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Chemokines and Inflammation in Osteoarthritis: Insights From Patients and Animal Models

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Abstract

Evidence has been building that the pathologic drive for development of osteoarthritis (OA) involves more than simple mechanical "wear and tear." Inflammatory mechanisms play an important role in the tissue response to joint injury, and are involved in development of post-traumatic OA. Inflammation also appears integral to the progression of OA, whether post-traumatic or spontaneous, contributing to the evolution of joint tissue degradation and remodeling as well as joint pain. Both patient-based studies and in vivo models of disease have shed light on a number of inflammatory pathways and mediators that impact various aspects of this disease, both structurally and symptomatically. Recent work in this field has implicated inflammatory chemokines in osteoarthritis pathogenesis. Expression of multiple chemokines and their receptors is modulated during disease in both patients and animal models. Although best known for their effects on leukocyte migration and trafficking within the immune system, chemokines can have a wide variety of effects on both motile and non-motile cell types, impacting proliferation, differentiation, and activation of cellular responses. Their role in OA models has also demonstrated diverse effects on disease that exemplify their wide-ranging effects. Understanding how these important mediators of inflammation impact joint disease, and whether they can be targeted therapeutically, is actively being investigated by many groups in this field. This narrative review focuses on evidence published within the last 5 years highlighting chemokine-mediated pathways with mechanistic involvement in osteoarthritis and joint tissue repair.

Keywords

osteoarthritis; chemokines; inflammation; repair

It is increasingly evident that inflammatory mechanisms play a central role in mediating the effects of biomechanical derangement on joint tissues that may lead to the development of osteoarthritis after joint trauma. A plethora of inflammatory mediators are unleashed acutely

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in the joint after injury, and have the potential to be biomarkers of disease or therapeutic targets for prevention or treatment of post-traumatic osteoarthritis (OA). But perturbation of many inflammatory mediators and pathways persists beyond the acute post-injury phase, and are also evident in idiopathic OA. It is likely that individual mediators play roles in persistent leukocytic infiltration, catabolic enzyme production, and activation of articular chondrocytes and synoviocytes within the joint leading to disruption of joint tissue structure and function. However, many inflammatory molecules also play a role in regulating the response to persistent tissue damage and can drive attempts at tissue repair. Within this complex inflammatory milieu, a number of chemokines, or "chemotactic cytokines," are detectable within the joint and have been the subject of subsequent investigation. Chemokines are small peptides (generally 8–12 kDa) classified into four families (C, CC, CXC, and CX_3C) based on the number and spacing of cysteine residues within their N-terminal regions. The vast majority of chemokines belong to the CC and CXC families, and they exert their cellular effects by binding to G-protein coupled cell-surface receptors. Their function in driving cellular motility during inflammatory responses has been well characterized; populations of leukocytes will express a specific set of chemokine receptors, and will migrate to sites of infection or tissue damage along gradients of their cognate chemokine ligands. In addition, chemokines orchestrate the recruitment of pluripotent cell types to sites of tissue repair. An emerging literature from both clinical and laboratory investigators has revealed that chemokines have pleiotropic effects on multiple cell types that are relevant to OA pathogenesis. The impact of chemokines on joint health encompasses effects beyond cellular motility. The purpose of this review is to highlight chemokine-mediated pathways that have evidence of mechanistic involvement in joint tissue health and disease, focusing on studies published within the last 5 years. Specific examples with supportive evidence from both patient-based studies and animal models of disease were chosen to provide insight into the myriad functions of chemokines in joint tissue degeneration and repair.

METHODS

A PUBMED search using the search string "chemokine AND osteoarthritis NOT rheumatoid," limited to last 5 years, humans and other animals, returned 138 articles, 133 of which were in English language. The abstracts of these references were reviewed. Articles that did not directly focus on chemokine activities in the joint and osteoarthritis, as well as review articles were removed. A small number of articles not revealed by this search, but known to the author were added, and articles published more than 5 years prior were only included if they added important context. This resulted in the final reference list of 53 articles.

