Journal of Orthopaedic Translation 47 (2024) 223–234

Contents lists available at ScienceDirect

Journal of Orthopaedic Translation

journal homepage: www.journals.elsevier.com/journal-of-orthopaedic-translation

Pyroptosis-related crosstalk in osteoarthritis: Macrophages, fibroblast-like synoviocytes and chondrocytes

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ARTICLE INFO

Keywords:
Cell function
Chondrocytes
Fibroblast-like synoviocytes
Macrophages
Osteoarthritis
Pyroptosis

ABSTRACT

The pathogenesis of osteoarthritis (OA) involves a multifaceted interplay of inflammatory processes. The initiation of pyroptosis involves the secretion of pro-inflammatory cytokines and has been identified as a critical factor in regulating the development of OA. Upon initiation of pyroptosis, a multitude of inflammatory mediators are released and can be disseminated throughout the synovial fluid within the joint cavity, thereby facilitating intercellular communication across the entire joint. The main cellular components of joints include chondrocytes (CC), fibroblast-like synoviocytes (FLS) and macrophages (MC). Investigating their interplay can enhance our understanding of OA pathogenesis. Therefore, we comprehensively examine the mechanisms underlying pyroptosis and specifically investigate the intercellular interactions associated with pyroptosis among these three cell types, thereby elucidating their collective contribution to the progression of OA. We propose the concept of ' CC-FLS-MC pyroptosis-related crosstalk', describe the various pathways of pyroptotic interactions among these three cell types, and focus on recent advances in intervening pyroptosis in these three cell types for treating OA. We hope this will provide a possible direction for diversification of treatment for OA.

The Translational potential of this article. The present study introduces the concept of 'MC-FLS-CC pyroptosis-related crosstalk' and provides an overview of the mechanisms underlying pyroptosis, as well as the pathways through which it affects MC, FLS, and CC. In addition, the role of regulation of these three types of cellular pyroptosis in OA has also been concerned. This review offers novel insights into the interplay between these cell types, with the aim of providing a promising avenue for diversified management of OA.

1. Introduction

The global population affected by osteoarthritis (OA), the most common type of arthritis, surpasses 500 million individuals, with a notable emphasis on older adults and females [1,2]. The process of OA involves not only the degeneration of articular cartilage, but also periarticular tissues such as synovium and subchondral bone. These interconnected components mutually influence each other in a complex and multifaceted manner, resulting in intricate and diverse effects [3]. Due to the unclear molecular mechanisms underlying the onset and progression of OA, effective interventions for reversing or eradicating this disease are currently lacking [4]. Therefore, a deeper exploration of the pathogenesis of OA and new insights into it are of great value for achieving breakthrough in OA treatment.

The cells involved in interactions between synovial and cartilage tissues mainly include macrophages (MC), synovial fibroblasts (FLS), and chondrocytes (CC). The synovium is rich in MC, which are the predominant immune cells responsible for producing chemokines and cytokines that regulate inflammatory responses and facilitate tissue repair [5,6]. The release of pro-inflammatory cytokines by FLS not only

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https://doi.org/10.1016/j.jot.2024.06.014
Received 21 January 2024; Received in revised form 28 April 2024; Accepted 20 June 2024

accelerates the degradation of cartilage matrix but also contributes to synovial fibrosis, thereby exacerbating cartilage damage [7]. The CC, as resident cells within the articular cartilage, possess the unique ability to modulate their metabolic activity in response to changes in the microenvironment [8]. Undoubtedly, there are a diverse array of interactions between MC, FLS, and CC, which promote the progression of OA through various pathways and mechanisms of action. Unraveling the intricate interactions and communication between these cells holds the potential to enhance our comprehensive understanding of the pathogenesis of OA and provides innovative perspectives for the development of therapeutic strategies.

The role of cellular pyroptosis in OA has received wide attention in recent years, and the potential mechanisms by which pyroptosis regulates the development of OA have been identified [9,10]. Throughout the progression of OA, pyroptosis can possibly induce pathological alterations within inflamed joints, such as impairments in cartilage integrity, fractures, and synovial tissue inflammation and fibrosis [11–14]. Consequently, pro-inflammatory cytokines associated with pyroptosis are transported and interact among cells within the joint, potentially serving as a pathway for the initiation of inflammation in OA. Therefore, the concept of 'MC-FLS-CC pyroptosis-related crosstalk' is proposed in this study. This article presents an extensive examination of the molecular mechanisms that drive pyroptosis and investigates different pathways implicated in the interactions between MC, FLS, and CC associated with pyroptosis. The objective of this review is to offer fresh perspectives on the intercellular communication occurring among these various cell types. In addition, we have focused on researching molecules related to pyroptosis targeting in the treatment of OA, with the hope of providing a viable direction for diversifying OA treatments.

2. Materials and methods

The literature related to the concepts of "pyroptosis" and "osteoarthritis" was retrieved from Web of Science database, focusing on publications within the past two decades. Relevant reviews and articles are gathered for the purpose of collation and analysis.

