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REVIEW

Role of Pyroptosis in the Pathogenesis of Osteoarthritis: An Updated Review

Fengrui Yang*, Debin Li*, Wei Long, Ermao Li, Bo Wei

Institute of Translational Medicine, School of Basic Medical, Hengyang Medical College, University of South China, Hengyang Central Hospital, Hengyang, Hunan, 421001, People's Republic of China

*These authors contributed equally to this work

Correspondence: Bo Wei, Institute of Translational Medicine, School of Basic Medical, Hengyang Medical College, University of South China, Hengyang Central Hospital, Hengyang, Hunan, 421001, People's Republic of China, Tel +8618640130803, Email usc-wb@usc.edu.cn

Abstract: Osteoarthritis (OA), a prevalent degenerative inflammatory joint disorder, imposes a substantial global health burden, affecting over 500 million people worldwide and representing a leading cause of pain and disability. Its pathogenesis is characterized by the progressive degradation of articular cartilage, concomitant synovitis, and aberrant subchondral bone remodeling. Contemporary management strategies primarily aim to alleviate symptoms rather than halt disease progression, underscoring the critical need to elucidate fundamental pathogenic mechanisms to identify novel therapeutic targets. Recently, pyroptosis—a lytic, pro-inflammatory cell death mediated by inflammasomes (eg, NLRP3) and gasdermin D (GSDMD)— has emerged as a key mechanism linking inflammation to tissue damage. This review integrates pyroptosis research with OA pathomechanisms to establish their interplay. This review synthesizes contemporary research to delineate the intricate interplay between pyroptosis and OA pathomechanisms across joint tissues. Our integration of evidence reveals that: (1) The pyroptosis-inflammation axis involves NLRP3 activation, caspase cleavage, and GSDMD pore formation, releasing IL-1β/IL-18 that amplify synovitis and tissue destruction; (2) Chondrocyte pyroptosis is regulated by NF-κB and Hedgehog signaling, suppressible by inhibitors (eg, loganin); (3) Synovial cells undergo pyroptosis under stimuli like LPS, perpetuating fibrosis via HIF-1α activation; (4) Subchondral bone pyroptosis disrupts remodeling, targetable via PI3K/AKT pathways.

Keywords: osteoarthritis, pyroptosis, pathomechanism, Mechanism

Introduction

In recent years, Osteoarthritis (OA) has emerged as a major global health challenge and one of the key risk factors threatening human well-being. OA is a pervasive global health issue, affecting 595 million people (7.6% of the world's population) in 2020. Its prevalence has surged by 132% since 1990. Driven by population growth and aging, cases are projected to rise dramatically, cementing OA as a leading cause of disability worldwide.[1] Some studies have projected that OA will become one of the most prevalent diseases in the coming decades.[2] The economic burden is substantial, with an annual cost of $303 billion attributable to medical expenses and productivity losses caused by OA.[3] Given its widespread impact, addressing OA is a critical public health issue that is directly linked to population health and indirectly influences social and economic dynamics. Consequently, extensive research has been conducted on OA. It is now well-established that OA is a disease of the entire joint organ, involving inflammatory and metabolic crosstalk between cartilage, subchondral bone, synovium, menisci, and the infrapatellar fat pad.[4,5] Studies have revealed that its pathogenesis is driven by a complex network of catabolic enzymes (eg, MMPs, ADAMTS), pro-inflammatory signaling pathways (eg, NF-κB), and a plethora of inflammatory mediators (eg, cytokines IL-1β, IL-18) that disrupt joint homeostasis.[6]

Notably, pyroptosis, a newly identified form of pro-inflammatory programmed cell death, has drawn significant attention. Recent studies have demonstrated that both pyroptosis and OA are associated with the release of large amounts

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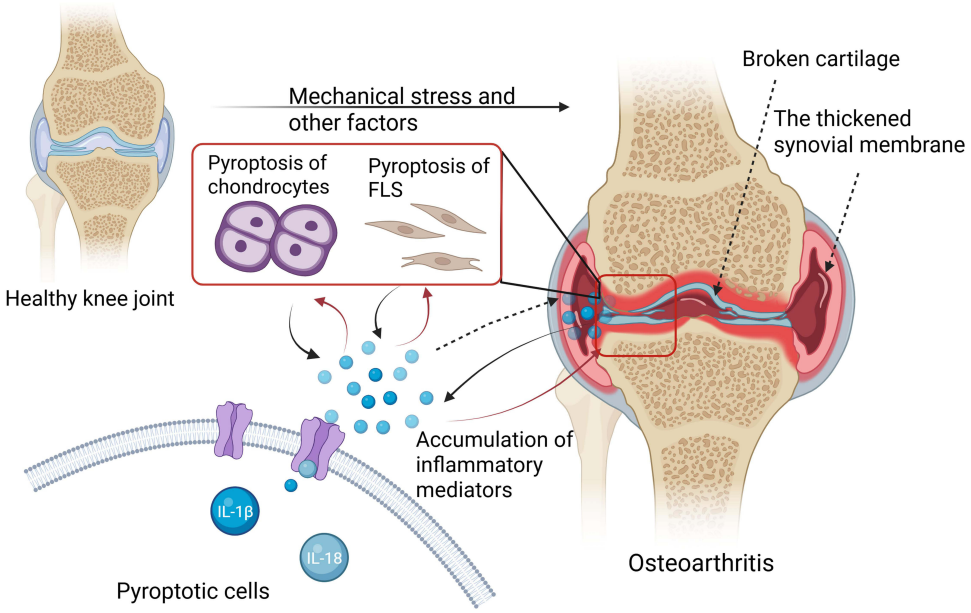
Graphical Abstract