CC Chemokines and Receptors

CCL2—CCL2 (MCP-1) is a chemokine that can be produced by multiple cell types and was originally described for its potent effects on monocyte recruitment in response to inflammatory stimuli,[1] but subsequently found to also induce recruitment of memory T-lymphocytes, and natural killer (NK) cells. Its effects on cellular migration are mediated by binding to multiple receptors, but most strongly to CCR2.[2] Multiple studies have reported

CCL2 levels elevated in synovial fluids from patients with knee and ankle injuries.[3–6] SF levels have been associated with knee OA radiographic changes in a small study of 18 patients,[7] and there are multiple reports of association with knee symptoms in OA and joint injury.[6,8,9] A recent report suggests variation in the *CCL2* gene may be relevant to OA risk, as single nucleotide polymorphism (SNP) and haplotype analysis in 183 patients compared to 191 controls revealed both disease-associated and disease-protective variants.[10] The association with symptoms is particularly intriguing, as MCP-1/CCR2 signaling is involved in neuropathic pain and neuroinflammation.[11] To explore a role in OA pain, Miller et al.[12] investigated symptomatic outcomes in the destabilization of the medial meniscus (DMM) model of murine OA. They found that both CCL2 and CCR2 were upregulated in the innervating dorsal root ganglia (DRG) of the knee 8 weeks after surgical injury in this model, a time point that corresponded to maximal DRG macrophage infiltration. Also at 8 weeks, movement-provoked pain-related behaviors (decreases in climbing and locomotion) were observed compared to controls. CCR2 null mice were protected from developing these pain-related behaviors, despite developing similar degrees of cartilage degeneration, suggesting a specific role in pain-related functional outcomes in this model. In a follow-up study,[13] these investigators reported that MCP-1 production by murine DRG neurons was induced by molecular “danger signals” implicated in OA pathogenesis (the alarmin S100A8 and the plasma protein α2 macroglobulin). MCP-1 production in response to these substances was dependent on Toll-like receptor-4 (TLR-4) signaling. These findings suggest a mechanism by which products of tissue damage and stress elaborated in the joint during OA development can stimulate nociceptive pathways via TLR-4 dependent MCP-1 production.

Human articular chondrocytes express both CCL2 and CCR2, and CCL2 increases MMP-3 expression and proteoglycan loss from human cartilage in vitro.[14,15] As mentioned above, in the DMM model no effect of CCR2 deficiency on cartilage integrity was observed.[12] However, other models support a role for CCL2/CCR2 signaling in cartilage metabolism that may be relevant to human disease. Using both in vitro chondrocyte culture and a rat ACL tear/partial meniscectomy model,[16] Appleton and colleagues explored the interaction between CCR2 and TGFα, a growth factor previously implicated in chondrocyte catabolism and inflammatory cytokine production.[17] These authors found that CCL2 and TGFα were both upregulated in chondrocytes 4 weeks after injury in the rat model. In vitro, TGFα induced CCL2 production, and promoted collagen and aggrecan proteolysis in cartilage explants. This effect of TGFα on cartilage matrix breakdown could be blocked by CCR2 signaling inhibition. To determine whether these effects were relevant in vivo, they treated rats with a CCR2 signaling inhibitor after joint injury, and found it to be partially protective of cartilage degeneration in this model. Thus, some effects of TGFα on chondrocyte metabolism appear to be mediated through CCL2/CCR2 signaling. There may be species or model-specific differences in the importance of CCR2 signaling that account for the differences observed in this model and the DMM model.[12] More work is needed to resolve these issues, but the earlier observations in human cartilage[14,15] suggest a direct effect of CCL2 on cartilage catabolism.

CCL3/4/5—Other members of the CC family of chemokines are upregulated in joint injury and OA, including CCL3 (alternate name macrophage inflammatory protein 1α, or MIP-1α), CCL4 (MIP-1β), and CCL5 (RANTES, or regulated on activation, normal T cell expressed and secreted). A recent study[18] compared plasma chemokine levels in Chinese patients, comparing those with radiographic knee OA (Kellgren-Lawrence score ≥2, $n = 50$), pre-radiographic knee OA (normal x-rays but evidence of cartilage degeneration on MRI, $n = 47$), and controls without knee OA ($n = 75$). In this study, plasma CCL3 levels discriminated best between controls and pre-radiographic knee OA patients, and levels increased in OA patients with increasing radiographic severity. Although there were some important differences between groups in this study (age, gender ratios, and body mass indices) that limit the strength of conclusions, CCL3 levels did not appear significantly associated with age or BMI. Other studies suggest that there is a local source of these chemokines in the joint. A small but comprehensive study in which a panel of 47 SF cytokines and chemokines were profiled in 18 patients compared to controls, CCL5 levels were among five mediators most significantly elevated in OA SF compared with controls, whereas CCL4 levels showed less profound elevations.[19] A more recent study also documented CCL5 elevations in OA SF in 18 additional patients.[7] CCL4 SF levels were found elevated in a study of six patients after ankle fracture.[5] CCL3 mRNA was expressed at higher levels in cartilage from 32 patients with femoral acetabular impingement (FAI) at the hip compared to controls.[20] CCL3, CCL4, and CCL5 are also among the most highly upregulated gene products in primary human chondrocytes in response to IL-1β[21] and the alarmin HMGB1,[22] demonstrating that chondrocytes may be a source. Although each of these chemokines binds to multiple receptors, they all are ligands for CCR5. Therefore, Takebe et al.[23] tested whether deficiency of CCR5 in mice influences development of post-traumatic OA. In the DMM model, CCR5 deficient mice were partially protected against cartilage erosion by 8 and 12 weeks post-injury compared to controls. Interestingly, loss of CCR5 did not impact synovitis or bone remodeling, suggesting that the protective effect was mediated via a direct effect on cartilage. However, whether a specific CCR5 ligand is primarily responsible for these observations needs further clarification.

