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Role of low-grade inflammation in osteoarthritis

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Abstract

Purpose of review—Inflammatory changes in joint tissues can be detected by modern imaging techniques in osteoarthritis patients, but may be clinically subtle compared with many other types of arthritis. These changes associate with disease progression and clinical severity, and many inflammatory mediators may have biomarker utility. Moreover, a number of inflammatory mechanisms play a role in animal models of disease, but it is still not clear which mechanisms predominate and might be therapeutically manipulated most effectively. This review highlights specific examples of recent advances published in the past 18 months that have advanced this field.

Recent findings—Clinical investigators now show that synovial inflammation is associated with pain sensitization, and similar to knee osteoarthritis, is a common and important feature of hand osteoarthritis. In addition, recent advances in basic studies demonstrate inflammatory markers and mechanisms related to leukocyte activity, innate immune mechanisms, and the chondrocyte-intrinsic inflammatory response that might provide better opportunities for early detection, prognosis, or therapeutic intervention.

Summary—Inflammation plays a central role in osteoarthritis pathogenesis, but additional translational work in this field is necessary, as are more clinical trials of anti-inflammatory approaches.

Keywords

inflammation; osteoarthritis; pattern-recognition receptors; synovitis

INTRODUCTION

Signs of inflammation such as synovitis can be identified in knee osteoarthritis patients using magnetic resonance imaging (MRI) and ultrasonographic imaging. Imaging signs often correlate cellular inflammation and inflammatory cytokine production in the joint. A variety of cytokines are produced by multiple joint tissues and cell types, and can promote

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inflammatory and catabolic responses in chondrocytes [1]. Many of these cytokines may be biomarkers of inflammatory activity, but their clinical utility in early detection, diagnosis, or prognosis needs further assessment. Studies in both osteoarthritis patients and animal models have revealed that innate inflammatory pathways triggered by pattern-recognition receptor (PRR) signaling are activated in the joint. In this review, we focus on recent studies that advance current knowledge of how low-grade inflammation impacts clinical features, and the inflammatory mechanisms involved that may impact stratification of patients for clinical trials and options for osteoarthritis therapy in the future. The references included highlight common themes, and span clinical and basic sciences.

IMAGING OF SYNOVITIS

Recent MRI and ultrasonographic imaging studies [2–4] advance methodology for synovitis detection, and confirm the relationship between synovitis, symptoms, and progression of structural disease in knee osteoarthritis. At least two groups have now linked synovitis to signs of pain sensitization [5,6■■]. Quantitative sensory testing in 1111 patients enrolled in the Multicenter Osteoarthritis Study (MOST) revealed associations between synovitis and signs of peripheral and central sensitization even after adjusting for depression and catastrophizing. Recent work also indicates that the relationships between synovitis seen on imaging and disease severity are relevant to hand osteoarthritis [7,8■,9■,10,11]. In these cohorts, synovitis correlates with joint tenderness [7,12■], joint space narrowing [9■,10], and development or progression of erosive disease [11,12■]. In one study [8■], synovitis was more frequent and severe in patients with erosive hand osteoarthritis. But multivariate analysis suggested the increased risk of radiographic progression was not fully explained by the presence of synovitis. The authors speculated there might be differences, not detectable by imaging, in the nature of the synovitis in erosive osteoarthritis that might explain increased risk. This hypothesis needs further investigation.

LEUKOCYTES IN OSTEOARTHRITIS

Synovitis defined on imaging may reflect a variety of histopathologic features, including increased leukocytes or synovial thickening and fibrosis. Abnormalities in peripheral leukocytes have been reported and might reflect local or systemic inflammation [13]. A number of investigators have begun to evaluate the nature and activity of leukocytes in osteoarthritis. Work in this area is just emerging, but is needed to fully understand the impact of immune responses in disease.

PERIPHERAL LEUKOCYTES POPULATIONS

Recent phenotyping of peripheral blood leukocytes (PBLs) from 114 osteoarthritis patients compared with healthy controls [14■] showed that CD8+ cell proportions were increased in osteoarthritis, particularly memory or inflammatory subsets. Age-related declines in T-lymphocytes seen in healthy controls in this study were not observed in knee osteoarthritis patients, suggesting alteration by the disease process. The significance of expanded T-lymphocyte subsets in osteoarthritis needs additional evaluation, but at least one group has reported reduced disease in both CD4 [15] and CD8 deficient mice [16] in a surgically

induced model. Another recent study reported increased PBL inflammatory activity in three cohorts of patients with knee osteoarthritis [17■]. In this study, plasma levels of arachidonic acid metabolites prostaglandin E2 (PGE2) and 15-hydroxyeicosatetraenoic acid, which act as lipid mediators of inflammation, showed utility in discriminating symptomatic knee osteoarthritis patients from controls. PBL expression of cyclooxygenase-2 (COX-2), a key enzyme in arachidonic acid metabolism, was associated with progression of joint space narrowing over 2 years. These results are interesting but need to be replicated, particularly in 'preradiographic' disease wherein identifying active inflammation as the cause of joint pain may be difficult.