3. Mechanisms of pyroptosis

As early as the 1990s, researchers observed pyroptosis in MC infected with Salmonella, which attracted significant attention and interest from the scientific community [15]. The research carried out by Cookson

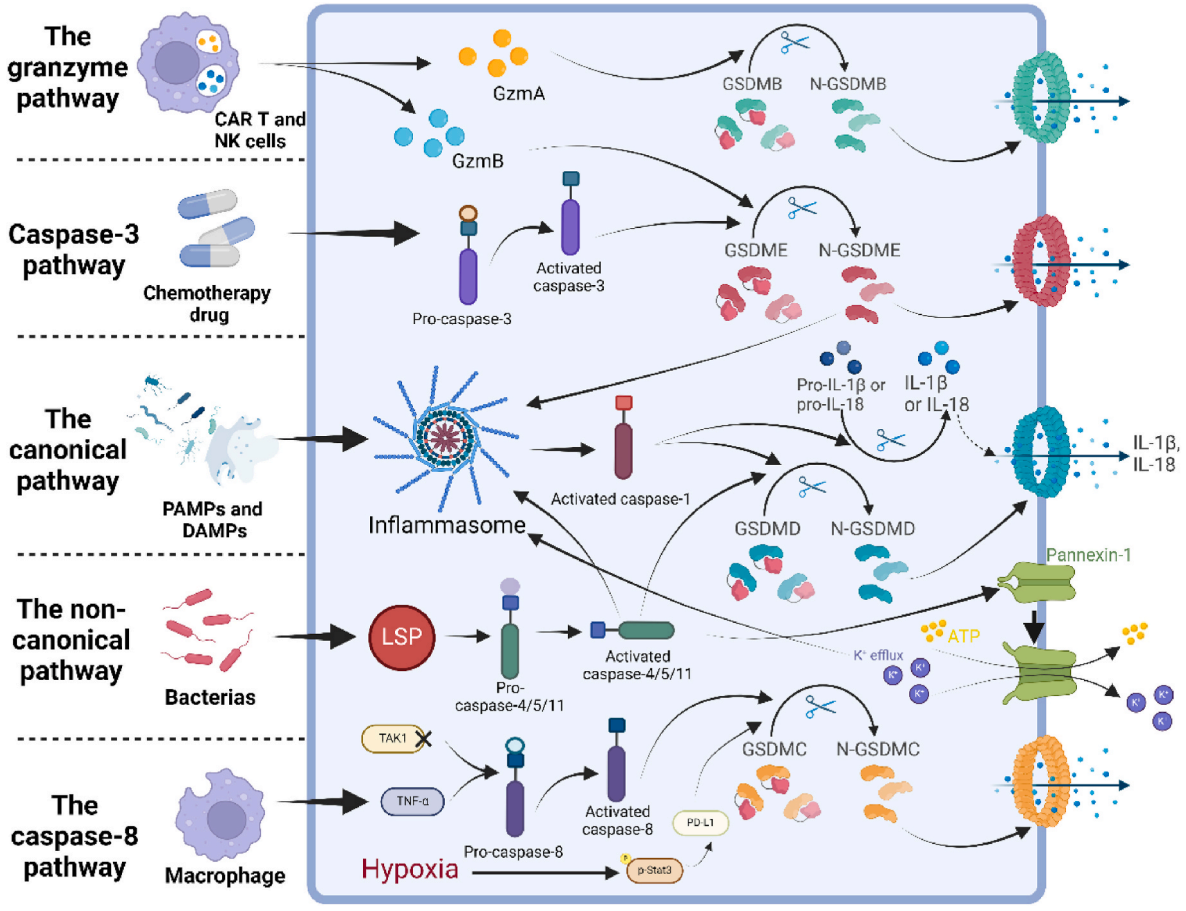

Figure 1. The molecular mechanism underlying pyroptosis involves the recognition of PAMPs and DAMPs by PRRs, which subsequently assemble into inflammasomes, leading to the activation of caspase-1. The activated caspase-1 then cleaves GSDMD and pro-IL-1β/18. N-GSDMD forms nonselective pores in the cell membrane, resulting in an influx of water, efflux of IL-1β/18, cell lysis, and ultimately cell death. In the alternative pathway, caspase-4/5/11 is activated by LPS, triggering pyroptosis through GSDMD cleavage. Moreover, the activation of caspase-4/5/11 leads to the induction of Pannexin-1, resulting in enhanced efflux of K+ and ATP. This process initiates the classical pathway of pyroptosis through stimulation of inflammasomes. Additionally, activated caspase-11 also facilitates maturation and release of IL-1β/18 by activating inflammasomes. In the caspase-3-mediated pathway, GSDME is cleaved by activated caspase-3 to induce pyroptosis. Subsequently, N-GSDME activates inflammasomes to trigger the classical pathway. In the caspase-8-mediated pathway, TNF-α triggers the activation of caspase-8, leading to the initiation of pyroptosis. However, this process requires the translocation of PD-L1 to the nucleus and co-regulation between GSDMC transcription and p-Stat3 under hypoxic conditions. Furthermore, inhibition of TAK1 prompts caspase-8 activation, resulting in GSDMD cleavage and subsequent induction of pyroptosis. In the granzyme-mediated pathway, CAR T cells and NK cells release GzmB to activate cysteinase-3 within target cells. This enzyme then cleaves GSDME, ultimately causing pyroptosis. Additionally, GzmA found in cytotoxic lymphocytes can enter target cells for cleaving GSDMB and inducing pyroptosis.

