

Role of Inflammation in Osteoarthritis

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Osteoarthritis (OA) was never classically considered to be an inflammatory arthropathy. However, recently this concept has been questioned due to ever increasing evidence suggesting that inflammation plays a key role in the progression of this debilitating degenerative joint disease. Over 55 million Americans suffer from OA for which there is no effective treatment outside of complete joint replacement surgery. Although routine, the invasiveness of this surgical procedure renders it a last resort for alleviating pain associated with the severe late stages of this disease. Today, our current understanding of OA pathogenesis and its intrinsic link to joint inflammation can open up new and innovative avenues of thinking about potential treatment options outside of surgical intervention. The traditional definition of OA differs quite significantly from rheumatoid arthritis (RA), which is primarily classified as a systemic autoimmune disease where inflammation is pivotal to its manifestation. However, recently many have acknowledged that there is also an underlying chronic inflammation present, not only in cartilage tissue but also within the synovium, which perpetuates tissue destruction of the OA joint. While not as pronounced as the inflammatory imbalances characteristic of RA, chronic low levels of inflammation of the OA joint nonetheless persists as a major factor regulating tissue catabolism.

While aging, injury, and excessive loading may all act as contributing factors that potentiate cartilage damage during OA, the exact biological mechanism that causes and sustains OA remains to be elucidated. The consideration of inflammation in OA takes into account synovitis and/or other cellular and molecular events in the synovium during the progression of OA. It is now known that synovial markers of joint inflammation and degradation correlate with OA progression and with more and more emerging studies describing increased cytokine levels in the joints of OA patients, it becomes difficult to rule out inflammation as a fundamental characteristic of the disease. Different cytokines may play different roles during OA onset and progression (Table 1). While many cytokines elevated during OA pathogenesis are not always simply associated with inflammation (i.e. IL-4, -6, -8, -10, -13, and IFN- γ), there are several, such as IL-1 and TNF- α , that are now accepted as strong inflammatory cytokines pivotal to the process of OA induced tissue destruction [1,2]. IL-1 levels have been reported to be significantly increased in osteoarthritic synovial fluids during early and late stages of the disease [3]. Furthermore, IL-1 β is notorious for its ability to induce the expression and release of a number of degenerative proteases, including MMPs and aggrecanases [4,5]. Additionally, it stimulates the production of highly reactive oxygen species such as nitric oxide (NO) [6]. These mediators of cartilage tissue catabolism wreak havoc in arthritic joints as OA progresses towards later stages. Although not as destructive as IL-1 is during OA, TNF- α is reported present during the onset of the disease where it too initiates similar catabolic effects [1,6]. In addition to regulating cellular processes during embryonic development through interaction with CXCR4, a seven transmembrane G protein-coupled receptor, stromal cell derived factor 1 (SDF-1) is yet another cytokine of the chemokine family that is found to be elevated during both primary and secondary OA as well as RA. A study by Kanbe et al. 2002 found SDF-1 chemokine levels elevated by more than 3 fold and 10 fold, respectively, in the joint synovial fluids of OA and RA patients [7]. Although the amplitude of the increase of SDF-1 in OA is less than that of RA, it persists during the course of the disease. SDF-1 increases the concentration of MMP-3 released from

chondrocytes in a dose-dependent manner; the positive correlation exists between SDF-1 levels and that of OA associated MMPs: MMP-1, -9 and -13 in serum [8]. And blocking CXCR4 or inhibiting p38 MAP kinase suppresses SDF-1 induced MMP-1 gene expression thereby verifying its involvement in cartilage tissue destruction [9]. During OA pathogenesis, SDF-1 produced by synoviocytes mediate catabolic effects on the surrounding joint tissue by signaling through the CXCR4 receptor for the transcription and release of these tissue degrading proteases (Figure 1). Given all that is known, it is not surprising that SDF-1 levels in synovial fluid are observed to be elevated during aging and injury. A recent study has shown that complement levels were activated in OA patients [10]. So compelling is the destruction caused by inflammatory mediators that anti-cytokine therapy has recently received much attention in OA research.

Classical paradigms of cartilage aging biology do not readily and completely explain OA pathogenesis. Chronic inflammation is a quintessential characteristic of OA that has been overlooked for some time and its investigation may contribute towards attaining a fuller understand of the biological processes involved in this disease. In addition to further investigating effects of cytokines and chemokines that are considered to be the usual suspects in tissue degradation (i.e. IL-1, TNF- α and SDF-1), it is also imperative to screen for other cytokines that may play a role in perpetuating the disease. Today, we finally understand that inflammatory processes are common to the

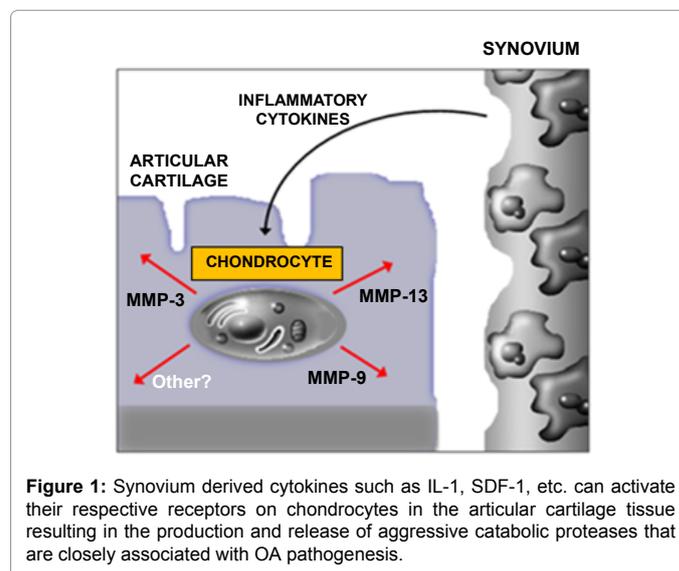


Figure 1: Synovium derived cytokines such as IL-1, SDF-1, etc. can activate their respective receptors on chondrocytes in the articular cartilage tissue resulting in the production and release of aggressive catabolic proteases that are closely associated with OA pathogenesis.

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The good (Anti-inflammatory)	IL-4	Reduces nitric oxide production by OA associated inflammatory cytokines
	IL-10	Elevated during OA and acts to inhibit IL-1 and TNF- α expression
	IL-13	Inhibits IL-1 and TNF- α expression while elevating IL-1Ra expression
	IFN- γ	Inhibits various catabolic effects of IL-1
The bad (Inflammatory)	IL-1	Elevated during early and late stage OA and promotes MMP production and inhibits cartilage anabolism
	TNF- α	Elevated during OA onset and increases nitric oxide and catabolic protease production by chondrocytes
The regulatory	IL-6	Negative regulator of chondrocyte proliferation
	IL-8	Regulator of chondrocyte hypertrophy

Table 1: Different cytokines may play different roles during OA onset and progression.

pathology of OA and RA thus the similarities between these diseases are beginning to unravel. Therefore it is reasonable to expect emerging OA therapies/treatments to make more of an effort at readily addressing the chronic inflammation underlying this arthropathy.

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