of inflammatory mediators. In addition to pyroptosis, other forms of programmed cell death—such as apoptosis, ferroptosis, and the recently described chondroptosis—have also been implicated in the pathogenesis of OA, contributing to the loss of chondrocytes and cartilage destruction.[7] However, these modes of cell death differ fundamentally in their mechanisms and immunological consequences. Apoptosis is typically immunologically silent or tolerogenic, characterized by cell shrinkage and controlled dismantling without significant inflammation.[8] Necroptosis and ferroptosis, while both lytic and releasing damage-associated molecular patterns (DAMPs) that can provoke inflammation, are not primarily orchestrated by inflammasome activation and do not directly involve the proteolytic maturation and explosive release of IL-1β and IL-18.[9,10] In contrast, pyroptosis is distinctively characterized by the inflammasome-mediated, lytic release of potent pro-inflammatory cytokines (eg, IL-1β, IL-18) that actively perpetuate the inflammatory cascade and tissue damage, a feature that is particularly central to the chronic inflammatory milieu of OA.[11,12] Furthermore, components of pyroptosis-related signaling pathways, including NOD-like receptor family pyrin domain containing 3 (NLRP3), caspase-1, interleukin-18 (IL-18), and interleukin-1β (IL-1β), play crucial roles in the pathological process of OA. These findings strongly suggest that pyroptosis may be intricately involved in the occurrence and progression of OA.[13] Thus, summarizing the characteristics and mechanisms of pyroptosis and clarifying its relationship with OA is imperative for advancing our understanding of the disease and exploring novel therapeutic approaches. Moreover, emerging evidence suggests that pyroptosis does not occur in isolation but engages in extensive crosstalk with other inflammatory signaling pathways (eg, NF-κB, JAK/STAT) and metabolic pathways (eg, those regulating glycolysis, oxidative stress, and mitochondrial function).[14,15] These interactions can create vicious cycles that amplify the initial inflammatory insult, potentially influencing OA severity, progression rate, and the emergence of distinct phenotypic subtypes (eg, highly inflammatory vs metabolic OA).[16]

This narrative review aims to synthesize current evidence on the role of pyroptosis across major joint tissues—including articular cartilage, synovium, subchondral bone, menisci and infrapatellar fat pad, etc.— in OA pathogenesis, with a particular focus on its interplay with key signaling and metabolic networks, thereby providing a theoretical foundation for targeting pyroptosis as a potential therapeutic strategy for this whole-joint disease.

To achieve this, we conducted a comprehensive literature search across databases such as PubMed and Web of Science, focusing on recent and seminal works discussing pyroptosis and its intersection with osteoarthritis pathophysiology. As a narrative review, our objective was to provide a broad, critical, and synthesized overview of the field.

Pathological Progression of OA

OA is a whole-joint disease characterized primarily by the degeneration and injury of articular cartilage, accompanied by reactive hyperplasia of the articular margin and subchondral bone sclerosis. Notably, the pathological process extends beyond these tissues to include meniscal degeneration, as well as inflammation and fibrosis of the infrapatellar fat pad (IFP), which contribute significantly to pain and joint dysfunction.[17,18] These changes are driven by factors such as aging, obesity, mechanical strain, trauma, and congenital joint abnormalities. The pathological process of OA is complex and primarily involves inflammatory and metabolic factors.[19,20] Inflammation promotes cartilage degeneration, which, in turn, exacerbates inflammation, creating a vicious cycle.[21] Cartilage degeneration predominantly occurs in the early stages of OA. As the cartilage covered by the meniscus deteriorates, joints begin to infiltrate and swell, resulting in structural destruction.[22] Chondrocytes regulate cartilage homeostasis in part by synthesizing the extracellular matrix (ECM) rich in typeIIcollagen, proteoglycan and related macromolecules.[23] However, as OA progresses, chondrocytes undergo pathological functional changes that disrupt ECM homeostasis and lead to its progressive erosion. The destruction of the collagen mesh structure and the degradation of proteoglycans fundamentally weaken the mechanical properties (eg, tensile and compressive strength) of the cartilage tissue, altering the pericellular biomechanical microenvironment.[24] Concurrently, these biomechanically compromised chondrocytes begin to express inflammatory mediators.[25] This process eventually leads to a positive loop of further degradation of the cartilage matrix.[26] Recent clinical studies have observed that large amounts of IL-1β accumulate on the surface of chondrocytes and within the cell matrix of articular cartilage in OA patients.[27] Experimental evidence further indicates that IL-1β induces both cytotoxicity and apoptosis in chondrocytes, thereby exacerbating cartilage damage.[28]

The inflammatory milieu is not confined to cartilage. The IFP and the synovial membrane are now recognized as an anatomically and functionally integrated unit, often referred to as the "synovio-entheseal complex", which plays a pivotal role in OA-related inflammation.[29] Synovial cells and IFP-derived stromal cells can be activated under abnormal conditions induced by degenerated cartilage, such as high-magnitude mechanical stress and inflammatory cytokines,[30] which, in turn, trigger the production of additional inflammatory cytokines and further exacerbate synovial and perisynovial inflammation.[31] It has been confirmed that active synovitis plays a critical role in the pathogenesis of OA. Hence, cartilage degradation and the crosstalk with adjacent tissues like the IFP are likely key factors linking active synovitis and OA.[32] Additionally, researchers have confirmed the presence of inflammatory cytokines, chemokines, and other inflammatory mediators in the synovial fluid of OA patients.[33] The elevated expression of inflammatory cytokines in the joint synovium and IFP disrupts joint tissue metabolism in OA, promoting tissue degradation. This evidence demonstrates that inflammatory cytokines are closely associated with the progression of joint structural changes in OA.[34]

As one of the main features of OA, the degeneration of articular cartilage leads to the increased secretion of inflammatory factors, such as IL-1, TNF, and IL-6, in chondrocytes and synovial cells, which further intensifies OA-associated inflammation.[35] Similarly, the inflamed IFP contributes a significant quantity of adipokines and cytokines to the joint environment.[36] Meanwhile, other secondary inflammatory cytokines (such as IL-1β, IL-17, IL-21, and IL-22, etc.) also play significant roles in this process.[37] The synergistic interactions between chondrocytes, synovial cells, and IFP-derived cells ultimately exacerbate the inflammation of OA.