et al. demonstrated that this specific form of cellular demise exhibits distinctive characteristics different from those observed in apoptosis [16]. D'souza and colleagues coined the term "pyroptosis" to describe a phenomenon of cell death characterized by the release of pro-inflammatory cytokines and cellular swelling [17]. When pyroptosis occurs, cells undergo swelling, cell membrane pore formation, release of inflammatory factors, condensation of chromatin and fragmentation of DNA while the nucleus remains condensed yet intact [18–20]. Corrected sentence: Despite the numerous technical and safety issues that still need to be resolved, there is great optimism and interest in novel anticancer drugs capable of modulating pyroptosis [21–24]. We show multiple pathways in the mechanism of pyroptosis (Fig. 1).

3.1. The canonical pathway

In the canonical pyroptosis pathway, activation of pattern recognition receptors (PRRs) on the cell membrane induces the assembly of inflammasomes and initiates pyroptosis. This process further leads to cleavage of the gasdermin (GSDM) D and subsequent pore formation in the cell membrane, ultimately resulting in the release of proinflammatory factors and rupture of the cell membrane [25–28]. The inflammasomes are multi-protein complexes consisting of PRRs and effector proteins located in the cytoplasm [29]. GSDMs are a group of genetically conserved genes that have the ability to initiate pore formation, disrupting cell membranes and releasing inflammatory cytokines [30]. The structural domains of GSDM at the N- and C-termini are directly linked, maintaining a repressed state [31]. In the course of pyroptosis, GSDMs undergo hydrolytic cleavage by proteases, resulting in the liberation of a structural domain at the N-terminus which exhibits affinity towards acidic phospholipids present on the cellular membrane. The binding event triggers the assembly of pores composed of 16 symmetrical protomers, leading to pyroptosis characterized by the release of proinflammatory cytokines, as well as water influx that causes cellular swelling and osmotic lysis [30–33]. The assembly of the N-terminal structural domains of GSDMs, which form pores in the cell membrane leading to the efflux of cellular contents, constitutes a pivotal factor in initiating pyroptosis [31].

In the canonical pathway of pyroptosis, completion of inflammatory vesicle assembly is a prerequisite for cellular stimulation leading to precaspase-1 autocleavage [34,35]. Upon activation, caspase-1 undergoes a process of hydrolysis resulting in the production of two fragments. These fragments subsequently combine to form mature cleaved caspase-1 [36]. The caspase-1 cleavage event triggers the proteolytic division of GSDMD at ASP275, resulting in the generation of a 22 kDa fragment known as C-GSDMD and a 31 kDa fragment referred to as N-GSDMD [37]. The N-GSDMD protein engages with the acidic phospholipids present in the cellular membrane and undergoes self-assembly, resulting in the formation of a pore consisting of 16 identical proteins. This subsequently triggers the liberation of interleukin-1 (IL-18) and IL-1β, accompanied by an influx of cellular water. Ultimately, this cascade triggers cellular swelling and pyroptosis [30–33]. On the other hand, caspase-1 activated in the cytoplasm induces the formation of mature forms of IL-1β/18 from their precursors. Subsequently, the cell swells and releases these active cytokines through a pore formed by GSDMD [32,38,39]. Furthermore, the occurrence of cellular pyroptosis involves the liberation of immunogenic DAMPs like high mobility group box 1 (HMGB1), which can induce an escalated inflammatory reaction [40–42]. The presence of GSDMD is crucial for the release of HMGB1 upon inflammasome activation; however, it does not directly facilitate the translocation of HMGB1 across cell membrane pores. The liberation of HMGB1 occurs only subsequent to the disruption of the cell membrane [43].

3.2. The non-canonical pathway

The occurrence of the non-canonical pyroptosis pathway primarily relies on human caspase-4/5 and its mouse counterpart, caspase-11, for its mediation. Lipopolysaccharide (LPS) derived from intracellular or Gram-negative bacterial sources activates by binding to the CARD structural domain of caspase-4/5/11 [44]. Activation of the caspase results in cleavage of GSDMD at Asp276, generating N-GSDMD, which undergoes oligomerization and translocates to the plasma membrane where it forms a pore, contributing to cellular pyroptosis [45]. The auto-activation of pro-caspase-4/11 is indispensable for the generation of the P10 fragment, which plays a pivotal role in facilitating GSDMD cleavage and initiating pyroptosis. This mechanism potentially enables caspases to selectively recognize and interact with GSDMD, thereby leading to its activation [46]. Notably, in contrast to caspase-1, the activation of caspase-4/5/11 does not directly trigger the maturation of IL-1β/18. Nevertheless, NOD-like receptor thermal protein domain associated protein 3 (NLRP3) can be activated by caspase-11 to facilitate the maturation and release of IL-1β/IL-18 [47]. In addition, caspase-4/5/11 activation induces the classical pathway of pyroptosis. This is due to the fact that GSDMD activation and the formation of a pore in the cell membrane leads to the release of potassium ions. Subsequently, this event can initiate the assembly of NLRP3 inflammatory vesicles and ultimately lead to pyroptosis via the conventional pathway [48–50]. The involvement of Pannexin-1 is pivotal in an alternative caspase-11-mediated pathway of pyroptosis [51]. The findings suggest that the cleavage and modification of Pannexin-1 may potentially underlie intracellular potassium ion (K+) efflux and ATP release [51].

