# **Pathophysiological Perspective of Osteoarthritis**

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Osteoarthritis (OA) is the most well-known disease among the geriatric and the main cause of significant disability in daily living. It has a multifactorial aetiology and characterized by pathological changes of knee joint structure including cartilage erosion, synovial inflammation and subchondral sclerosis with osteophyte formation. To date, no efficient treatment is capable of altering the pathological progression of OA. This topic described significant mediators such as cytokines, proteolytic enzymes, and nitric oxide, that trigger the loss of the normal homeostasis and structural changes in the articular cartilage during the progression of OA.

Keywords: Osteoarthritis ; Pathogenesis ; Cytokines ; Proteolytic enzymes

## 1. Introduction

Osteoarthritis (OA) is the most common cause of chronic joint pain among the geriatric population. OA is defined as the progressive deterioration of articular cartilage, followed by inflammation in the synovial cavity. Due to the extreme pain in the joint caused by OA, patients experience significant disability in their daily living.

Prior to the 1990s, OA had been described as cartilage wear and tear, where the articular cartilage is degraded due to incremental pressure on a particular joint. With the advancement of molecular biology, the paradigm of OA pathophysiology has shifted to it being described as an inflammatory joint disease <sup>[1][2][3]</sup>. This follows the discovery of several inflammatory mediators that actuate chondrocytes to produce matrix metalloproteinases (MMPs), a major player in articular matrix degradation.

In more recent years, the establishment of a direct correlation between age-related inflammation and the disturbance in gut microbiota has brought attention to the gut–joint axis hypothesis of OA. The link between the disturbance in gut microbiota, defined as gut dysbiosis, and OA has been demonstrated in several studies <sup>[4]</sup>.

Maintenance of the articular cartilage is tightly regulated by the anabolic and catabolic pathways of the cartilage matrix. In a healthy joint, the articular chondrocytes adapt to the various stresses to which they are subjected by altering their metabolism, resulting in the degradation or synthesis of the cartilage matrix to suit the demands of the body  $\frac{[5][6][7]}{2}$ .

The complex pathogenesis of OA comprises the interplay of numerous factors ranging from hereditary inclination to alteration of gene expression via changes in the mechanical loading experienced by articular chondrocytes <sup>[5]</sup>. Dysregulation in these molecular repertoires can prompt the deterioration of the articular cartilage and the risk of progression into OA, either directly or indirectly <sup>[1]</sup>.

### 2. Pathological Changes in OA

Considering its complexity, the initiation, progression, and severity of OA are each driven by a plethora of factors. Furthermore, in all individuals, OA does not progress at a similar rate. At the cartilage–bone interface, an inverse relationship between subchondral bone changes and articular cartilage degeneration has been reported. As the subchondral bone thickens, a higher stage of cartilage degeneration is observed <sup>[8]</sup>.

The earliest pathological changes in OA are commonly seen on the articular cartilage surface, with fibrillation occurring in focal regions experiencing maximal load. The proliferation of chondrocytes, the only cell type present in cartilage, dramatically accelerates in response to the loss of matrix. Some chondrocytes undergo a phenotypic change to hypertrophic chondrocytes, which is similar to the cells found in the growth plate's hypertrophic zones. As OA progresses, extensive matrix degradation and loss occurs due to the continuous production of proteases driven by proinflammatory cytokines, which stimulate chondrocytes to produce more cytokines and proteases in an autocrine and paracrine manner. As significant matrix damage occurs, areas of the matrix devoid of cells can be seen as a result of chondrocyte apoptosis.

The bone changes in OA include subchondral sclerosis due to increased collagen production, with osteophyte formation and bone cysts at more advanced stages. Osteophytes have been described as bone and cartilage outgrowths occurring at the joint area. The direction of osteophyte growth is sensitive to the size and local cartilage narrowing, except for the lateral tibia and medial patella <sup>[9]</sup>. Biomechanical factors support osteophyte development. Most patients with symptomatic OA exhibit synovial inflammation and hypertrophy <sup>[10]</sup>. However, synovitis inflammation is not the triggering factor for primary OA, but contributes to the progression of pain and disease <sup>[11]</sup>.

Plain radiographs underestimate the joint tissue involvement in OA, since they only visualize a component of the condition including cartilage loss that result in joint space narrowing and bony changes that result in subchondral sclerosis, cysts, and osteophyte formation. Once these changes are apparent on radiographs, the condition has significantly advanced <sup>[12]</sup>.