Pyroptosis

As a new way of pro-inflammatory programmed cell death, pyroptosis was first reported by Sansonetti et al in macrophages infected with *shigella flexneri*.[38] The mechanisms of pyroptosis can be categorized into two pathways (as shown in Figure 1): caspase-1-dependent and non-caspase-1-dependent. The former represents the classical pathway of pyroptosis, which is primarily mediated by the NLRP3 inflammasome leading to caspase-1 activation,[39,40] while the latter, induced by human caspase-4, caspase-5, or their murine ortholog caspase-11, is referred to as the non-classical pathway.[41,42] Both pathways result in cellular structural changes and the release of IL-1β and IL-18, inflammatory

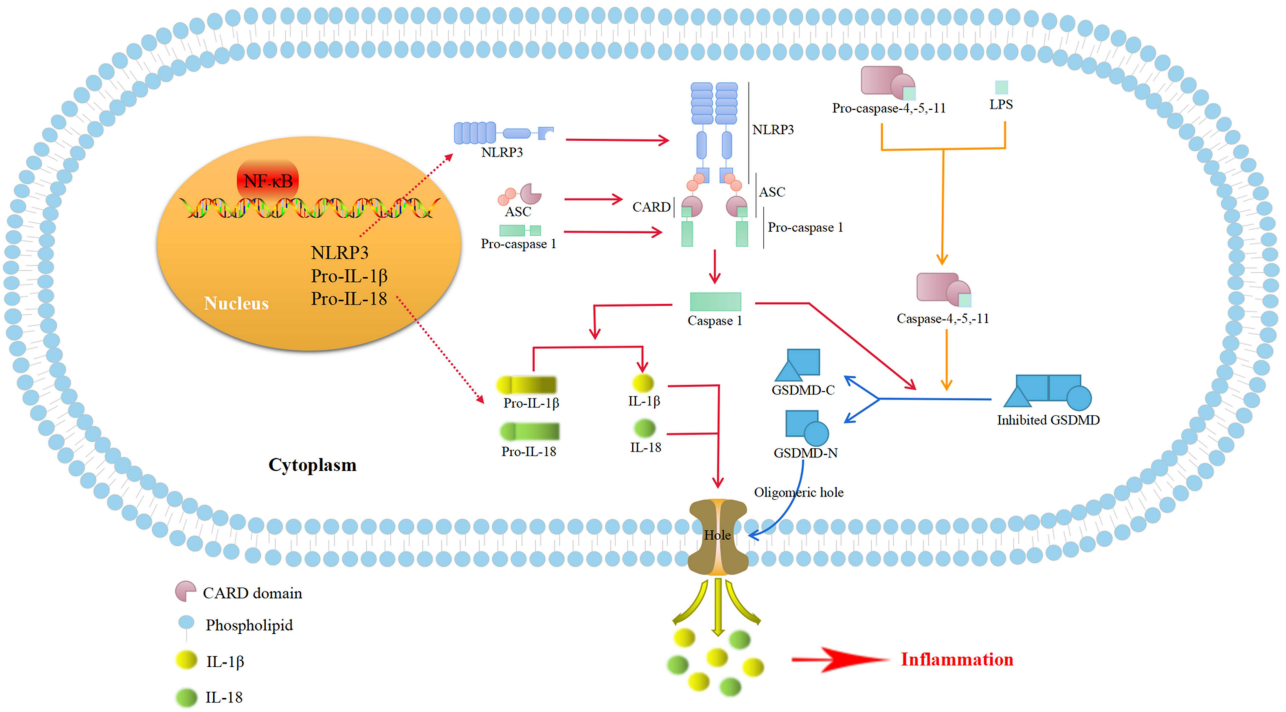


Figure 1 Mechanisms of pyroptosis. The red arrow represents the process of caspase-1-dependent pyroptosis. After the preparation is done in the nucleus, NLRP3, pro-IL-1β and pro-IL-18 enter the cytoplasm from the nucleus (shown by the red dotted arrow). Subsequently, they are activated to form active caspase-1, IL-1β and IL-18 in the second step. On the other hand, the Orange arrow indicates non-caspase-1-dependent pyroptosis. In this pathway, pro-caspase-4, −5, −11 are activated by binding to LPS. The active caspase-4, −5, −11 and active caspase-1 act on GSDMD together (shown by the blue arrow), which causes GSDMD to be cleaved and releases the N-terminal structure from the self-inhibitory GSDMD-C domain. Next, the active GSDMD-N binds to the lipids of cytomembrane and forms large oligomeric pores. Consequently, cellular contents such as IL-1β and IL-18 are released, ultimately leading to inflammation.

