse joints. Targeting this receptor pharmacologically induced strong anti-inflammatory effects *in vitro*, demonstrating the potential to leverage the ECS as a strategy to block macrophage-mediated inflammation [14]. In human osteoarthritis patients undergoing end-stage total knee arthroplasty, macrophages, T cells, and neutrophils were found to be highly enriched in synovial fluid [15▪]. Neutrophils are potent producers of reactive oxygen species, elastase, and cytotoxic granules and are usually enriched in the acute inflammatory phase [16], so their abundance and persistence into end-stage osteoarthritis raises questions about the true extent of their role in osteoarthritis pathoetiology. Using flow cytometric-based intracellular staining, the same study demonstrated that macrophage-derived TGF-β1 and neutrophil-derived elastase served as sensitive biomarkers for radiographic knee osteoarthritis severity and, strikingly, as strong predictors of knee osteoarthritis progression. Mast cells, another granulocytic innate immune cell type, are scarce in synovium but have been shown to promote inflammation and cartilage degradation in the DMM model of osteoarthritis [17]. Intra-articular delivery of mast cells has been used as a model to mimic osteoarthritis inflammatory flares in mice [18]; however, the mechanisms underpinning their activation and degranulation remain to be fully elucidated.

Pain and inflammation

Pain is a key clinical feature of osteoarthritis and the chief complaint of osteoarthritis patients [19], but its manifestation is both multifaceted and difficult to predict. Mounting evidence points towards the importance of inflammation in the onset and persistence of pain in osteoarthritis [20], and multiple studies have established strong correlations between the severity of synovial inflammation and patient-reported pain [21–24]. Using the monoiodoacetate (MIA) injection model in mice, Morgan *et al.* observed acute histological

features of synovial inflammation prior to the emergence of disease in subchondral bone or articular cartilage [25■]. Concurrent with early inflammation, knee joint afferent neurons in the joint capsule/synovium, but not subchondral bone afferents, were activated and sensitized, underlying an acute and marked pain phenotype. Pain in late-stage disease was associated with sensitization of both joint capsule/synovial and subchondral bone afferent neurons. These findings link the early inflammatory response with a concomitant pain response and onset, but further work is needed to better assess the causality and directionality of this notion. In a 2021 study, synovial regions of higher pain in knee osteoarthritis patients were profiled by single-cell RNA-seq (scRNA-seq) and found to harbor more fibrotic, neurogenic, and pro-inflammatory-skewed stromal and immune populations [26■■], supporting the notion that distinct anatomically distributed cellular profiles with pro-algesic gene expression signatures underpin patient pain experiences. The authors found a distinct subset of human synovial fibroblasts enriched with a neurotrophic secretome that may recruit innervation during osteoarthritis, including neurotrophins such as glial cell line-derived neurotrophic factor, oncostatin M, leukemia inhibitory factor, and interleukin 6 (IL-6). IL-6 is a pleiotropic cytokine that has long been implicated in osteoarthritis inflammation [27]. New findings in 2022 have uncovered a role for IL-6 both in mediating cartilage degradation via JAK/STAT3 signaling, and in pain sensitization and neurite outgrowth, in an ERK-dependent manner [28■■]. An IL-6-expressing synovial fibroblast subset has recently been described in mice, which may orchestrate immune cells as part of the inflammatory response to joint injury [29■]. The CCL2–CCR2 axis, relevant in macrophage chemotaxis during inflammation [30], is now recognized to also promote nociceptive innervation in the joint. Intra-articular delivery of the ligand CCL2, which is elevated in osteoarthritis synovial fluid as part of the inflammatory milieu, excited knee joint sensory afferents and caused a transient pain response [31■■]. The receptor, CCR2, is expressed by nociceptors and its blockade by CCR2 receptor antagonist ameliorated knee hyperalgesia, building on previous finding that *Ccr2* knockout mice are resistant to hyperalgesia [32].