Magnetic resonance imaging (MRI) studies can detect early disease and have provided evidence of matrix changes in cartilage, synovitis, bone marrow lesions, and degenerative changes in soft-tissue structures beyond the cartilage including ligaments and the knee menisci [13].

The arthroscope can play an important diagnostic role in patients with unexplained knee pain and swelling or in patients with established knee arthritis whose symptoms are disproportionate to radiographic findings <sup>[14]</sup>.

Moreover, apart from these above mentioned pathological changes, the paradigm has shifted to the involvement of various inflammatory mediators, proteinases, cell proliferation, and biochemical parameters in the development of the disease.

### 3. Inflammatory Mediators

#### 3.1. Cytokines and Chemokines

Inflammatory mediators such as cytokines are the key component of most inflammatory processes. Accordingly, a multitude of cytokines have been associated with OA pathogenesis. In OA patients, cartilage matrix homeostasis is disrupted by proinflammatory cytokines and chemokines <sup>[15][16]</sup>. Investigation of the cytokines and chemokines involved during OA progression revealed the upregulation of IL-1, IL-6, and IL-8 <sup>[17][18][19]</sup>.

These cytokines act as both autocrine and paracrine agents, to stimulate the collective production of proteases, nitric oxide (NO), and eicosanoids such as prostaglandins and leukotrienes by macrophages and chondrocytes. Subsequently, the action of these inflammatory mediators in the cartilage results in the induction of the catabolic pathways, inhibition of matrix synthesis, and promotion of cellular apoptosis <sup>[19]</sup>. The cellular apoptosis, particularly in chondrocytes, is driven by the inhibition of autophagy by the proinflammatory cytokines <sup>[20][21]</sup>.

The production of IL-1 by the stimulated chondrocytes in turn induces the synthesis of MMPs, namely MMP-1, MMP-3 and MMP-13. This is accompanied by the amplification of proinflammatory cytokines such as TNF- $\alpha$ , IL-6 and the chemokine IL-8, which magnifies the cartilage matrix breakdown effects in the catabolic cascade, further enhancing articular chondrocyte destruction <sup>[17][22]</sup>. IL-1 has also been proposed to contribute to the decline in cartilage matrix by inhibiting the synthesis of key components of ECM, such as proteoglycans, aggrecan, and type II collagen <sup>[23][24][25]</sup>.

Moreover, the involvement of fibronectin in cartilage degradation is also apparent when fragments of the protein induce the expression of inflammatory cytokines, chemokines, and MMPs in chondrocytes <sup>[26][27]</sup>. In normal adult cartilage, chondrocytes synthesize matrix components very slowly. Finally, chondrocyte senescence is the other major contributor to OA development and progression. This is due to the senescent cells' loss of the capacity for maintaining and repairing the cartilage ECM <sup>[28]</sup>. Both IL-6 and IL-8 are a key cytokine and chemokine, respectively, also known to be secreted by senescent cells, which is known as the senescence-associated secretory phenotype <sup>[29]</sup>.

#### 3.2. Proteases

The MMP family plays a major role in articular cartilage homeostasis. Collagenases (MMP-1, MMP-13) are responsible for degradation of the collagenous framework, whereas stromelysin (MMP-3) and aggrecanase (ADAMT-4), which is responsible for proteoglycan degradation, play prominent roles in ECM degradation  $\frac{16|30|}{20}$ . The inflammatory cytokines synthesized by OA chondrocytes, i.e., IL-1 and TNF- $\alpha$ , can trigger increased MMP expression, suppress MMP enzyme inhibitors, and decrease ECM synthesis. Active stromelysin serves as an activator of collagenase 1, 2, and 3 (MMP-1, MMP-8, and MMP-13, respectively) implicated in type II collagen degradation  $\frac{23|24|25|}{23}$ .

MMP-13, the protease that preferentially degrades type II collagen, may be the most important in OA progression, considering type II collagen as the main collagen type in ECM. Indeed, MMP-13 expression is of greatly increased in OA <sup>[19][31]</sup>. In contrast to MMP-1 and MMP-3, which are present in high levels in OA synovial fluid, MMP-13 is highly expressed in OA cartilage, indicating its important role in the degradation of human articular cartilage throughout OA <sup>[30][31]</sup> <sup>[32]</sup>. Moreover, only hypertrophic chondrocytes express the MMP-13 encoding genes, which can all be detected in OA cartilage <sup>[27]</sup>.