markers associated with inflammasome activation, ultimately leading to cell death and a robust inflammatory response.[43] In the classical pathway of pyroptosis, the activation of caspase-l is mediated by inflammasome, with NLRP3 being the most extensively studied member.[39] This process involves two critical steps: The first step, occurring in the nucleus, is closely related to the NF-κB signaling pathway, during which pro-inflammatory mediators such as pro-IL-1β, NLRP3, and pro-IL-18 are transcribed, preparing for subsequent activation.[44] The canonical inflammasome pathway relies on caspase-1, which is typically present in an inactive form as pro-caspase-1. Its cutting and activation are regulated by the NLRP3 inflammasome.[45] After inflammasome assembly, pro-caspase-1 is recruited by Speck-like protein with a caspase activation and recruitment domain (ASC) and undergoes hydrolysis and self-cleavage, converting into active caspase-1. Activated caspase-1 then cleaves the precursors of pro-IL-1β and pro-IL-18 into their active forms, IL-1β and IL-18, respectively.[46–48] Subsequently, the innate immune response is initiated, leading to cell damage and, in some cases, cell death.[49] IL-1β plays a central role in amplifying the inflammatory response by inducing the synthesis of inflammatory cytokines (such as IL-6), chemokines, and adhesion molecules through the recruitment and activation of other immune cells. This cascade further promotes the maturation and release of related inflammatory cytokines, providing a potent signal to initiate the inflammatory cascade reaction.[38,50–52] Consequently, the immune-inflammatory response becomes exacerbated, resulting in significant tissue damage.[53]

At the same time, non-classical pathways also contribute to the execution of pyroptosis. Pro-caspase-4, −5, and −11 are the key initiators of the non-classical pathway. In this pathway, the recognition of lipopolysaccharide (LPS) within the cytoplasm of Gram-negative bacteria is mediated by the caspase activation and recruitment domain (CARD), which triggers the oligomerization of proteases. This process leads to the formation of active caspase-4, −5, and −11, ultimately driving pyroptosis.[54,55]

Next, caspase-1 activated by the classical pathway and caspase-4,-5,-11 activated by the non-classical pathway cooperate to act on GSDMD, initiating pyroptosis.[56,57] GSDMD is the executor of pyroptosis. After being activated,

GSDMD is split into an N-terminal fragment of 31kDa and a C-terminal fragment of 22kDa. With the separation of the N-terminal pore formation domain (PFD) and the C-terminal inhibition domain (RD), the effect of GSDMD-N is no longer inhibited. Then it binds to the lipids in the plasma membrane and forms the oligomeric pore of 1~2nm,[58] leading to the loss of membrane integrity. This leads to swelling and rupture of organelles and cytoplasm, and a large number of cell contents including pro-inflammatory factors are released into the cellular stroma through the pores in the membrane.[40,59,60] GSDMD-N is directly involved in forming these pores on the cell membrane surface, thereby inducing pyroptosis.[40] Meanwhile, GSDMD-N can cause the activation of NLRP3-dependent caspase-1 inflammasome. The critical role of GSDMD cleavage in executing pyroptosis has been firmly established, for instance, by studies employing CRISPR-Cas9 technology to generate GSDMD-deficient mice.[61] Importantly, the GSDMD-mediated pyroptotic pathway is not limited to cardiomyocytes but is also mechanistically implicated in OA. For example, in the context of OA, GSDMD-N terminal pore formation in chondrocytes and synovial fibroblasts facilitates the release of IL-1β and IL-18, thereby amplifying the local inflammatory response and contributing to cartilage degradation.[59,62]

Pyroptosis Is Involved in the Pathological Process of OA

Both the pathological process of OA and the occurrence of pyroptosis lead to the release of a large amount of inflammatory mediators. Among them, IL-1β and IL-18, key components in the signaling pathways related to pyroptosis, are well-established central drivers of inflammation and tissue degradation in the pathological process of OA.[43,62,63] Therefore, researchers have explored the connection between OA and pyroptosis primarily from the perspective of inflammation. Pyroptosis is likely involved in the occurrence and development of OA, and even contributes to the maintenance of the OA inflammatory environment. Through summarizing a large number of studies, we have observed that the pyroptosis of cartilage tissue and synovial tissue significantly influences the pathological progression of OA.

Multiple Signaling Pathways in Chondrocytes in OA Affect Its Pyroptosis

The primary pathological hallmark of OA is the progressive degeneration of articular cartilage.[25] The progressive destruction of articular cartilage is one of the important hallmarks of the pathogenesis of osteoarthritis.[64] Histopathology is characterized by chondrocyte degeneration, various forms of cell death (including pyroptosis and apoptosis), and joint structural disorders.[65] The survival of chondrocytes is essential for maintaining normal articular cartilage.[66] Therefore, how to suppress the degeneration of chondrocytes is also a key point of OA drug treatment.[67,68] Studies have reported the presence of empty lacunae and reduced cellularity in cartilage as OA progresses, providing histomorphometric evidence of chondrocyte death that contributes to OA development[69,70] (Table 1).

Nuclear Factor-Kappa B (NF-κB) Signaling Pathway

NF-κB signal transduction plays a vital role in the pathogenesis of various inflammatory diseases, including OA.[80,81] The NF-κB signaling pathway participates in the pathogenesis of OA by up-regulating the expression of collagen-degrading enzymes, including matrix metallo-proteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), leading to articular cartilage breakdown.[73] It is important to note that the impact of NF-κB extends beyond chondrocytes and is equally critical in driving synovial inflammation (synovitis), a key aspect of OA pathology that will be discussed in detail in the following section.[82,83] Moreover, the NF-κB signaling pathway can promote chondrocyte hypertrophy in the progression of OA. Due to its close connection with OA, NF-κB is considered a promising target.[84] It is worth noting that NF-κB is also a necessary upstream activator of NLRP3 inflammasomes, triggering their assembly by inducing NLRP3 expression.[85] In the experiments of Hua et al, loganin (a strong inhibitor of NF-κB signaling) was used as an intervention to reduce pyroptosis in chondrocytes and improve cartilage degradation.[72] Similarly, the study conducted by Zheng et al utilized a mouse model of meniscus instability to investigate the impact of paroxetine on extracellular matrix synthesis and degradation, revealing that paroxetine effectively inhibits pyroptosis through the suppression of the NF-κB pathway.[71] Existing studies have found that the expression of caspase-1 in OA cartilage is significantly higher than in normal cartilage, while caspase-1 activation is mediated by NLRP3.[63] Therefore, the NF-κB signaling pathway,as an upstream activator of NLRP3 inflammasomes, contributes to the pathological