CCL19/21—Additional CC chemokines are modulated in human joint injury and OA. Some of these studies show interesting correlations with radiographic severity[24,25] suggesting potential biomarker utility. Others have been implicated in disease pathogenesis in animal models[26] but the relevance to human disease is unclear. Our own work has implicated a set of chemokines that could be involved in the development or the clinical impact of post-injury synovitis. Using high throughput microarray gene expression analysis, we identified a set of transcripts expressed in synovial tissues and associated with microscopic synovitis in 33 patients undergoing arthroscopic partial meniscectomy.[27] Gene products identified included CCL19 and CCL21, which are known to function in normal homeostatic leukocyte trafficking by binding to their shared receptor CCR7.[28] In our analyses, expression levels of CCL19 and CCR7 were also associated with severity of symptoms in these patients,[27] and similar associations were demonstrated in a second cohort of patients with more extensive radiographic OA.[29] Modulation of CCL19 or CCL21 expression has been reported in at least three murine models of OA.[30–33] A mechanistic role in disease has yet to be demonstrated, but is a focus of current investigation.[34]

CXC Chemokines and Receptors

CXCL12—CXCL12, otherwise known as stromal cell derived factor-1 (SDF-1), is one of the most extensively studied chemokines in tissue repair. CXCL12 mobilizes mesenchymal stem cells (MSCs) to sites of injury by binding to a single receptor, CXCR4.[35] CXCL12/CXCR4 signaling has been demonstrated to be important for fracture repair and bone remodeling.[36] Elevated serum levels of CXCL12 in OA patients have been noted by a number of investigators, and most recently synovial fluid levels measured in 252 patients were associated with radiographic severity.[37] In horses with osteochondral injuries, serum levels were decreased whereas synovial fluid concentrations increased in comparison with uninjured animals.[38] Shen and coworkers recently studied the effects of human meniscus-derived stem/progenitor cells (hMeSPCs) in a rat menscectomy model. These cells were injected intra-articularly 1 week after meniscectomy, and homed to the injured meniscus. The homing of these stem cells was blocked by inhibition of CXCR4 signaling.[39] The authors went on to show that meniscal repair was superior in the hMeSPCs-treated mice, and at 12 weeks post-meniscectomy, cartilage degeneration in the animals that received the hMeSPC's was less extensive with greater maintanence of chondrogenic gene expression. A recent in vitro study supports and extends these findings.[40] Bovine cartilage explants with full-thickness cartilage defects were used to test the effect of an SDF-1-loaded hydrogel on recruitment of endogenous chondrogenic progenitor cells and tissue repair. The SDF-1 loaded gels promoted cellular recruitment into the site of the defect, integration and repair of the defect, and the SDF-1 treated explants demonstrated improved biomechanical properties of the repair tissue.

In addition to its effects on stem cells and repair, there is evidence that adult articular chondrocytes express CXCR4, and CXCL12 induces MMP13 and other catabolic mediators in adult articular chondrocytes.[41] It can also promote IL-6 production from synovial fibroblasts in vitro.[42] In the Hartley guinea pig model of spontaneous OA, pharmacologic blockade of CXCR4 signaling reduced cartilage degeneration and expression of inflammatory and catabolic mediators.[41] Clearly, SDF-1 has multifaceted effects that depend on the cellular targets, which may in part relate to the findings in spontaneous versus post-traumatic models. In addition, other factors expressed in the joint after injury or during OA development may limit the reparative activity of CXCL12-activated MSCs. One potential candidate could be CCL2 (MCP-1), which like SDF-1 can promote MSC recruitment in vitro, but then blocks chondrogenesis thereby limiting MSC potential for cartilage repair.[43]

CXCR2—In addition to CXCR4, human articular chondrocytes express CXCR2. This receptor binds multiple chemokine ligands, specifically CXCL1 through CXCL8 that function in neutrophil chemotaxis. In contrast to CXCR4, recent evidence demonstrates a homeostatic function for CXCR2 signaling in chondrocytes.[44] Normal human cartilage expressed both CXCR2 and its ligand CXCL6, with decreased expression of CXCL6 seen in degenerative cartilage. Blockade of CXCR2 signaling in chondrocytes resulted in a loss of phenotype, and in the DMM model CXCR2 deficient mice developed more severe OA. These intriguing results suggest an important role for CXCR2 signaling in maintenance of the adult chondrocyte phenotype in health, and a protective role in disease. Interestingly, expression of CXCR2 was also recently demonstrated in nucleus pulposis cells from the

human inter-vertebral disc.[45] It remains to be seen whether signaling through this receptor plays a similar physiologic role in this tissue as well.