3.3. Caspase-3 pathway

The conventional view has long considered the activation of caspase-3 as a distinctive characteristic of apoptosis. Nevertheless, recent research discoveries propose that caspase-3's function goes beyond apoptosis and encompasses its capacity to trigger pyroptosis in cellular systems [22]. It has been discovered that chemotherapeutic agents can induce this type of pyroptosis pathway to occur, specifically due to the activation of caspase-3 which leads to the cleavage of GSDME into N-GSDME. The aggregation of N-GSDME then triggers cellular pyroptosis [52,53]. Furthermore, TNF-α has also been found to possess the ability to activate caspase-3, which subsequently triggers cleavage of Asp267 or Asp270 in GSDME [53]. In addition to inducing the formation of cell membrane pores, GSEDME-N generated through caspase-3 cleavage of GSDME has the ability to trigger the conventional pathway of pyroptosis, leading to the enhancement and release of inflammatory mediators [53].

3.4. The caspase-8 pathway

Previously, it was believed that caspase-8 could not trigger pyroptosis through GSDM stimulation. However, a study conducted on mice infected with the pathogenic *Yersinia pestis* revealed that the activation of caspase-8 was induced by the YopJ protein, which inhibited the activity of transforming growth factor-β-activated kinase 1 (TAK1). Consequently, this led to caspase-8 activation and subsequent cleavage of GSDMD, resulting in cellular pyroptosis. Additionally, the fragmented GSDMD also played a role in IL-1β release through NLRP3 inflammasome-dependent mechanisms [54,55]. However, caspase-8 activation occurred only when caspase-1 or GSDMD were suppressed, leading to pore formation through pyroptosis that was independent of GSDMD [56]. It should be emphasized that TNF-α normally induces apoptosis in breast cancer cells. Under hypoxic conditions, p-Stat3 assists in the entry of (programmed death-ligand 1) PD-L1 into the nucleus, promoting an increase in GSDMC transcription. This results in the activation of caspase-8 by TNF-α, which specifically cleaves GSDMC and produces N-GSDMC. Consequently, pores are formed in the cell membrane, inducing cellular pyroptosis [57].

3.5. The granzyme pathway

Granzymes are exogenous serine proteases released by cytotoxic lymphocytes and natural killer cells. It has been demonstrated that granzyme B secreted by chimeric antigen receptor T cells is able to activate caspase-3, and the activated caspase-3 subsequently forms GSDME-N by cleaving GSDME and forming stomata in the plasma membrane leading to pyroptosis [58,59]. Moreover, lymphocyte-secreted granzyme A induces cleavage of GSDMB in cancer cells, resulting in the generation of GSDMB-N with pore-forming activity and subsequent initiation of pyroptosis [60].

4. Regulatory feedback loop of macrophage (MC), fibroblast-like synoviocytes (FLS) and chondrocyte (CC) pyroptosis-related crosstalk

CC, which are encapsulated in their own secreted extracellular matrix, are the only cells in articular cartilage that have the function of synthesizing and secreting matrix and fibers [61]. Due to the absence of blood vessels in cartilage tissue, CC primarily rely on substance exchange with synovial fluid for metabolism [62]. Whereas synovial fluid is mainly produced by synovial tissue, FLS and MC secrete and inflammatory mediators and cytokines also populate the synovial fluid [63]. Additionally, exosome-like vesicles have been identified in synovial fluid. These extracellular vesicles are thought to function in intercellular communication within joint tissues and can influence extracellular matrix turnover as well as inflammation [64,65]. Therefore, synovial fluid functions as a medium for the exchange of substances between these cells, facilitating the interaction of decaying cartilage debris, cytokines, and proteases released into the synovial fluid and various cellular components. This subsequent interaction triggers pyroptosis or an inflammatory response, leading to the development of pathological alterations in joint inflammation [9,66–70]. During the process of 'mechanical crosstalk', CC pyroptosis disrupts the balance between extracellular matrix (ECM) synthesis and catabolism, leading to cartilage breakdown. The shedding of cartilage fragments into synovial fluid induces secondary damage to the synovium [71–73]. On the other hand, pyroptosis occurring in FLS and MC can accelerate synovial fibrosis [13,70]. The fibrotic synovium, which impairs the maintenance of low friction features and nourishment of cartilage cells, will worsen cartilage damage [74–76] (Fig. 2).