Table 1 Summary of Key References on Pyroptosis in Chondrocytes in OA

Category	Cellular/Animal Model	Key Findings on Pyroptosis in Chondrocytes	Signaling Pathway/ Mechanism	Reference
NF-κB Signaling	Mouse meniscus instability model	Paroxetine inhibited chondrocyte pyroptosis and delayed OA progression.	NF-κB pathway	Zheng et al[71]
	Primary murine chondrocytes	Loganin (NF-κB inhibitor) reduced pyroptosis and improved cartilage degradation.	NF-κB / NLRP3 / Caspase-1 / GSDMD	Hu et al[72]
	In vitro chondrocyte model	Indole-3-propionic acid alleviated inflammation and OA via the AhR/NF-κB axis.	AhR / NF-κB axis	Zhuang et al[73]
Hedgehog Signaling	In vitro and mouse OA model	GANT-61 (Hedgehog inhibitor) + low-dose indomethacin synergistically attenuated cartilage damage by controlling pyroptosis.	Hedgehog / GLI1 / NLRP3	Liu et al[74]
	Col2a1-CreERT2; Ihhfl/fl mice	Knockout of Indian Hedgehog (Ihh) significantly reduced cartilage damage.	Indian Hedgehog (Ihh) signaling	Zhou et al[75]
	Mouse model	Hedgehog signaling inhibition protects against OA progression.	Hedgehog / β-catenin	Rockel et al[76]
	Chondrocyte culture	Lithium chloride inhibits Hedgehog signaling by modulating primary cilia.	Hedgehog signaling	Thompson et al[77]
	In vitro study	Characterized metal complexes of the Hedgehog pathway inhibitor GANT61.	Hedgehog signaling inhibition	Ryan et al[78]
General Pyroptosis & OA	Human chondrocytes / KOA model	NLRP1 and NLRP3 inflammasomes mediate LPS/ATP-induced pyroptosis in KOA.	NLRP1/NLRP3 Inflammasome	Zhao et al[12]
	Human OA cartilage	Expression of caspase-1 is significantly higher in OA cartilage than in normal cartilage.	NLRP3 / Caspase-1	Wang et al[63]
Cell Death in OA	Various OA tissue engineering models	Reported the presence of empty lacunae, providing histomorphometric evidence of chondrocyte death.	Histological evidence of cell death	Kim et al[69]
	Review of aging and OA	Discussed chondrocyte death as a feature of OA pathogenesis linked to aging.	Aging / cell death	Loeser et al[70]
Therapeutic Implications	Mouse OA model	Autophagy attenuates OA by inhibiting chondrocyte pyroptosis and improving bone remodeling.	Autophagy-Pyroptosis crosstalk	Yan et al[79]

progression of OA by influencing chondrocytes. These findings collectively help explain the occurrence of pyroptosis in OA chondrocytes.

Hedgehog Signaling Pathway

It is worth mentioning that another pathway closely related to the physiological and pathological processes of OA chondrocytes is the Hedgehog signaling pathway,[86] which plays a key role in the formation and differentiation of cartilage.[87] The activation of this pathway is also involved in articular cartilage degeneration and ectopic bone formation.[88] Changes in the Hedgehog signaling pathway have been shown to contribute to the occurrence and development of OA by inducing catabolic reactions.[89,90] The study by Zhou et al found that after knocking out the expression of Indian hedgehog (Ihh) in mice, cartilage damage was significantly reduced, suggesting that Ihh promotes cartilage damage.[75] The downstream effector of the Hedgehog signaling pathway is the GLI family of proteins (eg, GLI1, GLI2), which function as transcription factors with a characteristic zinc finger structure.[91] With the activation of the Hedgehog signaling pathway, GLI proteins are activated and translocate into the nucleus, where they function as transcription factors to regulate the transcriptional initiation of downstream genes. For example, GLI enhances the expression of Runx2, leading to chondrocyte hypertrophy.[92] As a well-known Hedgehog/GLI pathway inhibitor, GANT-61 has been shown to significantly inhibit cartilage degradation in OA.[76–78] Moreover, recent research demonstrated that the combined administration of GANT-61 and a low dose of indomethacin synergistically attenuates cartilage damage in

OA by controlling pyroptosis in chondrocytes both in vitro and in a mouse model.[74] The molecular link between these two processes is believed to be mediated by the downstream transcription factor GLI1. Upon activation of the Hedgehog pathway, GLI1 translocates to the nucleus and functions as a potent transcriptional activator. It can promote the expression of pro-inflammatory and catabolic mediators.[93] Crucially, the expression of key pyroptosis-related components, such as the NLRP3 inflammasome and pro-IL-1β, is known to be transcriptionally regulated by factors like NF-κB.[85] Given that Hedgehog/GLI signaling can crosstalk with and potentiate other inflammatory pathways, it creates a permissive cellular state that significantly lowers the threshold for NLRP3 inflammasome assembly and activation, thereby facilitating GSDMD cleavage and pyroptosis. Therefore, the Hedgehog signaling pathway can regulate the release of NLRP3, caspase1, and IL-1β through the downstream gene GLI, thereby affecting pyroptosis in OA chondrocytes.

