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Review Paper

# Molecular and Cellular Mechanisms of Cartilage Degeneration in Knee Osteoarthritis: A Narrative Mini-review

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## ABSTRACT

Knee osteoarthritis (KOA) is a complex degenerative joint disease characterized by progressive cartilage degradation, subchondral bone remodeling, and chronic low-grade inflammation. Recent advances in basic science have transformed the understanding of KOA from a purely mechanical disorder into a multifactorial disease driven by molecular and cellular mechanisms. This narrative mini-review summarizes current insights into cartilage degeneration in KOA, focusing on inflammatory signaling pathways, extracellular matrix (ECM) breakdown, oxidative stress, mitochondrial dysfunction, and chondrocyte senescence. These interconnected processes highlight potential therapeutic targets for disease-modifying interventions and provide a critical link between basic science and clinical practice.

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## Introduction

Knee osteoarthritis (KOA) is one of the most prevalent causes of disability worldwide and imposes a significant socioeconomic burden. Traditionally described as a consequence of mechanical "wear and tear," KOA is now recognized as a whole-joint disease involving intricate interactions between cartilage, subchondral bone, synovium, and biochemical mediators [1, 2]. Articular cartilage plays a central role in joint function due to its unique biomechanical properties, which largely depend the organization of type II collagen and proteoglycans, such as aggrecans. Chondrocytes tightly regulate the maintenance of this extracellular matrix (ECM), the sole resident cell type in cartilage, which balance anabolic and catabolic processes under physiological conditions.

In the osteoarthritic joint, this balance is disrupted by increased pro-inflammatory mediators, particularly interleukin-1β and tumor necrosis factor-α, which are considered key drivers of cartilage degradation [3, 4]. These cytokines activate intracellular signaling pathways, such as nuclear factor kappa B and mitogen-activated protein kinases, including ERK, JNK, and p38, resulting in the transcriptional upregulation of catabolic enzymes and suppression of matrix synthesis [5, 6]. Consequently, matrix metalloproteinases (MMPs), especially MMP-13, along with aggrecanases, such as ADAMTS-4 and ADAMTS-5, mediate the progressive degradation of collagen and aggrecan, leading to structural breakdown of cartilage [7, 8]. This enzymatic imbalance is a hallmark of KOA and represents a critical step in its progression.

In parallel, oxidative stress has emerged as a major contributor to cartilage degeneration. Increased production of reactive oxygen species (ROS) in osteoarthritic joints leads to oxidative damage of cellular components, including lipids, proteins, and DNA [9, 10]. Mitochondrial dysfunction further exacerbates ROS generation and disrupts cellular energy metabolism, impairing the capacity of chondrocytes to maintain ECM homeostasis [10, 11]. Moreover, oxidative stress enhances inflammatory signaling pathways, creating a vicious cycle that accelerates cartilage destruction.

Another important aspect of KOA pathogenesis is chondrocyte apoptosis and senescence. Apoptotic pathways, often mediated by mitochondrial dysfunction and caspase activation, contribute to the loss of functional chondrocytes [11, 12]. In addition, senescent chondrocytes accumulate in osteoarthritic cartilage and adopt a senescence-associated secretory phenotype, characterized by increased secretion of inflammatory cytokines, chemokines, and matrix-degrading enzymes [13]. This phenotype not only impairs tissue repair but also amplifies local inflammation and matrix degradation, thereby perpetuating disease progression.

Beyond cartilage, subchondral bone plays a crucial role in the pathophysiology of KOA. Structural and mechanical alterations in subchondral bone, including sclerosis and increased stiffness, can disrupt load distribution across the joint [2]. These changes influence mechanotransduction pathways in chondrocytes, leading to abnormal cellular responses and further contributing to cartilage degeneration [14]. The concept of the joint as an integrated organ underscores the importance of crosstalk between different tissues in osteoarthritis.

Recent developments in basic science have also highlighted the role of epigenetic regulation and non-coding ribonucleic acids (RNAs), including microRNAs and long non-coding RNAs, in modulating gene expression in osteoarthritic cartilage [15-17]. These molecules regulate key pathways involved in inflammation, apoptosis, and matrix degradation, offering novel insights into disease mechanisms. Additionally, emerging evidence suggests that extracellular vesicles, particularly exosomes, may serve as mediators of intercellular communication and potential therapeutic tools for cartilage regeneration [15].

Collectively, these molecular and cellular mechanisms demonstrate that KOA is driven by a complex network of interconnected pathways involving inflammation, oxidative stress, cellular aging, and biomechanical factors. This integrated perspective provides a strong foundation for developing disease-modifying therapies targeting specific molecular pathways rather than merely alleviating symptoms.

## Conclusion

KOA is a multifactorial disease characterized by the interplay of inflammatory, oxidative, and biomechanical mechanisms that collectively drive cartilage degeneration. Advances in basic science have significantly expanded our understanding of these processes, revealing multiple potential therapeutic targets. Future research should focus on translating these findings into clinically effective strategies to modify disease progression and improve patient outcomes.

## Ethical Considerations

### Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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### Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interception of the results and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

### Conflict of interest

The authors declared no conflict of interest.

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