Gene regulation in the inflammatory response

Transcription factors govern gene expression to tightly control the inflammatory response and downstream sequelae. Members of the Krüppel-like factor (KLF) family of transcription factors, KLF2 and KLF4, are downregulated in aged and osteoarthritis human cartilage [33■■]. Through direct transcriptional activation of core cartilage and extracellular matrix (ECM) genes such as *SOX9* and *COL2A1*, and suppression of inflammatory and catabolic genes *iNOS, IL-6*, and *MMP13*, both KLF2 and 4 were shown to confer protection against unchecked inflammation and ECM degradation. Elayyan *et al.* [34■■] shed light on the interplay between inflammation and pathological mineralization in osteoarthritis. Their findings uncovered the Wnt/β-catenin pathway transcription factor LEF1 to be induced during inflammation and responsible for driving mineralization in a mouse model of posttraumatic osteoarthritis (PTOA). Ablation of LEF1 reduced pro-inflammatory NF-κB signaling, with a concurrent increase in chondrogenic and ECM genes, protecting against ectopic mineralization. In a mouse model of spontaneous age-related osteoarthritis, Catheline *et al.* [35■] dissected the nuanced signaling functions of NF-κB, showing that loss of the p65 (RELA) subunit of NF-κB blocked induction of senescence-associated

genes, whereas loss of the p50 (NFKB1) subunit induced senescent gene expression in chondrogenic cells. The role of senescence in osteoarthritis was recently reviewed in detail in [36].

RECENT CLINICAL EVIDENCE FOR OSTEOARTHRITIS AS AN INFLAMMATORY DISEASE AND SYNOVITIS AS A PROGNOSTIC DISEASE MARKER

A critical aspect of osteoarthritis disease that has mystified the field is the clear disconnect between radiographic findings and patient symptomatology: some individuals exhibit advanced joint disease with minimal disability, whereas others experience extensive pain, stiffness, and disability at relatively early stages of disease. This is further supported by the much higher incidence of asymptomatic, radio-graphically diagnosed osteoarthritis compared with symptomatic osteoarthritis, evidence obtained from large imaging cohort studies such as the Osteoarthritis Initiative [37]. Recent studies have sought to rectify this disconnect by describing synovitis as the ‘missing link’ between radiographic findings and clinical symptoms, and MRI studies evaluating synovitis in knee osteoarthritis patients have associated synovitis with symptoms and pain. Yang *et al.* [38] found that increased perimeniscal and suprapatellar synovitis were associated with worse knee symptoms. They also found that serum markers of matrix turnover, type III collagen degradation (C3M) and metabolite of C-reactive protein (CRPM) were inversely related to knee symptoms. Another study by Perry *et al.* [39] correlated increased whole-joint and site-specific synovial tissue volume with knee pain and proposed using synovial tissue volume relative to the size of the femoral condyle as a synovitis-relevant outcome measure of knee osteoarthritis in clinical trials. Fan *et al.* [40▪] observed that osteophytes were associated with pain and dysfunction only when presenting with concurrent bone marrow lesions or effusion-synovitis, indicating that intra-articular inflammation may drive or contribute to the pain-promoting effects of other pathological manifestations such as osteophytes.

Further recent clinical studies have assessed the composition of inflamed synovium by MRI, particularly the infrapatellar fat pad, and have shown a reduced fat fraction in joints with more advanced osteoarthritis [41,42], indicative of inflammatory edema and fibrosis. Loss and/or fibrotic remodeling of the infrapatellar fat pad are, therefore, potential imaging markers of osteoarthritis progression. Despite the importance of inflammation in tissue healing, especially in the case of injury, the long-term effects of chronic inflammation are largely deleterious in the joint, and recent clinical evidence supports that chronic synovitis leads to faster rates of progression in osteoarthritis patients compared with those without chronic inflammation [43]. In addition to the chronic effects, Markus *et al.* [44▪] found that increased inflammation-relevant biomarker concentrations in synovial fluid at the time of injury, namely MCP-1, VEGF, and IL-1Ra, were associated with worse articular cartilage disease 8 years following ACL reconstruction surgery, directly implicating the pathogenic role of the early inflammatory response in driving osteoarthritis progression.

Although inflammation is strongly associated with pain in osteoarthritis, the exact mechanisms are still not fully understood. Changes in osteoarthritis pain scores have

been shown to improve with exercise therapy while not demonstrating any differences in inflammatory activity [45]. The triggers of painful osteoarthritis flares have been a target of recent studies. The ACT-FLARE study in 2021 was a recent effort to characterize the nature, duration, and causes of osteoarthritis flares in adults with knee osteoarthritis. They found that flares last for a median of 5 days and interestingly, were more frequent in younger than older patients [46]. In agreement with previous studies [47,48], the strongest positive physical activity associations included knee buckling, squatting/kneeling, lifting heavy objects, and standing or walking for long periods without a rest. Weaker associations were found with sitting for long periods and moderate-to-vigorous physical exercise. Positive associations were also found for psychosocial and environmental triggers ranging from poor sleep, and low mood or depression, reinforcing the complex causes of inflammatory flares in osteoarthritis. This study demonstrates the multifaceted contributions of biomechanical, environmental, and psychosocial factors to osteoarthritis inflammation.