The Effect of Synovial Tissue-Related Cells Pyroptosis on OA Pathological Progress

Knee osteoarthritis (KOA) is characterized by the gradual destruction of articular cartilage and surrounding tissues, especially the synovium, resulting in pain, stiffness, and chronic disability.[5] As foreshadowed in the previous section, NF-κB signaling is a master regulator of inflammation in the synovial membrane, driving the expression of pro-inflammatory cytokines (eg, IL-1β, TNF-α) and catabolic enzymes that contribute significantly to synovitis and joint destruction.[83] This inflammatory microenvironment, rich in NF-κB-dependent signals, is now recognized as a potent trigger for pyroptosis in resident synovial cells.[94] Recent studies have confirmed that the synovial cells in the OA synovial tissue undergo pyroptosis.[12] Notably, there are two main types of synovial cells: macrophages (also known as type A synovial cells) and synovial fibroblasts (also known as type B synovial cells),[95] a growing body of experimental evidence has confirmed that pyroptosis occurs in both synoviocyte populations within the OA synovium, driven by the NLRP3 inflammasome and GSDMD cleavage.[96] Both of which are susceptible to NF-κB-mediated pyroptotic cell death under inflammatory conditions (Table 2).

Type A Synovial Cells

The infiltration and activation of macrophages in synovial tissue contribute to synovitis, a key driver of OA pathogenesis.[106] Initially, research on macrophage pyroptosis focused on infections caused by bacteria and viruses.[107] However increasing evidence suggests that macrophage pyroptosis in different tissues is a key driver of chronic aseptic inflammation and fibrosis, as demonstrated in models of liver disease.[108] Zhang et al found that synovial macrophage pyroptosis may occur in the pathological processes of KOA, and its inhibition alleviates synovitis and fibrosis in KOA model rats.[97] Importantly, a recent innovative study demonstrated that targeted modulation of synovial macrophage pyroptosis, specifically by disrupting its crosstalk with impaired mitophagy using functionalized nanoparticles, effectively mitigated OA progression in vivo, highlighting its significant therapeutic potential.[98] While the protein

Table 2 Summary of Key References on Pyroptosis in Synovial Tissue in OA

Cell Type/Category	Cellular/ Animal Model	Key Findings on Pyroptosis in Chondrocytes	Signaling Pathway/ Mechanism	Reference
Type A: Macrophages	Rat KOA model	Inhibition of synovial macrophage pyroptosis alleviates synovitis and fibrosis.	NLRP3 Inflammasome / GSDMD	Zhang et al[97]
	In vivo OA model	Targeted modulation of macrophage pyroptosis and mitophagy crosstalk using nanoparticles mitigated OA progression.	Mitophagy-Pyroptosis Crosstalk	Qi et al[98]
	Mouse OA model	Targeted knockdown of PGAM5 repolarized M1 to M2 macrophages and alleviated OA.	PGAM5 / Macrophage Polarization	Liu et al[99]
	Review	Discusses pyroptosis-related crosstalk among macrophages, FLS, and chondrocytes in OA.	Inflammatory Crosstalk in Joint	Kuang et al[100]

(*Continued*)

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Table 2 (Continued).

Cell Type/Category	Cellular/ Animal Model	Key Findings on Pyroptosis in Chondrocytes	Signaling Pathway/ Mechanism	Reference
Type B: Fibroblast-like Synoviocytes (FLSs)	Human FLSs / KOA model	NLRP1 and NLRP3 mediate LPS/ATP-induced pyroptosis; siRNA attenuation confirms.	NLRP1 / NLRP3 Inflammasome	Zhao et al[12]
	Human FLSs	HIF-1α aggravates synovial fibrosis via FLS pyroptosis; silencing HIF-1α reduces pyroptosis markers.	**HIF-1α** / NLRP3 / Caspase-1	Zhang et al[44]
	Human FLSs	Identifies the ROS/GRK2/HIF-1α axis as a key upstream pathway activating NLRP3 and mediating pyroptosis.	**ROS / GRK2 / HIF-1α** / NLRP3	Hong et al[101]
	Review (Mechanism)	Exogenous particles and endogenous crystals are potent activators of the NLRP3 inflammasome.	Crystal-induced NLRP3 activation	Shirasuna et al[102]
	Synovial cells	Cis-resveratrol blocks crystal-induced NLRP3 activation via inhibiting the TRPV4-Ca^{2}+-phagocytosis-ROS axis.	**TRPV4-Ca^{2}+-Phagocytosis-ROS** Axis	Lei et al[103]
	Gouty arthritis model	Osteostatin mitigates crystal-associated arthritis by inhibiting caspase-1 and upregulating Nrf2.	Caspase-1 / Nrf2	Catalán et al[104]
	Human FLSs	Estradiol inhibits NLRP3 inflammasome in FLSs activated by LPS and ATP.	LPS+ATP / NLRP3	Shi et al[105]
General Synovial Pathology	Human synovium	Role of synovial macrophages and macrophage-produced cytokines in driving destructive responses in OA.	Synovial Macrophages	Bondeson et al[82]
	Review	Review on the role of synovitis in osteoarthritis pathogenesis.	Synovitis	Mathiessen et al[83]

phosphoglycerate mutase 5 (PGAM5) is well-established as a key regulator of necroptosis, emerging evidence indicates crosstalk between necroptotic and pyroptotic signaling pathways,[109] with PGAM5 implicated in inflammasome activation and gasdermin-mediated pore formation.[110] Notably, In a study by Liu et al, targeted inhibition of PGAM5 facilitated the repolarization of M1 macrophages to M2 macrophages —a cell type central to synovial pyroptosis—, effectively alleviating OA symptoms in mice.[99] This suggests that targeting PGAM5 may exert therapeutic effects by concurrently modulating multiple inflammatory cell death pathways. Critically, the pathological impact of macrophage pyroptosis extends beyond the cells themselves; it engages in extensive crosstalk with other joint cells, including fibroblast-like synoviocytes and chondrocytes, creating a self-amplifying inflammatory network that potently drives OA pathogenesis.[100] Therefore, these findings indicate that macrophages in synovial tissue can regulate the occurrence and progression of synovitis through pyroptosis, which in turn influences KOA progression.

