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Innate Inflammation and Synovial Macrophages in Osteoarthritis Pathophysiology

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Abstract

Although osteoarthritis (OA) was historically referred to as the non-inflammatory arthritis, it is now considered a condition involving persistent low-grade inflammation and activation of innate inflammatory pathways. Synovitis increases the risk of OA onset and progression and involves the recruitment of monocytes, lymphocytes, and other leukocytes. In particular, macrophages are important mediators of synovial inflammatory activity and pathologic cartilage and bone responses that are characteristic of OA. Advances in understanding how damage-associated molecular patterns (DAMPs) trigger monocyte/macrophage recruitment and activation in joints provide opportunities for disease-modifying therapies. However, the complexity and plasticity of macrophage phenotypes that exist *in vivo* have thus far prevented the successful development of macrophage-targeted treatments. Current studies show that synovial macrophages are derived from distinct cellular lineages, which correspond to unique functional roles for maintaining joint homeostasis. An improved understanding of the etiology of synovial inflammation in specific OA-subtypes, such as with obesity or genetic risk, is a potential strategy for developing patient selection criteria for future precision therapies.

Keywords

Macrophages; Innate Immunity; Osteoarthritis; Synovitis

Introduction

The name osteoarthritis (OA) implies that it is an inflammatory disease. However, for many years the role of inflammation was contested, spawning the use of alternative names such as

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osteoarthrosis and degenerative joint disease (1). This controversy was based in part on the belief that the central pathological features of the disease were articular cartilage erosion and pathological bone growth, as seen by osteophytes and subchondral bone sclerosis. In addition, compared to "inflammatory joint diseases" such as rheumatoid arthritis, OA patients were characterized by lower levels of pro-inflammatory serum biomarkers and less remarkable synovitis (2,3). Questions continued as studies linked biomechanical factors to OA risk (4–7), and clinical trials testing anti-inflammatory therapies failed to modify OA progression (8–10). Yet, evidence connecting inflammation and OA remained (11,12) and eventually flourished with the advent of more sophisticated techniques to broadly interrogate cellular, molecular, and genetic factors associated with OA. These studies revealed persistent low-grade inflammation, and in particular activation of innate inflammatory pathways, as central mediators of OA pathogenesis (13–15).

The persistent low-grade activation of innate inflammatory pathways has led OA to be likened to a chronic wound (16). This concept is based on evidence of an aberrant wound-healing response in the OA joint (17). Classically, the wound-healing response involves a clotting reaction to stop bleeding, inflammation, cellular proliferation, and tissue remodeling, resulting in the resolution of inflammation and formation of a scar. The initial inflammatory response is triggered by danger/damage associated molecular patterns (DAMPs), which are endogenous molecules released into the extra-cellular space following tissue damage or cellular stress (18–20). DAMPs stimulate innate immunity by interacting with pattern-recognition receptors, including toll-like receptors (TLRs), expressed on sentinel tissue-resident immune cells and joint tissue stromal cells (21). The resulting cellular signaling cascade leads to the production of cytokines, chemokines, growth factors, and matrix proteases, which coordinate cellular proliferation and tissue remodeling responses. There is increasing evidence that tissues throughout the whole joint contribute to this wound-like response in an autocrine and paracrine-like manner (22,23). Notably, sustained protease-mediated breakdown of cartilage and meniscus tissue generates an ongoing source of DAMPs, which feed into a continuing cycle of inflammation and tissue destruction (18,20,24). Altered joint biomechanics may also contribute to the cycle of inflammation with the recognition that mechanically induced tissue damage and mechanotransduction stress signaling can trigger cytokine production and cell-derived DAMPs (25–27). These observations have helped to unite what previously seemed like distinct pathological mechanisms under the umbrella of inflammation. Many questions remain, however, about the specific cellular and molecular mediators that initiate the onset of disease and drive its progression (28,29). These topics have been discussed in numerous other recent reviews (30–35). In this review, we focus on evidence surrounding the role of synovial macrophages in OA pathophysiology.