4.1. Crosstalk between macrophages and fibroblast-like synoviocytes

Knee OA patients exhibit a high abundance of MC within the synovial tissue, which can migrate into the synovial fluid and become predominant leukocytes. These cells play a crucial role in maintaining intra-articular material homeostasis, modulating inflammatory responses, and participating in intercellular signaling pathways [5,77]. Some studies have shown a close relationship between MC pyroptosis and aseptic chronic inflammation, chronic inflammation, which can result in synovial fibrosis and exacerbation of OA symptoms [10,70]. Zhang et al. found that coculture of MC transfected with GSDMD siRNA with FLS downregulates fibrosis markers in the latter, suggesting that inhibiting macrophage pyroptosis could potentially reduce fibrosis in knee OA [70].

Assembly and activation of NLRP3 inflammasome vesicles is a key pathway for the onset of pyroptosis [78]. The researchers observed a significant elevation in NLRP3 protein levels within the synovium of patients with OA, exceeding those detected in individuals with healthy joints by more than 109-fold [79]. In OA synovial membrane cells, the activation of NLRP3 is triggered by various DAMPs, leading to subsequent release into the synovial fluid. Consequently, there is an elevation in IL-1β levels within the synovial fluid, subsequently stimulating FLS to produce a greater quantity of pro-inflammatory cytokines [80]. The research conducted by Xin and colleagues has revealed that the development of OA in the temporomandibular joint is significantly influenced by the formation of NLRP3 inflammasome. Specifically, it induces synovial inflammation and subsequent pyroptosis of synovial cells, thereby perpetuating an inflammatory response [11]. The study suggests

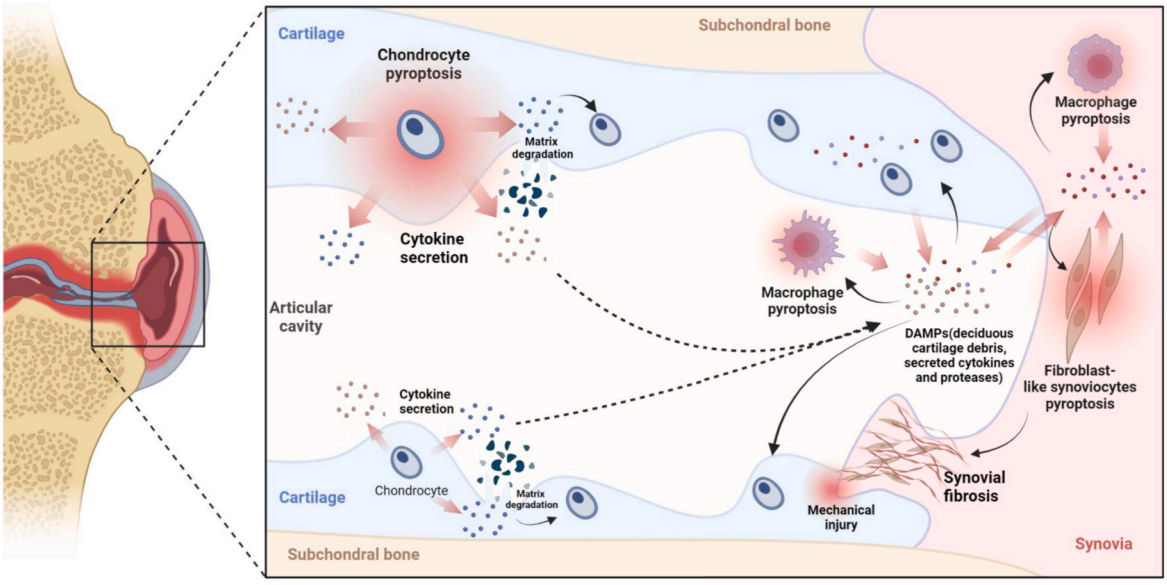

Figure 2. Various pathways are involved in interactions among macrophages, fibroblast-like synoviocytes and chondrocytes. Inflammatory mediators and cytokines, which are secreted by chondrocytes, fibroblast-like synoviocytes, and macrophages as a result of pyroptosis or other patterns of injury, flood the synovial fluid. Synovial fluid acts as a conduit for the transfer of substances between these cells, allowing the deciduous cartilage debris, secreted cytokines and proteases secreted in the synovial fluid, which act as DAMPs, to interact with cell membrane receptors and mediate the subsequent pyroptosis or inflammatory response, causing the pathological changes of joint inflammation. During the process of "mechanical crosstalk", chondrocytes pyroptosis disrupts the balance between extracellular matrix synthesis and catabolism, leading to cartilage breakdown. The shedding of cartilage fragments into synovial fluid induces secondary damage to the synovium. On the other hand, pyroptosis occurring in fibroblast-like synoviocytes and macrophages can accelerate synovial fibrosis. The fibrotic synovium, which impairs the maintenance of low friction features and nourishment of cartilage cells, will worsen cartilage damage.

that the cytokine expression of monocytes (THP-1) differentiated MC may activate FLS and amplify the inflammatory response during inflammation, leading to an inflammatory cascade and triggering subsequent destruction. Repression of pyroptosis and inflammation, which may result in tissue damage, can be achieved through the use of two highly specific inhibitors that target NLRP3 and caspase-1 in MC [11].