LOCAL INFILTRATION OF CELLS

Cell counts in osteoarthritis synovial fluid are categorized as 'noninflammatory', but can vary over 10-fold (i.e., <100 to 2000 cells per ml). An interesting new report shows that knee synovial fluid leukocyte counts correlate with synovial volume on MRI, and might predict symptomatic response to intra-articular corticosteroid injection [18■]. If these results can be replicated in larger populations, synovial fluid leukocyte counts could provide a cost-effective marker of inflammation to guide targeted application of anti-inflammatory therapies.

Two recent studies [19■,20■] employ flow cytometry to study synovial membrane infiltration; both found CD14+ macrophages most abundant, followed by CD4+ T lymphocytes. In the second study [20■], pain scores available from a subset of patients correlated with proportions of synovial CD4+ cells, indicating a role for infiltrating T cells in osteoarthritis pain that needs further investigation. The second study [20■] reported similar infiltration in the infrapatellar fat pad (IFP). IFP inflammation is reported in animal models of joint injury and osteoarthritis [21], so future investigation of the underlying mechanisms and consequences should be forthcoming.

Molecular markers of macrophage activation in both synovial fluid and serum were recently associated with progression of joint space narrowing and severity of pain in knee osteoarthritis [22■]. Macrophage imaging for detection of active joint inflammation is now being investigated in both animal models [23■■] and humans [24■■]. In a small pilot study of knee osteoarthritis patients [24■■], administration of a labeled folate-receptor agonist to identify activated macrophages using SPECT/CT (single photon emission computed tomography) imaging was reported [24■■]. 76% of knees demonstrated positive signal in capsule, synovium, and subchondral bone, which correlated with radiographic and symptom severity. In a rat model, a labeled formyl peptide receptor-1 (FPRI) agonist was used for similar purposes [23■■]. Computed tomography (CT) and PET imaging 5 days after intra-articular injection of mono-iodoacetate to induce osteoarthritis showed that this agent preferentially localized to the treated knee, and confocal imaging of tissue sections confirmed localization to synovial macrophages. These imaging techniques provide an important tool for investigations of macrophage-related mechanisms in osteoarthritis going forward. Clinical utility in humans is not yet clear, but may be helpful to distinguish patients with active inflammation for trials.

MECHANISMS OF INFLAMMATION

In osteoarthritis, inflammatory signaling pathways, including those mediated by nuclear factor-κB (NFκB), are likely triggered by products of tissue damage and stress through a variety of cell-surface PRRs. A central role for NFκB signaling in chondrocyte-intrinsic inflammatory responses is supported by many studies [25]. A number of PRRs have been implicated in osteoarthritis including the Toll-like receptors (TLRs) and receptor for advanced glycation end products (RAGE). Ligands for these receptors include pathogen associated molecular patterns (PAMPs, i.e., lipopolysaccharide or LPS), damage associated molecular patterns (DAMPs, including products of extracellular matrix damage), and the endogenously produced alarmins (i.e., HMGB1 or S100A proteins). Multiple cell types within the joint express PRRs, including macrophages, fibroblasts, and chondrocytes [1,26]. Here, we highlight recent studies that describe how mechanisms related to epigenetics, noncoding RNAs (ncRNAs), intracellular energy balance, glycobiology, and obesity-related disturbances can promote or interact with inflammatory pathways in osteoarthritis.

DAMAGE ASSOCIATED MOLECULAR PATTERNS AND ALARMINS

Recent studies have demonstrated the importance of certain DAMPs and alarmins in promoting inflammation in osteoarthritis basic studies. It has been hypothesized that catabolic fragments of articular matrix can act as DAMPs in osteoarthritis, but a recent study [27■■] was the first to characterize a specific fragment from articular matrix. Lees *et al.* [27■■] showed that a 32-mer peptide of aggrecan, generated by sequential enzymatic cleavage in joints of patients with osteoarthritis, promotes catabolism and suppresses anabolic gene expression via MyD88 and TLR-2 in murine and human chondrocytes, synovial fibroblasts, and macrophages. Another group provided evidence that pharmacologic interference with alarmins may provide therapeutic opportunities [28■■]. The S100A8 and S100A9 proteins can drive cartilage inflammatory activity and catabolic responses via TLR-4, as well as disease progression in the collagenase murine model of osteoarthritis. These investigators have now used paquinimod, which prevents S100A9/TLR binding, to block synovial inflammatory activity *in vitro* and ameliorate joint damage in the same model [28■■]. Interference with PRRs and their ligands has not yet been translated to human disease, but these studies provide promise for future developments.