Synovitis and Synovial Macrophages in OA

Inflammatory cell infiltration of the synovial membrane occurs to a lesser degree and is more heterogeneous in patients with OA compared to those with rheumatoid arthritis (3,36). Nevertheless, many features of inflammatory arthritis, including lymphoid follicles and perivascular fibrosis, occur in a portion of OA cases (3). Neovascularization and mild synovitis are also present in the joints of patients at risk for OA due to soft-tissue injuries

(36). In a large prospective epidemiological study, joint effusion and synovitis were detected in approximately half of the study participants who had OA symptoms but no radiographic pathology (37), further indicating that synovitis is not restricted to late stages of disease. Moreover, baseline synovial thickening and synovitis were shown to increase the rate of OA progression and are associated with increased pain and dysfunction (38,39). Micro-array analysis of inflamed synovial tissue revealed a distinct transcriptional C-C family chemokine signature, suggesting that synovitis in patients at risk for OA involves the recruitment of monocytes, lymphocytes, and other leukocytes (39).

Macrophages are well established as key cellular mediators of innate immunity and tissue remodeling in the wound healing response following injury (40,41). Macrophages also appear to play similar roles in OA. For example, more than 10 years ago, Bondeson and colleagues showed that depletion of macrophages in OA synovial explants significantly reduced the production of numerous cytokines, including tumor necrosis factor (TNF), interleukin-1 (IL-1), IL-6, and IL-8 (14). Importantly, macrophage depletion and neutralization of macrophage-derived TNF and IL-1 also downregulated matrix metalloproteinase (MMP) production, thereby linking synovial macrophages to cartilage degradation (14). Blom *et. al.* confirmed a role for synovial macrophages in MMP-mediated cartilage degeneration *in vivo*, using the murine collagenase-induced model of OA and intra-articular injection of clodronate to deplete macrophages prior to inducing OA (42). The same investigators previously demonstrated a critical role for synovial macrophages in promoting osteophytosis in the model (43). The effect on pathologic bone formation in OA was attributed to a decrease in macrophage-derived growth factors that are typical of wound-healing responses, but are also important in chondrogenesis and bone formation (TGFβ, BMP-2 and BMP-4) (43,44). In follow-up studies, this group showed that the Collagenase model of OA used in these studies, in contrast to injury-induced models, has a robust synovial inflammatory component and is dependent on activation by the S100A8/9 family of DAMPs (45). This body of work has implicated macrophage-mediated inflammatory activity in pathologic cartilage and bone responses characteristic of OA, although it also suggests that the impact of inflammation in OA is complex and influenced by the inciting stimulus.

The focus on macrophages and OA has continued to build in recent years. In a revealing set of studies, Kraus and colleagues investigated the presence of activated macrophages in patients with knee OA (KL: 1–4) directly *in vivo* using etarfolatide (EC20) imaging, which selectively detects folate receptor expression on activated, but not resting, macrophages (46). They found that the quantity of activated macrophages in knee joints correlated with radiographic OA severity and symptoms (46,47). In addition, etarfolatide uptake positively correlated with OA symptoms in joint sites throughout the body (47). Kraus and colleagues also compared etarfolatide uptake to soluble macrophage markers in synovial fluid and serum (46). The markers CD14 and CD163 are shed when macrophages are activated by pro- and anti-inflammatory cytokines, respectively. Notably, both CD14 and CD163 were detected in synovial fluid and correlated with EC20-quantified knee macrophage abundance (46). These data suggest that macrophages are etiological factors in OA pain and that measurement of soluble macrophage markers may predict the risk of OA progression.

If macrophages indeed drive OA progression then strategies that target their recruitment and accumulation in the synovium may be one approach for a disease-modifying OA therapy. The C-C family chemokine receptors CCR2 and CCR5 are important mediators of monocyte/macrophage recruitment to sites of inflammation. In OA patients, synovial fluid levels of CCR2 ligands (i.e., CCL2, CCL7, and CCL8) but not CCR5 ligands (i.e., CCL5, CCL3) were increased compared to a cohort of control individuals with a knee injury but no OA (48). CCL2 was expressed in OA chondrocytes and OA synovial fibroblasts stimulated with cartilage-derived debris and the OA-associated alarmin S100A8 (48). CCR2-positive macrophages were also observed in OA synovium adjacent to damaged cartilage (48). Further studies in mouse models of post-traumatic knee OA showed that genetic or pharmacologic inhibition of CCL2/CCR2 signaling reduced OA pathology and pain-related behavior, although differences have been reported between investigators in the effectiveness of targeting CCL2/CCR2 and may be dependent in part on the timing of inhibition (48–51). Therapeutically targeting the recruitment and accumulation of monocytes/macrophages to OA joints is one of several strategies to modify macrophage-mediated inflammation and OA pathology.