HMGB1 is a DAMP that is released upon cell membrane rupture during pyroptosis. Inflammatory stimuli trigger the active secretion of HMGB1 by certain cell types, including MC. Additionally, when cellular pyroptosis occurs, HMGB1 is released passively [81]. In vitro studies conducted by Wu et al. revealed that the induction of MC pyroptosis resulted in the release of HMGB1, which subsequently led to increased levels of fibrosis markers in FLS. Further analysis demonstrated that inhibiting HMGB1 effectively reduced synovial fibrosis [10]. Xiao et al. observed increased levels of HMGB1 and fibrosis markers in synovial tissues of rats with knee OA, which was attributed to elevated HMGB1 production resulting from FLS pyroptosis [82]. HMGB1 also acts on FLS, promoting the aggregation of pro-inflammatory factors and leading to synovitis [83].

Overall, MC pyroptosis exacerbates synovitis and promotes fibrosis of the synovial tissue, while cytokines secreted by FLS pyroptosis reciprocally induce MC pyroptosis. IL-1β and HMGB1, as cytokines associated with pyroptosis, play pivotal roles in the crosstalk between MC and FLS (Fig. 3).

4.2. Crosstalk between macrophages and chondrocytes

The pro-inflammatory factors generated during synovial MC or CC pyroptosis can directly contribute to synovial inflammation and cartilage matrix degradation, thereby promoting the progression of OA [70,80]. The recognition of DAMPs stimulates MC, triggering caspase-1 activation and subsequent pyroptosis, which promotes the assembly and generation of inflammasomes. This process results in elevated IL-1β/18 concentrations around the CC, both contributing to the promotion of CC pyroptosis and inflammatory responses [80,84]. The aforementioned cytokines also stimulate the release of catabolic enzymes in CC, leading to the degradation and breakdown of cartilage [85]. The pro-inflammatory production of CC pyroptosis therefore accelerates cartilage tissue degradation and free cartilage fragments can move into the joint cavity to mix with synovial fluid. These fragments can act as DAMPs and trigger synovial MC pyroptosis [86].

The microcrystals, such as basic calcium phosphate (BCP), possess the ability to induce inflammasome activation by functioning as DAMPs [87]. BCP has been shown to be present in the joints of patients with confirmed knee and hip OA [88]. The detection of these microcrystals and ATP released by necrotic cells triggers the activation of intracellular NLRP3 inflammasomes, leading to the production of pro-inflammatory cytokines, which ultimately results in cartilage degeneration [89,90].

The production of Lipoxin A4 (LXA4) occurs through cellular interactions in capillaries and subpatellar fat pads, making it a vital biomarker for inflammation [91]. The observation of LXA4 demonstrated an enhancement in M2 polarization within synovial MC, resulting in the suppression of nuclear factor-κ binding (NF-κB) translocation from CC. This results in reduced formation of NLRP3 and thus inhibits CC pyroptosis [92].

In the inflammatory microenvironment of the joints, MC undergo polarization towards an M1-like phenotype and secrete significant amounts of pro-inflammatory cytokines and mediators [93,94]. In particular, extracellular vesicles secreted by M1-type MC have been found to be capable of inducing CC to undergo a non-canonical pathway through the activation of the caspase-4/11-GSDMD pathway [9]. The promotion of CC pyroptosis and catabolism by M1-type MC extracellular vesicles can be counteracted by caspase-11 inhibitors [9].

In summary, the proinflammatory factors generated by MC pyroptosis exacerbate damage to cartilage tissue and induce an inflammatory response in CC. Additionally, CC pyroptosis further promotes catabolism of cartilage tissue, while the release of DAMPs mediates pyroptosis in synovial MC (Fig. 3).