Chemokines and Synovial Inflammation

Most of the work discussed above has focused on the impact of chemokines on cartilage health and chondrocyte activity during OA development. Much less is understood regarding the role of chemokines in promoting synovitis and modifying synovial function in OA. Given the well-established role of chemokines in leukocyte trafficking and activation during inflammation, it is highly likely that chemokines play central roles in development and perpetuation of synovitis in OA. The predominant leukocytes infiltrating synovium in OA are macrophages and T-lymphocytes.[46,47] Many chemokines that have been detected in OA synovial fluid could drive recruitment of these cell types, including the examples already discussed as well as CCL18[48] and CX3CL1.[49,50] However, it remains to be demonstrated which if any of these chemokines play central roles in driving or maintaining leukocyte infiltration in the complex in vivo milieu of the arthritic joint. Nonetheless, a number of in vitro studies demonstrate that chemokines might influence the behavior of fibroblast-like synoviocytes (FLS). A recent report shows that FLS express CCR3 and respond to CCL11 (eotaxin-1) with production of catabolic proteases such as MMP-9.[51] Another group demonstrated FLS upregulate Vascular Cell Adhesion Molecule-1 (VCAM-1) in response to CCL2 to promote monocyte adhesion in culture.[52] Still others have demonstrated a role for CCL5/CCR5 signaling in promoting FLS IL-6 production.[53] Although these studies are interesting and suggest mechanisms by which chemokines promote inflammatory and catabolic activity of synoviocytes, additional investigation is needed to understand which chemotactic factors perpetuate synovitis and modulate the activity of the synovial tissue in vivo.

CONCLUSIONS

There are clearly many chemokines and chemokine receptors that are expressed by cells within the joint, and are relevant to osteoarthritis pathogenesis. Most need further investigation to confirm their specific impact on OA-related pathology and clinical features, and whether they may be targeted therapeutically using in vivo models. Some may be good biomarkers whereas others may be directly involved in disease pathogenesis via effects on multiple joint tissues and cell types. The specific signaling pathways downstream of chemokine/receptor binding on chondrocytes needs further elucidation, as this may differ from other cell types. The role of chemotactic factors in driving synovitis in OA, although likely, needs particular investigative attention. This will require in depth cellular and molecular analysis of specific aspects of synovitis (i.e., leukocyte infiltration, fibroblastic hyperplasia and activation, fibrosis, and angiogenesis). Better understanding of the synovial responses in different animal models of disease and different species is clearly needed. Moreover, analysis of chemokine influence on synovial production of cytokines, catabolic factors, and protective synovial fluid constituents such as lubricin will aid in understanding how these factors influence tissue function in disease.

As a family, chemokines exemplify the complex nature of the inflammatory response in joint injury, joint repair, and osteoarthritis. Individual chemokines have effects on both motile and non-motile cell types within the joint, and exhibit sometimes-opposing effects on joint tissue catabolism and repair. Depending on the context and cellular targets, chemokines may promote cartilage phenotypic stability, catabolic cascades and tissue destruction, leukocyte infiltration and inflammation, or MSC recruitment and tissue repair. In addition, certain chemokines and receptors are expressed within the peripheral and central nervous system and may play a role in OA-related pain separate from effects on structural tissue remodeling. How the mixture of chemokines within the joint might impact the development of pain sensitization, seen in patients and animal models, is an important emerging area that needs better understanding to address the complex variation in OA symptoms. With a few exceptions, most chemokine ligands bind to more than one receptor, and individual receptors may bind multiple ligands, making selective targeting difficult. Dissecting the role of individual chemokines in OA is made even more complex by potential interactions with other inflammatory molecules expressed within the osteoarthritic joint. Still, the recent examples highlighted in this review are already pointing to potential therapeutic targets to protect joint tissues from degeneration, and to modulate pain in OA. Future efforts will require the comparison of multiple in vitro and in vivo models to understand the complexity of chemokine interactions and targeting within the joint in order to advance this field.

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