Taken together, cytokine regulation of the equilibrium between the anabolic and catabolic processes determines the integrity of articular joint tissue. In pathogenesis, the occurrence of anabolic activity overwhelms that of catabolic activity, resulting in tissue degeneration <sup>[33]</sup>.

#### 3.3. Inflammatory Mediator Enzymes

Other than cytokines and proteases, the expression of enzymes such as inducible NO synthase (iNOS), which generates the free radical NO, and cyclooxygenase-2 (COX- 2), which produces prostaglandin E2 (PGE2), are also altered in OA <sup>[22]</sup>. Here, the proinflammatory cytokine IL-1 stimulates the upregulation of both PGE2 and NO by inducing the gene expression or activity of COX-2 and iNOS <sup>[23]</sup>.

Akhtar et al. (2011) noted that IL-1, together with mechanical loading of the cartilage, induced upregulation of the iNOS gene, which in turn increased the NO production. NO contributes to articular degradation by upregulating synthesis of MMP via cyclic GMP (cGMP)-dependent pathways while simultaneously inhibiting the synthesis of both proteoglycans and collagen [34][35].

Notably, NO has also been implicated to play a role in mediating chondrocyte apoptosis, a common feature in progressive OA <sup>[19][33][36]</sup>. Moreover, NO also alters mitochondrial function in OA chondrocytes, resulting in reduced cell survival by inhibiting the activity of the mitochondrial respiratory chain and ATP synthesis <sup>[37]</sup>.

COX activation enhances the production of MMP-3 while inhibiting proteoglycans and collagen synthesis and inducing chondrocyte apoptosis <sup>[37]</sup>. With IL-1 stimulation, the chondrocyte is upregulated, eventually leading to increased production of PGE2 <sup>[38]</sup>. Martel-Pelletier et al. (2003) suggested the role of PGE2 in inflammation, apoptosis, angiogenesis, and probably the structural changes characterizing arthritic diseases <sup>[39]</sup>. Increased PGE2 production causes cartilage resorption by suppressing proteoglycans production, enhancing the degradation of both aggrecan and type II collagen and potentiating the effects of other inflammatory mediators such as IL-6 and MMP-13 <sup>[40]</sup>.

Even without cytokine stimulation, when cultured in vitro, both NO and COX-2 levels are already highly expressed in chondrocytes from OA tissues <sup>[41][42]</sup>. Such metabolic changes may indicate a permanent phenotypical shift in OA chondrocytes. Moreover, the discovery of COX-2-induced PGE2 in fibrocartilage implies a role for PGE2 in the secondary remodeling of the tissue that causes osteophyte formation of in the pathogenesis of OA <sup>[43]</sup>.

Matriptase, a novel protease found in OA articular chondrocytes, initiates cartilage matrix degradation by activating proteinase-activated receptor 2 (PAR-2) <sup>[44]</sup>. The absence of PAR-2 results in the absence of OA-associated pain and osteophyte formation <sup>[45]</sup>. Therefore, it is possible that the PAR-2 system is involved in the inflammatory response-mediated ECM degradation in OA. In addition, secreted proinflammatory cytokines up-regulate the expression of PAR-2, inducing greater production of proinflammatory cytokines (IL-6, IL-8), metalloproteinases, and PGE2 to enhance the inflammatory responses <sup>[46][47]</sup>. Boileau et al. (2007) demonstrated that PAR-2 expression and protein levels in OA chondrocytes have increased significantly and that the levels are regulated by the proinflammatory cytokine IL-1. The PAR-2 activation resulting in increased rates of MMPs (MMP-1, MMP-13) and COX-2 indicates that it could play a key role in the catabolic and inflammatory pathways during the progression of OA by inducing major catabolic and inflammatory mediators <sup>[47][48][49][50]</sup>. The interaction of various inflammatory mediators in the event of OA is summarized in Table 2 and Eigure 1.



Figure 1. Inflammatory mediators in OA.