Macrophage activation and polarization states are tightly controlled and vital for regulating effective wound healing (40). Activated macrophages have traditionally been defined as “M1” and “M2” polarization states based on *in vitro* stimulation models that drive pro-inflammatory or immuno-regulatory phenotypes, respectively (52). In OA synovium and cartilage, cytokines associated with M1 macrophages (e.g., TNF, IL-1β, IL-6) are well established for their role in stimulating pro-catabolic mediators, such as aggrecanases and MMPs. However, it has been difficult to assess the polarization state of synovial macrophages at earlier stages of disease or even prior to the onset of OA. At the end stage of OA, both M1- and M2-like macrophages are present in joint synovium and adjacent adipose tissue (53). Using a genetic approach, Zhang and colleagues generated mice with either M1- or M2-enhanced macrophage polarization to evaluate the positive and negative effect of polarization bias on OA risk (54). Mice were subjected to two models of knee OA, Collagenase and meniscal destabilization, to evaluate the effect of macrophage polarization bias on OA models with high and low levels of synovitis, respectively. As predicted, mice with a pro-inflammatory M1 bias developed greater synovial inflammation and cartilage pathology; whereas, mice with an M2 bias were protected, albeit at later time points only (54). When analyzed in detail, M1-enhanced macrophages were found to promote cartilage degradation and osteophyte development through the production of *Rspo2*, a cytokine previously identified as a Wnt signaling agonist (54).

The focus on synovial macrophages as drivers of OA symptoms and pathology has led to therapeutic strategies involving the removal of synovial macrophages to slow the progression of disease. These strategies presuppose that macrophages primarily modulate OA pathology through their pro-inflammatory and pro-catabolic actions. However, in compelling preclinical study by Wu and colleagues, the authors showed the depleting joint macrophages using macrophage Fas-induced apoptosis (MaFIA)-transgenic mice did not reduce OA pathology (55). Although macrophage depletion acutely reduced both M1 and M2 macrophages in the joints of mice following meniscal destabilization surgery, it increased the infiltration of CD3+ T cells and neutrophils into the injured joint, resulting in

greater synovitis and systemic inflammation (55). Thus, given that macrophages regulate synovial immune cell homeostasis, these findings indicate that a more detailed understanding of the functional roles of macrophage subtypes will be required for therapies that target macrophage removal.

Two studies published earlier this year bring new insight into macrophage subtypes in OA joints and their homeostatic role in synovial tissues. In the study by Wood et al. (56), flow cytometry was used to compare the population of immune cells in synovial tissue from OA patients undergoing total knee replacement and from inflammatory arthritis patients. The comparison showed that immune cells in OA patient synovium were overwhelmingly dominated by macrophages while T cells were dominant in the synovium of inflammatory arthritis patients (56). RNA sequencing of synovial tissue macrophages identified two distinct OA subgroups, one more similar to macrophages isolated from inflammatory arthritis synovium (i.e., proliferative, inflammatory-like OA subgroup) and one that was distinct and characterized by cartilage remodeling genes (i.e., classical OA subgroup) (56). An important observation was that neither subgroup aligned with an M1 or M2 phenotype. This points to the importance of detailed evaluations of macrophage phenotypes, and it also highlights the limitation of the M1/M2 paradigm to capture the complexity and plasticity of macrophage phenotypes that exist *in vivo*. Patient characteristics such as radiographic KL scores or serum C-reactive protein or erythrocyte sedimentation rate values were not predictive of the relative proportion of inflammatory and classical OA macrophages, suggesting that more specific biomarkers will be needed to identify patients with differing synovial macrophage subgroups.

Intriguingly, work by Culemann and colleagues showed that synovial macrophages are derived from distinct cellular lineages and that these differences are associated with different functional roles in the joint (57). Specifically, a population of CX_3CR1^+ tissue-resident macrophages were identified in mice that express tight junction proteins and create a barrier-forming population of macrophages that line the synovium (57). These “epithelial-like” macrophages are maintained through a local pool of proliferating CX_3CR1^- mononuclear cells in the synovial interstitium and are distinct from chemokine recruited monocyte-derived macrophages (57). The barrier-forming macrophage population was nearly gone in synovium from patients with inflammatory arthritis (57). Whether or not it is also impaired in the synovium of OA patients remains to be seen. Thus, understanding the origin and functional consequences of macrophage sub-populations will be vital for developing more specific macrophage-targeted OA-modifying therapies. Furthermore, developing biomarkers to assess the heterogeneity of macrophage sub-groups will likely be important for establishing patient selection criteria for macrophage therapies.

OA Risk Factors & Inflammatory Phenotypes: Targets for Future Therapies?