INFLAMMATION AND OBESITY

Obesity is a strong risk factor for osteoarthritis, and is characterized by a low-grade systemic inflammatory state. Metabolic derangement in obesity can promote inflammation in a variety of ways, and mechanisms are continuing to be elucidated. A novel mechanism recently hypothesized relates to LPS, which signals through TLR-4. Low levels of LPS are routinely detectable in obese patients even in the absence of infection, presumably due to disturbances in gut microbiome. Investigators from West China Medical School and Duke University postulated that this could be relevant to the impact of obesity on osteoarthritis [29■]. They optimized techniques for LPS detection in serum and synovial fluid, and showed that levels correlated with macrophage infiltration into the joint. Correlations between pain scores and radiographic features were seen with both serum and synovial fluid

LPS levels. In a separate study [30■], an agonist of the nuclear receptor peroxisome proliferator-activated receptor-alpha (PPAR-α) was shown to attenuate synovial fibroblast LPS responses, pointing to potential therapeutics. However, whether the relationship between LPS and osteoarthritis severity is directly mediated by TLR-4 interaction remains to be seen. In one surgical animal model, deficiency of TLR-4 did not affect structural disease [31], but additional studies using obesity or diet-related models are clearly warranted.

There is a single report exploring the micro-biome in a rat model of diet-induced obesity (DIO) and osteoarthritis [32■■]. DIO rats developed more osteoarthritis changes in the joint than control animals at 28 weeks, had higher serum LPS levels, and had a higher abundance of lactobacilli and clostridial species. Interestingly, osteoarthritis severity correlated with body fat percentage, but not body mass. Relationships between osteoarthritis histopathology and *Methanobrevibacter* and *Lactobacillus* species abundance were identified. Given the disturbance of the microbiome in obesity and evidence for roles in inflammatory arthritic diseases [33], this remains an important unexplored area in osteoarthritis.

GLYCOBIOLOGY AND INFLAMMATION

Galectins are glycan binding-proteins that modulate cell–cell and cell–matrix interactions, and play important roles in inflammation [34]. Differential expression of galectin-1 in osteoarthritic cartilage was previously noted [35]. These authors now further these observations [36■] by confirming increasing expression of galectin-1 by human chondrocytes with increasing cartilage degeneration. They also demonstrate that galectin-1 binding to chondrocytes mediates NFκB signaling and catabolic gene expression. Whether this pathway plays a central role *in vivo* in promoting chondrocyte-intrinsic inflammation remains to be tested.

Lubricin (a mucin-like glycoprotein) and hyaluronan (a polysaccharide) are major components of synovial fluid that synergize to provide boundary lubrication, protecting articular cartilage and maintaining joint function. Hyaluronan has been demonstrated to modulate inflammation through TLR interaction. The potential for lubricin to also influence TLR inflammatory signaling was investigated recently [37■■]. Using in-vitro approaches, lubricin binding to TLR-2, 4, and 5 was demonstrated. Lubricin did not activate TLR signaling in primary osteoarthritis synovial fibroblasts, but down-regulated signaling induced by other ligands (i.e., LPS). Finally, intra-articular lubricin lessened cartilage damage, synovial inflammation, NFκB activation, and pain in a rat osteoarthritis model. Although confirmation is needed that in-vivo effects are mediated by TLRs, this work suggests that lubricin protects against inflammatory challenges mediated by TLR ligands.

INFLAMMATION AND PAIN

The link between inflammation and pain in osteoarthritis has been a recent area of investigation. Miller *et al.* [38■] wondered whether TLR-4 could provide a direct link between tissue damage and pain sensitization. They demonstrated that murine dorsal root ganglion (DRG) neurons express TLR-4, and that LPS as well as the alarmins S100A8 and α2-macroglobulin could promote calcium influx and monocyte chemoattractant protein-1

production from neurons *in vitro.* Further, using the destabilization of the medial meniscus model of murine osteoarthritis, they showed that blockade and deficiency of TLR-4 prevented these responses. TLR-4$^{-/-}$ mice still developed allodynia in the model, so additional work is necessary to determine the contribution of this pathway to pain sensitization in osteoarthritis. Another group tested whether an ion channel involved in nociception (transient receptor potential ankyrin 1, or TRPA1), might also drive inflammation in the MIA (mono-iodoacetate) model of murine osteoarthritis [39■]. When injected into the hind paw of the mouse, MIA induced acute paw swelling, and TRPA1 deficiency or blockade significantly reduced swelling. They then measured hind limb weight bearing as a reflection of pain up to 28 days after intra-articular injection of MIA, and found attenuation in the difference between affected and unaffected limbs in TRPA1$^{-/-}$ mice. These studies reveal potential common pathways driving inflammation and nociception in osteoarthritis, but further work is necessary to ensure future translation.