4.3. Crosstalk between fibroblast-like synoviocytes and chondrocytes

The development of synovitis is accompanied by the production of

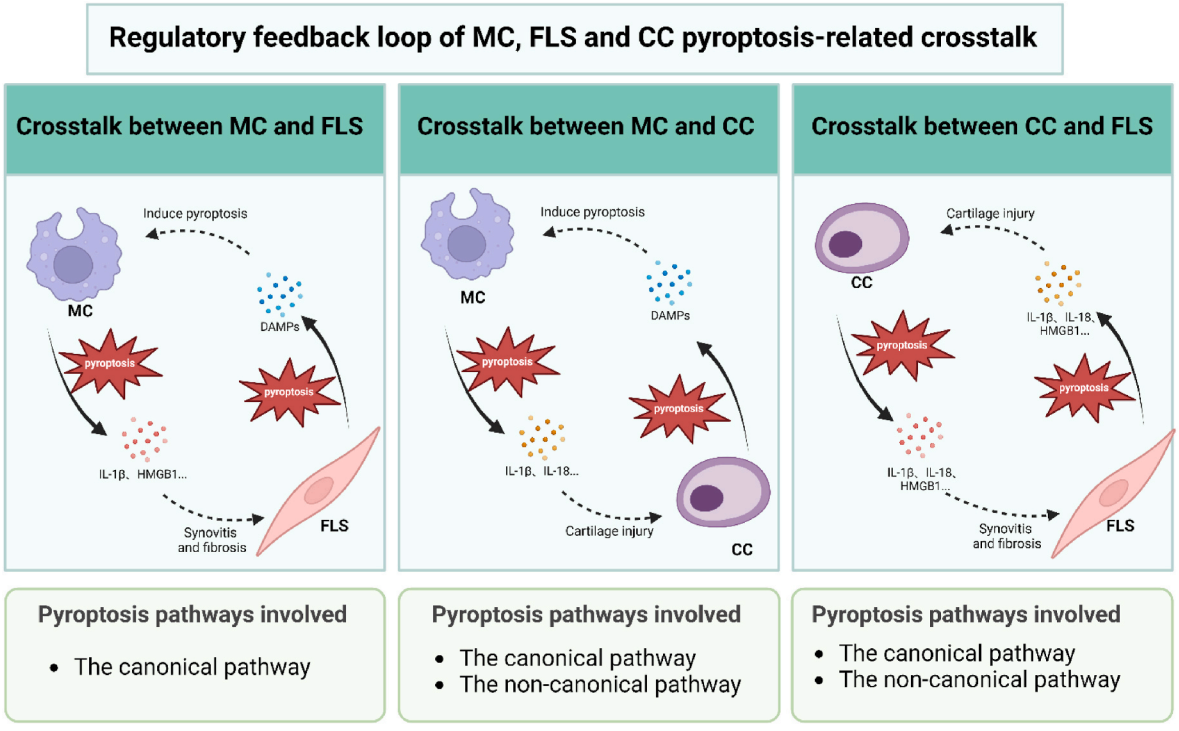

Figure 3. Interactive regulatory mechanisms between each pair of cell types. MC, macrophage; FLS, fibroblast-like synoviocyte; CC, chondrocyte; IL-1β, interleukin-1β; IL-18, interleukin-18; HMGB1, high mobility group box 1; DAMPs, damage associated molecular patterns.

large amounts of pro-inflammatory cytokines, which are subsequently released into the synovial cavity. These molecules can act as signaling molecules that affect all types of cells in the joint, and an excessive and persistent inflammatory response is a major contributor to the development of OA and cartilage degradation. FLS are critical components of the knee joint microenvironment, exerting their influence on CC through intricate interactions [95,96].

FLS undergoes pyroptosis secreting large amounts of HMGB1 [82]. Many studies have also confirmed that HMGB1 is overexpressed in synovial tissues of OA patients [97,98]. HMGB1 in the extracellular matrix induces an inflammatory response in CC [99].

NLRP3 has been found to play a role in the communication between FLS and CC through pyroptosis, as indicated by the elevated levels of NLRP3 protein expression observed in synovial tissue obtained from individuals with OA [12,100]. In addition, large amounts of NLRP3 activation were similarly observed in rat articular cartilage [101,102].

Increased NLRP1/NLRP3 inflammasome-mediated pyroptosis in LPS/ATP-induced FLS [82]. The use of NLRP1 and NLRP3 siRNA attenuated the occurrence of LPS/ATP-stimulated FLS pyroptosis in patients with knee OA, suggesting that NLRP1/3 may be a critical link in the process of FLS pyroptosis [103]. Upon activation of NLRP3 by LPS and ATP, FLS undergo a series of molecular events leading to IL-1β/18 secretion [97]. Activated IL-1β triggers apoptosis in CC cells and stimulates the secretion of a range of matrix-degrading enzymes, which contribute to cartilage degradation in the joint as one of the key factors in cartilage damage [104,105]. IL-18 also inhibits the synthesis of proteoglycan and the proliferation of CC [89]. HMGB1 and IL-1β/18 secreted by chondrocyte pyroptosis likewise diffuse into the synovial fluid secondary to the synovial inflammatory response [106,107].

Generally, FLS pyroptosis contributes to the establishment of an inflammatory microenvironment surrounding CC and facilitates chondrolysis. Inflammatory mediators generated as a result of CC pyroptosis may be secondary to synovitis. Synovial fluid serves as a conduit between FLS and CC, enabling pyroptosis-related crosstalk intercellular communication (Fig. 3).

5. Targeting the pyroptosis for the treatment of OA

5.1. Regulation of chondrocyte pyroptosis

The release of large amounts of pro-inflammatory cytokines by pyroptosis of CC may be one of the factors that influence the inflammatory microenvironment of cartilage. Various cytokines can degrade the structurally stable ECM of cartilage, thereby indirectly accelerating cartilage degeneration and contributing to joint inflammation. In addition, the pro-inflammatory factors generated by CC pyroptosis can impair FLS and MC, resulting in synovitis or synovial fibrosis and promoting the progression of OA. Therefore, exploring the potential of inhibiting CC pyroptosis could be considered a hopeful treatment strategy to impede extracellular matrix degradation and alleviate inflammatory responses. We summarized the relevant studies on the regulation of CC pyroptosis in OA (Table 1).