One of the most clinically significant risk factors for developing OA is obesity (58,59). Obesity increases OA risk in both knee and hand joints, although the greatest impact is on the knee where obesity doubles the lifetime risk of symptomatic OA compared to individuals with a body mass index (BMI) below 25 (60). Similarly, many components of the metabolic syndrome, such as central adiposity, dyslipidemia, hyperglycemia, and hypertension are

associated with OA pathology and the risk of progression (31,61–63). Although the causal role of metabolic syndrome and its components in knee OA progression remain unclear (64,65), related factors such as high dietary fat consumption (66) and type 2 diabetes (67) are each associated with more rapidly progressing joint space narrowing in individuals with knee OA, even after adjusting for BMI. Given the strong causal relationship between metabolic dysfunction and pro-inflammatory macrophage activation that occurs with obesity (68,69), it seems likely that metabolic inflammation ("metaflammation") also increases OA risk (31).

Chronic low-grade inflammation that occurs with obesity is due in part to the accumulation of pro-inflammatory macrophages in abdominal adipose tissue. This raised the question of whether a similar phenomenon occurs in the infra-patellar fat pad, thereby producing a local source of inflammation that increases OA risk. However, animal and clinical studies have largely shown that obesity does not increase the number of pro-inflammatory macrophages in the infra-patellar fat pad (70–73). Rather, obesity has a greater effect on the synovium where it causes synovial adipocyte hypertrophy, macrophage accumulation, fibrosis, and increased expression of TNF and TLR4 (73–76). In aged female mice fed a high-fat diet to induce obesity, genetic deletion of TLR4 prevented the development of knee OA, supporting a role for innate immune signaling via TLR4 in obesity-induced OA (77). A number of questions remain about which factors that are associated with obesity directly modulate synovial inflammation. Pre-clinical animal studies indicate that multiple factors could be involved, including synovial insulin resistance (74,78), dietary fatty acid composition (79–81), and gut microbiome composition (82,83). The complex and multi-factorial nature of these pro-inflammatory stimuli creates challenges for developing OA therapies for obese patients. Ongoing studies are seeking to establish better causal relationships between these factors and OA outcomes so that patient subsets might be identified for more precise therapies.

Genetic associations with OA also point to the importance of inflammatory mechanisms in OA. In 2014, polymorphisms in the IL-6 gene were found to be associated with radiographic hand OA in a British female twin cohort of Northern European ancestry, and in a Caucasian (Chuvash) population (84). That same year, an association between multi-joint (generalized) OA and a variant within the SMAD3 gene, a downstream mediator of TGFβ signaling, was reported (85). Although both TGFβ and IL-6 are products of synovial macrophages that have been implicated in driving OA-related joint pathology, the specific functional influence of these genetic polymorphisms on risk of OA remain to be described. More recently, two single-nucleotide polymorphisms (SNPs) within the Protease-activated receptor-2 (PAR-2) gene were associated with risk of knee OA in a Han Chinese cohort, and risk allele carriers expressed higher levels of IL-6 and IL-1β in synovial fluid (86). This receptor is activated by inflammatory proteases and plays an important role in promoting inflammatory signaling in a variety of cells. Genetic deficiency of PAR-2 in mice was shown to protect against injury-induced OA by two independent groups (87,88). The importance of TLRs in OA, which are highly expressed by monocyte/macrophage lineage cells and promote macrophage phenotypic differentiation, has also been mentioned earlier. Genetic studies in humans also support a role for these innate immune sensors in OA. TLR-related genetic associations have been reported in several populations. The T-1486C SNP in TLR9 was associated with knee

OA in both a Chinese (89) and Turkish populations (90). Subsequently, two TLR3 SNPs were significantly associated with OA (91), and associations between OA and TLR7 and TLR8 SNPs were also found, but only in males. Taken together, these studies implicate genetic variation in inflammatory responses as a risk factor for OA. Whether they reveal important targets for therapy remains to be seen.

Conclusion

Current evidence provides strong inference that innate inflammatory pathways are involved in the etiology of OA. However, the complexity of cell types involved, including heterogenous macrophages subtypes of distinct developmental origins (Figure 1), poses numerous challenges for developing strategies to resolve inflammation in the face of continuous DAMP activation. Strategies to resolve OA synovial inflammation may require a two-phase approach that combines inhibiting DAMP production and enhancing alternative macrophage activation, such as through exercise therapy, pre- or pro-biotic treatment, or increased consumption of anti-inflammatory ω–3 polyunsaturated fatty acids (PUFAs) (Figure 1). Indeed, metabolic approaches to tip the balance in favor of pro-resolving M2-like macrophages may be worth considering due to the distinct metabolic phenotypes between M1 and M2-like macrophages.