MECHANISMS MODULATING CARTILAGE-INTRINSIC INFLAMMATORY RESPONSES

Intracellular zinc transport is an important mechanism modulating cartilage catabolic responses and disease progression in a murine osteoarthritis model [40]. A recent DNA methylation study suggests that epigenetics links inflammation and zinc transport [41■■]. The DNA methylome of cartilage from 23 hip osteoarthritis patients demonstrated two clusters, one with significant hypomethylation of inflammation-related genes. These investigators now show that promoter hypomethylation correlates with increased expression of proinflammatory cytokines in these patients. Moreover, genes involved in zinc transport (*ZIP* genes) were coordinately expressed with proinflammatory genes and catabolic proteases. This work has implications for phenotyping patients via epigenetic profiling, to better identify those that might respond differently to antiinflammatory interventions.

ncRNAs also modulate transcriptional activity. One group of investigators recently identified micro-RNA (miRNA)-142-3p as an important regulator of cartilage-intrinsic inflammatory responses with relevance to osteoarthritis, using both in-vitro and in-vivo modeling [42]. The alarmin HMGB1 was identified as a potential target of this ncRNA, but more work is needed to confirm that their observations are due to effects on HMGB1. Long-intergeneic noncoding RNAs (lincRNAs) are a more recently discovered class of ncRNA. This year, Pearson *et al.* identified novel chondrocyte inflammation-associated lincRNAs [43■■], by comparing RNASeq profiles from nonstimulated and interleukin-1β (IL-1β)-stimulated human primary chondrocytes. They found that two previously unreported lincRNAs act as negative regulators of chondrocyte inflammatory responses, and were significantly downregulated in human osteoarthritis cartilage. These novel ncRNA species may provide future opportunities for therapeutic development.

The importance of intracellular bioenergy sensors AMPK (AMP-activated protein kinase) and SIRT1 (sirtuin 1, anNAD-dependent deacetylase) in chondrocyte inflammatory signaling has recently been reviewed [44■]. AMPK, which acts in part through SIRT1, senses intracellular adenosine nucleotide levels allowing cells to respond to changing energy

demands. AMPK is constitutively active in chondrocytes and maintains homeostasis despite hypoxia present in normal cartilage. In osteoarthritis, as well as in aging, chondrocyte catabolic responses to biomechanical injury and inflammatory cytokines are enhanced, whereas AMPK activity is reduced, and pharmacologic AMPK/SIRT1 activation can mitigate enhanced catabolism by promoting autophagy while attenuating NFκB activation. As a number of available pharmacologic agents can activate these sensors, a path to translational may be available to protect cartilage from inflammation-related stress.

CONCLUSION

There is now a wealth of evidence that inflammation plays a central role in osteoarthritis pathogenesis, by driving chondrocyte-intrinsic catabolic responses, promoting synovial inflammation, and contributing to joint pain. Inflammation can be triggered within the joint from tissue damage and stress responses, and obesity-related systemic inflammation might enhance these local responses. Recent clinical studies demonstrate that synovitis is an important disease feature linked to progression and pain, both at the knee and in osteoarthritis of the hand. Moreover, synovitis may predispose to development of pain sensitization in patients, and recent basic studies point to mechanisms that link inflammation and nociception. Emerging evidence suggests pathways that might be targetable by future anti-inflammatory therapies. Specific examples presented here include alterations in joint glycobiology that modulate innate responses, and epigenetic and ncRNA-related mechanisms involved in chondrocyte inflammatory transcriptional responses. Mechanistic links between obesity and systemic inflammation are providing a molecular framework for the impact of adiposity on osteoarthritis. It is likely that future anti-inflammatory interventions will be dependent on disease stage, clinical phenotypes, and cell type targeted. Multiple models including injury-induced and metabolically induced osteoarthritis need to be utilized to improve efforts at translation. But these recent advances by both clinical and basic scientists provide hope that specific targeting of inflammatory pathways, and perhaps subtyping patients based on inflammatory profiles, may expand treatment options for osteoarthritis.

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KEY POINTS

- Evidence from recent studies continues to support a central role for inflammatory pathways in processes relevant to osteoarthritis, including regulation of the chondrocyte catabolic response, development of low-grade synovitis, and modulation of pain responses.
- New clinical imaging studies now provide evidence that synovitis is related to disease severity measures in hand osteoarthritis, and may be related to pain sensitization. Moreover, imaging modalities to detect activated macrophages are being developed and may help distinguish active inflammation from inactive synovial thickening.
- Epigenetic mechanisms, ncRNAs, and intracellular bioenergy sensors may be important modulators of inflammatory and catabolic signaling in chondrocytes.
- The PRRs and their ligands (DAMPs and alarmins) may be targetable, and in disease models show promise for ameliorating osteoarthritis-related cartilage erosion, synovitis, and pain. More translational work in this field is greatly needed.