Type B Synovial Cells

Among the typical symptoms of OA, stiffness and pain are highly correlated with synovial fibrosis,[111] and fibroblast-like synoviocytes (FLSs) have been shown to be the main effector cells driving this fibrotic process.[112] Chang et al demonstrated that NLRP3 inflammasomes play a crucial role in KOA through pyroptosis in FLSs.[12] During KOA progression, chronic inflammation is the main pathological change of synovial tissue. Various exogenous and endogenous stimuli are recognized by the NLRP3 receptor and trigger the activation of inflammatory bodies.[113] Among these, exogenous particles and endogenous crystalline molecules, such as basic calcium phosphate (BCP) and calcium pyrophosphate (CPPD) crystals, are potent activators of the NLRP3 inflammasome.[102] These crystals are phagocytosed by FLSs and other synovial cells, a process that can lead to lysosomal rupture, potassium efflux, and reactive oxygen species (ROS) generation, culminating in NLRP3 inflammasome assembly, caspase-1 activation, and Gasdermin D-mediated pyroptosis.[102,103] This crystal-induced inflammatory pathway is a significant contributor to OA pathology. Importantly, this cascade presents a promising therapeutic target. For instance, cis-resveratrol has been shown to block crystal-induced NLRP3 activation specifically by inhibiting the TRPV4-Ca^{2}+-phagocytosis-ROS axis in synovial

cells.[103] Similarly, osteostatin mitigates crystal-associated arthritis by inhibiting caspase-1 activation and enhancing anti-oxidative pathways via upregulation of Nrf2,[104] demonstrating the translational potential of modulating this pathway. A recent study found that the increase in LPS and adenosine triphosphate (ATP) in the joint space may promote KOA through NLRP3 inflammasomes, and inhibition of NLRP3 inflammasomes may have a protective effect.[105] This mechanism is directly demonstrated in vitro; studies using FLSs derived from human subjects have shown that co-stimulation with LPS and ATP effectively induces pyroptosis.[44] Furthermore, it was observed that NLRP1 and NLRP3 siRNA significantly attenuated this pyroptotic response.[12]

In addition to this, hypoxia is a persistent factor in the pathological process of KOA, making it essential to examine the steady-state of the cellular environment from the perspective of oxidative stress.[114] Therefore, pyroptosis of FLSs may also be related to hypoxia-inducible factor-1α (HIF-1α) and synovial fibrosis.[44] HIF-1α is a transcription factor and a major regulator of cellular hypoxia. Clinical studies have demonstrated that the level of HIF-1α in the synovial of KOA patients correlates with the progression of joint injury.[115] Hypoxia-induced up-regulation of HIF-1α can trigger divergent pathological pathways: the classic pathway involves endoplasmic reticulum stress, ultimately leading to chondrocyte apoptosis.[116] Meanwhile, a rapidly growing body of evidence underscores that HIF-1α is a potent trigger of pyroptosis. This is powerfully demonstrated in FLSs, where the ROS/GRK2/HIF-1α axis has been identified as a key upstream signaling pathway that activates the NLRP3 inflammasome and mediates pyroptosis[101] —a finding that directly links hypoxia to synovial cell pyroptosis. The role of HIF-1α in promoting NLRP3 inflammasome generation, as noted by Gupta et al[117] is a key component of this process. Importantly, this hypoxia-HIF-1α-pyroptosis axis is not cell-type specific; it is a conserved mechanism, as evidenced by studies showing that hypoxia/reoxygenation injury promotes NLRP3-mediated pyroptosis in cardiomyocytes.[118] Notably, the number of dead FLSs and the expression levels of caspase-1, ASC, NLRP3, GSDMD, IL-1β, and IL-18 were significantly reduced after HIF-1α was silenced.[44]

Inflammation and hypoxia are both involved in the pathological process of KOA. Whether considered from the perspective of the inflammatory response or oxidative stress, the various manifestations of pyroptosis in fibroblasts within synovial tissue strongly indicate their close association with the occurrence and progression of OA.

Effect of Pyroptosis of Subchondral Bone-Associated Cells on the Pathological Progression of OA

The term "subchondral bone" generally refers to the subchondral bone plate and the underlying trabecular structure located beneath the deposition line of articular cartilage. The subchondral bone plate is situated between the calcified cartilage layer and the trabecular bone, which resembles cortical bone in its lamellar structure. In a physiological state, subchondral bone provides mechanical support for articular cartilage and collaborates with it to transmit intra-articular load.[119] It acts as a dynamic organ that undergoes constant remodeling; it absorbs mechanical shock, buffering a significant proportion (30–50%) of the load within the joint,[120] and helps maintain joint congruity to prevent the focal concentration of intra-articular stress. Furthermore, terminal blood vessels passing through the subchondral bone plate and calcified cartilage layer provide nutritional support to articular cartilage.[121] Critically, in osteoarthritis, the subchondral bone transitions from a passive support structure to an active driver of pathology. Its dysregulated remodeling,[120] aberrant biomechanical and biochemical crosstalk with cartilage,[122] and role in promoting sensory innervation and pain[123] are now recognized as central to disease progression.

Subchondral bone sclerosis — characterized by increased bone volume and thickening of the subchondral plate — is a prominent pathological characteristic of OA.[120,124] Pathological changes in subchondral bone evolve throughout the disease course, with early stages predominantly marked by bone resorption, while later stages are characterized by excessive bone formation.[125] Imaging studies have demonstrated significant trabecular fractures during early OA stages, leading to thinning of the subchondral bone plate.In the advanced stage of OA, there is a decrease in bone turnover, weakened bone resorption, relatively increased bone formation,[126] and imaging reveals subchondral bone plate sclerosis. In late-stage OA, the coupling mechanism between normal bone resorption and formation becomes disrupted, shifting toward excessive bone formation.