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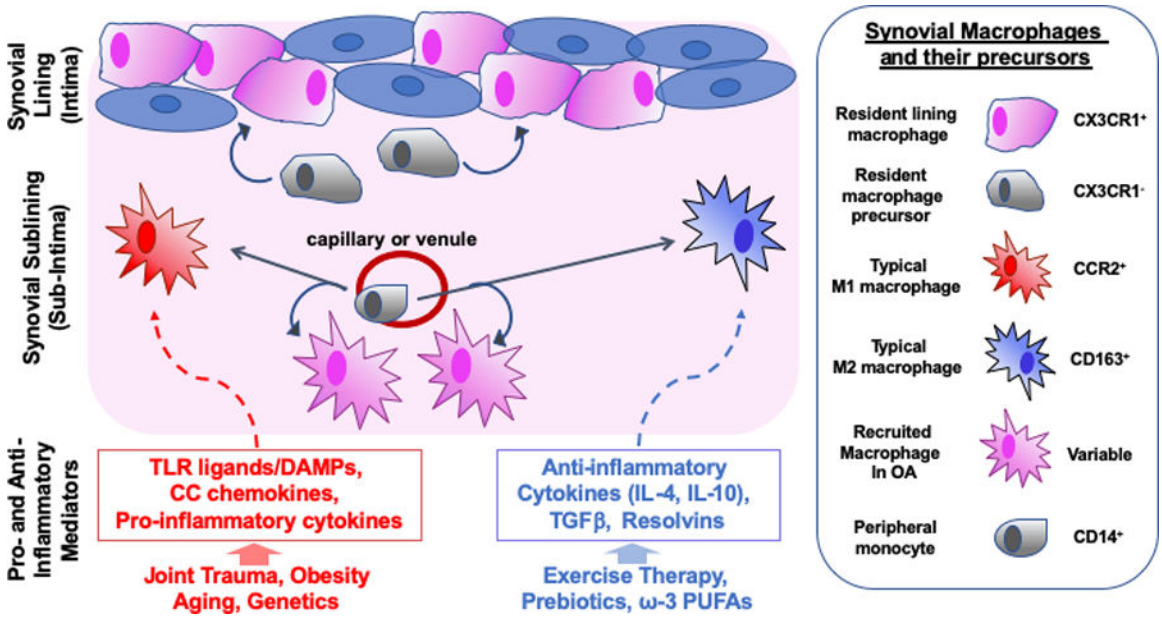

Figure 1: Complexity of Macrophage Phenotypes in the Osteoarthritic Synovial Membrane.

The synovial membrane of articular joints is typically separated into a lining layer (intima) composed of fibroblast-like synoviocytes (blue) and macrophage-like synoviocytes (pink), and a sublining layer (subintima) of vascularized loose connective tissue. Recent evidence suggests that the resident macrophages of the lining layer are derived from a distinct cellular lineage, express the fractalkine receptor (CX3CR1), and are repopulated by a proliferating pool of subintimal CX3CR1– precursors. In contrast, subintimal macrophages are largely derived from recruited monocytes from the periphery. In vitro, monocytes can differentiate into pro-inflammatory M1 macrophages in response to stimuli such as DAMPs, or into M2 anti-inflammatory or wound-healing macrophages in response to anti-inflammatory stimuli or resolvins. In OA, the majority of inflammatory cells in the synovium are macrophages, but recent studies suggest that these recruited macrophages do not clearly fit into M1 or M2 categories. This likely reflects a complex milieu of both pro- and anti-inflammatory stimuli in the OA joint. Whether the phenotypes and functions of the lining macrophages are similar to those of recruited macrophages is not yet clear, but their distinct phenotypic markers suggest a unique function. Attempts at “tipping the balance” of M1 and M2 stimuli have met with some limited success in preclinical models of OA. However, studies that have completely blocked macrophages in the joint have demonstrated that the anti-inflammatory functions of these cells may be critical in maintaining joint homeostasis. Thus, the complexity of synovial macrophage subtypes in the OA joint reflects functional variation important in both health and disease. This complexity and interactions with other immune and stromal cell types needs to be further explored to determine the most effective ways to target macrophage function or phentoypic modulation for an OA disease-modifying therapy.