Kanthawang *et al.* [49] found that being overweight or obese was associated with increased synovial inflammation imaging biomarkers, effusion synovitis, infrapatellar fat pad abnormalities, and a greater synovial proliferation score. These increased biomarkers were further correlated with pain symptoms and cartilage damage with substantial reproducibility. The link between obesity and osteoarthritis severity is continuing to evolve and is increasingly recognized as independent of greater joint loading, suggesting a multifactorial relationship between the comorbidities likely involving metabolic inflammation [50,51]. Further recent evidence links metabolic inflammation to osteoarthritis pain. Sellam *et al.* [52] found that higher serum levels of leptin–adiponectin ratio and usCRP were associated with higher knee/hip osteoarthritis pain in women. This study establishes that not only local intra-articular inflammation, but also systemic inflammation, contribute to joint nociception. Taken together, these recent studies confirm the disease-promoting and pain-promoting role of both local and systemic inflammation, and more work is needed to establish robust prognostic models based on local and systemic inflammatory biomarker profiles, which can aid in more personalized treatment for osteoarthritis.

THERAPEUTIC APPROACHES TO TARGETING INFLAMMATION IN OSTEOARTHRITIS

The results of phase 2 and 3 clinical trials for osteoarthritis were recently summarized in a detailed review by Vrouwe *et al.* in December of 2021 [53] in which they focused on various treatment targets for osteoarthritis, including inflammation-related targets. Since publication of that review, a few additional clinical trials have been approved and are recruiting. An Food and Drug Administration (FDA)-approved nutraceutical, astaxanthin, is being evaluated in patients with advanced stage osteoarthritis awaiting total joint replacement surgery (NCT05138549). Oral astaxanthin supplementation is proposed to reduce inflammation, mitigate pain, and improve physical function, and prior preclinical work demonstrated that astaxanthin may inhibit inflammation by activating Nrf2 signaling and blocking MAPK-mediated protease expression in chondrocytes [54]. Another clinical trial will evaluate the efficacy of the senolytic agents Quercetin and Fisetin (NCT05276895), two naturally occurring flavonoids shown to induce apoptosis in senescent cells [55,56].

Reduction of pain and inflammation is also the objective of a clinical trial assessing oral cannabidiol (CBD) in combination with physiotherapy compared with physiotherapy alone (NCT05020028). CBD, a nonpsychoactive cannabinoid found in the cannabis plant, has been a widely tested treatment for inflammatory conditions because of its demonstrated anti-inflammatory and analgesic effects.

Although a large number of osteoarthritis clinical trials are currently underway or pending publication, many of these trials are limited to patients with advanced or end-stage disease (i.e. Kellgren-Lawrence grades 3–4) and are, therefore, less likely to markedly improve patient symptoms and very unlikely to halt or reverse disease progression. Thus, trials in patients with earlier stages of disease (i.e. grades 1–2) are warranted and necessary to minimize the number of treatments that 'fail' because of their inability to affect a highly diseased joint.

CONCLUSION

Extensive recent advances have elucidated molecular mechanisms of inflammation in osteoarthritis and allowed us to more accurately understand its contribution to the clinical manifestation of osteoarthritis. To date, despite new evidence summarized herein, it remains controversial which resident and recruited cells are responsible for joint destruction versus inflammatory resolution and tissue regeneration. The refined yet increasingly complex understanding of the various phenotypes assumed by resident and infiltrating synovial macrophages in osteoarthritis is a key example of the need to abandon conventional notions about 'good vs bad cells' and move towards a more sophisticated understanding of the spatial and temporal dynamics of stromal and immune cells orchestrating inflammation in osteoarthritis. Lastly, considering the now recognized pathogenic contribution of inflammation to osteoarthritis disease progression, clinical trials testing anti-inflammatory drugs in early stages of disease, especially sustained-release intra-articular formulations, are critically needed to mitigate tissue destruction and the aberrant nociceptive innervation underpinning pain in advanced disease.

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KEY POINTS

- Recent studies have refined our understanding of dynamic immune cell phenotypes, notably macrophages, and conventional notions of a simple unidimensional macrophage phenotype spectrum (i.e. M1--M2) should be abandoned.
- Robust new clinical associations have linked joint inflammation to worse pain and disease progression, further solidifying intra-articular inflammation as a viable treatment target.
- No recent clinical trials have made major breakthroughs, and there is a critical need to test anti-inflammatory therapies, notably sustained-release intra-articular formulations, in early stages of disease.