Table 3 Summary of Key References on Pyroptosis in Subchondral Bone in OA

Cell Type/ Category	Cellular/ Animal Model	Key Findings on Pyroptosis in Chondrocytes	Signaling Pathway/ Mechanism	Reference
Direct Experimental Evidence	Mouse OA model	Picroside II inhibited pyroptosis-related cytokines and activity, mitigating subchondral bone destruction and osteophyte formation.	MAPK/NF-κB/ NLRP3 signaling	Wang et al[62]
	Mouse DMM model	Conditional knockdown of osteocyte lncRNA H19 alleviated cartilage damage and subchondral bone sclerosis. Proposed mediation via PI3K/ AKT/GSK3 pathway.	PI3K/AKT/GSK3 signaling	Wang et al[127]
Theoretical/ Indirect Link & Pathophysiology	Mouse OA model	Proposed that autophagy attenuates OA by inhibiting chondrocyte pyroptosis and improving subchondral bone remodeling. Suggests a link between chondrocyte death and bone changes.	Inflammatory Crosstalk (Cartilage-to-Bone)	Yan et al[79]
	Review	Describes the pathophysiology of subchondral bone remodeling in OA, providing the foundational context for how pyroptosis could disrupt this process.	Bone Remodeling	Burr et al[120]
	Review	Discusses the subchondral bone microenvironment as a regulator for OA treatment, setting the stage for targeting mechanisms like pyroptosis.	Microenvironment	Hu et al[125]
	Rat MMT model	Describes the histological stages of subchondral bone changes throughout OA progression.	Histological Progression	McKinney et al[126]

Existing studies predominantly demonstrate that the mechanical and morphological alterations of subchondral bone accelerate the progression of OA; however, limited research has investigated the relationship between subchondral bone and pyroptosis. Nevertheless, emerging evidence suggests that pyroptosis can affect pathological changes in subchondral bone, thereby influencing the pathogenesis of OA.

By constructing an OA animal model induced by medial meniscus destabilization (DMM), Wang et al[127] discovered that the PI3K/AKT/GSK3 signaling pathway may mediate osteocyte mechanotransduction by regulating the downstream Wnt/β-catenin signaling pathway. Their findings revealed that conditional knockdown of the osteocyte long non-coding RNA H19 alleviated cartilage damage and subchondral bone sclerosis in an OA mouse model. Additionally, experiments conducted by Fanchen Wang et al[62] demonstrated that Picroside II significantly inhibited the expression of pyroptosis-related cytokines and reduced pyroptotic activity, effectively mitigating subchondral bone destruction and osteophyte formation (Table 3).

Problems and Prospects

As a serious degenerative joint disease, OA significantly impairs normal joint mobility in affected patients.[128] Although extensive research has explored the mechanisms of pyroptosis in chondrocytes and synovial cells in OA,[71,73,99] studies on the role of NLRP3 inflammasomes, caspase-1 and IL-1 in the pathogenesis of arthritis have largely remained at the cellular level, with clinical trials still limited.[129] Furthermore, the identification of reliable biomarkers for pyroptosis is crucial for translating these mechanistic insights into clinical practice. Components of the pyroptotic pathway, such as circulating levels of GSDMD-N terminal fragments, caspase-1, and the hallmark inflammatory cytokines IL-1β and IL-18 in synovial fluid or serum, represent promising candidate biomarkers.[11,130] A primary challenge is the predominance of in vitro and rodent studies, with a critical shortage of clinical trials directly targeting pyroptosis components like the NLRP3 inflammasome, caspase-1, and IL-1β in humans.[129] The role of pyroptosis in key tissues such as subchondral bone, despite its known involvement in pathological remodeling,[79] remains inadequately explored.[127] To advance clinical treatment, further hypotheses and in-depth research are required.

The path to clinical application is being facilitated by studies that, although not directly targeting pyroptosis, influence the inflammatory environment central to its mechanism. A notable example is the clinical investigation of intra-articular carboxymethyl-chitosan (CM-C) by Manocchio et al, which demonstrated early improvements in pain relief and functional outcomes in patients with advanced OA.[131] The documented anti-inflammatory and pro-anabolic effects of CM-C make it a compelling example of how molecular mechanisms—such as the inhibition of the NLRP3/IL-1β axis—can be translated into meaningful clinical benefits. However, this case also illustrates a key challenge: the durability of

therapeutic efficacy remains limited, as evidenced by the diminishing effects of CM-C over time. This limitation underscores the urgent need for innovative approaches, including sustained-release drug formulations, rational combination therapies, and optimized retreatment protocols to extend the duration of therapeutic response.

At present, most studies show that pyroptosis of chondrocytes can accelerate the remodeling of subchondral bone,[79] However, limited research has confirmed the presence of pyroptosis in subchondral bone cells and its role in promoting the pathological progression of OA.[62,127] The link between subchondral bone and pyroptosis requires further experimental verification. In addition, subchondral bone is rich in blood vessels and provides nutrition for cartilage. Thus, whether inhibiting subchondral bone angiogenesis could slow OA progression has emerged as a new research focus.[125,132,133] Future research must navigate key challenges and opportunities to realize the full potential of pyroptosis inhibition. Promising opportunities lie in repurposing existing NLRP3 inhibitors (or developing safer analogues), designing novel combination strategies that target multiple nodes of the pyroptosis network and its regulators to validate pyroptosis as a bona fide therapeutic target in human OA.[72,85]

Conclusion

Inflammation is a key clinical manifestation of OA, and effectively modulating the inflammatory response is crucial for OA treatment. As a pro-inflammatory form of cell death, pyroptosis plays a significant role in the occurrence and progression of OA. Therefore, this review elaborates the specific situation of pyroptosis in the pathological progression of OA. Targeting pyroptosis regulation may emerge as a promising therapeutic strategy for OA in the coming years.

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