Table 2.	Potential	mechanisms	in the	event of	OA.
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Inflammatory Mediators	Description of Mechanism			
	<ul> <li>IL-1, IL-6, IL-8:</li> <li>autocrine/paracrine agent; induce chondrocytes to produce proteases, nitric oxide, and eicosanoids such as prostaglandins and leukotrienes <sup>[51]</sup>.</li> </ul>			
	• inhibit matrix synthesis, and promote cellular apoptosis [51][52][8].			
Cytokines and Chemokines	<ul> <li>IL-1:</li> <li>induce the synthesis of matrix metalloproteinases (MMP 1, MMP 3, MMP 13) TNFα, IL-6 and IL-8 to drives the cartilage matrix breakdown <sup>[53][9]</sup>.</li> </ul>			
	• decreases the synthesis of, such as proteoglycans, aggrecan, and type II collagen $^{[\underline{10}]}$ .			
	<ul> <li>IL-6 and IL-8:</li> <li>secreted by senescent cells, responsible for the loss of the cartilage extracellular matrix (ECM) the capability to maintain and repair <sup>[13][14]</sup>.</li> </ul>			
	<ul> <li>MMP-1, -3, -13 and ADAMT-4:</li> <li>degradation of collagenous framework and extracellular matrix <sup>[54][15]</sup>.</li> </ul>			
	<ul> <li>MMP-3:</li> <li>activator of other collagenases (MMPs 1, 8, and 13) that implicated in type II collagen degradation <sup>[10]</sup>.</li> </ul>			
Proteases	<ul> <li>MMP-13:</li> <li>most an important role during OA pathogenesis <sup>[51][16]</sup>.</li> </ul>			
	<ul> <li>secreted by hypertrophic chondrocytes in OA cartilage <sup>[12]</sup>.</li> </ul>			
	<ul> <li>degrades type II collagen as the main articular ECM <sup>[15][16][17]</sup>.</li> </ul>			
	• induce inhibition the synthesis of both proteoglycans and collagen <sup>[19][20]</sup> .			
inos (no)	<ul> <li>upregulate the synthesis of matrix metalloproteinases <sup>[19][20]</sup>.</li> </ul>			
	<ul> <li>induce chondrocyte apoptosis; reduced the survival of cells and inhibited mitochondrial respiratory chain function and ATP synthesis <sup>[51][10][18][21]</sup>.</li> </ul>			

Inflammatory Mediators	Description of Mechanism			
	<ul> <li>suppress the production of proteoglycans, enhances the degradations of both aggrecan and type II collagen <sup>[22][25]</sup>.</li> </ul>			
COX-2 (PGE2)	• involves inflammation, apoptosis, angiogenesis <sup>[24]</sup> .			
	• enhances the effects of IL-6, MMP-3 and MMP-13 $^{\underline{[22][25]}}$			
	• induces pain and osteophytes formation $^{[30]}$ .			
PAR-2	<ul> <li>induces production of IL6, IL8, MMPs (MMP1, MMP13) and PGE2 to enhance inflammatory responses [31][32][33][34][35]</li> </ul>			

#### 3.4. Other Potential Mediators of OA

Several studies have provided evidence for a number of potential mediators that induce OA but are not considered as inflammatory mediators. These factors also induce activating pathways that promote joint tissue destruction or inhibiting the ability of cells to repair damaged matrix of OA.

Hypoxia-inducible factor 1-alpha (HIF-1 $\alpha$ ) is an important mediator of cellular response towards an oxygen-deprived environment. Articular cartilage resides in an environment that is devoid of oxygen. Homeostasis of this tissue is mainly maintained by the HIF-1 $\alpha$  regulatory mechanism. Single nucleotide polymorphism (SNP) studies have revealed that a defect in HIF-1 $\alpha$  disrupts the catabolic pathways of the cartilage matrix. Instead of undergoing autophagy, defects of HIF-1 $\alpha$  resulted in chondrocyte hypertrophy in response to the hypoxia environment <sup>[55]</sup>.

The Wnt signaling pathways play a substantial role in the joint development. In OA, the interaction between the underlying subchondral bone and articular cartilage brought about the hypothesis of Wnt signaling pathways role in OA <sup>[56]</sup>. In a mouse model, activation of the Wnt signaling pathway in subchondral bone induces degradation of the articular cartilage. This reiterates the potential role of the Wnt signaling pathway in the pathogenesis of OA <sup>[57]</sup>.

Nerve growth factor (NGF) is a neurotrophin that transmits the pain information following inflammation. In bovine chondrocytes induced with TGF- $\beta$ 1 and IL-1 $\beta$ , NGF expression was found to be elevated. The elevated expression of NGF is mediated by activin receptor-like kinase 5 (ALK5) and the Smad 2/3 complex <sup>[58]</sup>. When cartilage explant was incubated with osteoarthritic synovium, TGF- $\beta$ 1 and Smad 2/3 were inhibited, suggesting a potential inhibition of NGF <sup>[59]</sup>. In conclusion, NGF might be an important mediator to the OA event.

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