5.1.1. Inhibition of NLRP3

NLRP3 is the prototypical inflammasome and a pivotal molecule in the classical pathway of cellular pyroptosis [108]. Zhang et al. demonstrated that CY-o9, an NLRP3 inhibitor, confers protection to CC against inflammation and mitigates the progression of OA by impeding pyroptosis mediated by NLRP3 inflammasome [109]. The research conducted by Yan et al. demonstrated the effective inhibition of NLRP3 inflammasome activation by metformin, resulting in a significant reduction in cartilage degradation. Furthermore, metformin demonstrates the ability to reverse subchondral bone remodeling and suppress CC pyroptosis [110]. Tian et al. reported an intriguing discovery regarding the effects of Ginsenoside Compound K (GCK) on CC. During the investigation, it was observed that GCK had a significant inhibitory effect on the induction of NLRP3 inflammasome, pyroptosis, and enzymes responsible for tissue degradation in CC [111]. The findings of an additional research study have demonstrated the potential of Icariin in mitigating inflammation induced by LPS and ameliorating symptoms associated with OA, achieved through its suppression of the NLRP3/caspase-1 signaling cascade [112]. Reactive oxygen species (ROS) are widely recognized to be a universal signal that induces NLRP3 activation [34]. Peroxisome proliferator-activated receptor γ (PPAR-γ) has been found to ameliorate oxidative damage induced by ROS in cells [113]. Researchers revealed that the activation of PPAR-γ by pioglitazone had a safeguarding effect on the cartilage that was impaired due to pyroptosis in OA [114]. Within a preclinical models investigating OA following trauma, CF101 has been found to effectively inhibit inflammation by activating the A3 adenosine receptor, which is also linked to NLRP3-mediated pyroptosis [115]. Bai et al. have reported that the specific inhibitor VX765 effectively inhibits caspase-1, thereby exerting a protective effect on H2O2-stimulated CC. This protection was achieved by inhibiting ROS-induced activation of the NLRP3 inflammasome, suggesting that the NLRP3/caspase-1 axis is involved in the pathogenesis of OA [115]. Moreover, modulating IRF7 levels to inhibit NLRP3-mediated pyroptosis could potentially serve as an innovative therapeutic approach for managing OA [116]. Reversing the linear ubiquitination modification of liver kinase B1 (LKB1) to target the AMPK pathway can also inhibit NLRP3-mediated inflammatory response and cellular pyroptosis in CC affected by OA, thereby potentially serving as a therapeutic approach for treating OA [117]. Therefore, interventions aimed at suppressing these inflammatory mediators through targeting the NLRP3 pathway hold great potential for mitigating disease symptoms and improving patient outcomes.

5.1.2. Dietary or lifestyle

Dietary or lifestyle interventions play a crucial role in regulating OA. Li et al. observed that rat chondrocyte autophagic responses could be triggered by moderate intensity physical activity, inhibiting the onset of pyroptosis. his research further validated a potential correlation between LC3B and NLRP3 in CC, highlighting the significance of effective triggering of p2x7-induced cellular autophagy in inhibiting pyroptosis through the degradation of NLRP3 [118]. The recently discovered myokine meteorin-like (metrnl), also referred to as suberin or cometin, is a crucial factor involved in adipose metabolism. It exhibits an upregulation in expression within skeletal muscle following exercise and subsequently undergoes release into the bloodstream [119]. It has been reported that metrnl is involved in the development of arthritis and may be a potential target for the treatment of OA [120]. Liu and colleagues made an intriguing discovery that metrnl effectively suppressed inflammation in the CC induced by IL-1β. Additionally, metrnl also attenuated pyroptosis in the CC by inhibiting NLRP3/caspase-1/GSDMD [121]. In addition, the administration of monounsaturated fats (MUFA) and omega-3 polyunsaturated fats (ω-3 PUFA) has been discovered to effectively inhibit the activation of toll-like receptor 4 (TLR4)/NF-κB and NLRP3/caspase-1/GSDMD signaling pathways. This indicates that MUFA/ω-3 PUFA inhibits the production of inflammatory vesicles associated with TLR4 and NLRP3, thereby demonstrating potent anti-inflammatory and pyroptosis-inhibiting properties. However, it should be emphasized that MUFA's impact is relatively less potent compared to ω-3 PUFA [122].

5.1.3. MicroRNAs regulate pyroptosis

MicroRNAs (miRNAs) have a significant impact on the regulation of gene translation and metabolic activity in OA [123]. Given their pivotal role in modulating gene expression and elucidating the pathophysiology of OA, these molecules possess the potential to serve as reliable indicators of disease progression and promising targets for the development of therapeutic interventions [124]. Rozi et al. demonstrated that miR-124-3p could inhibit OA chondrocyte pyroptosis and prevent cartilage damage [125]. Li et al. observed that the deficiency of miR-155

in mouse knee CC inhibited the onset of pyroptosis in a mouse model of OA [126]. Qian et al. discovered a decrease in miR-107 levels within CC affected by OA. Furthermore, they observed that increased expression of miR-107 promoted the proliferation of CC treated with LPS-ATP, while simultaneously suppressing the expression of Caspase-1, GSDMD, and IL-1β/18 in these cells. Therefore, it is believed that miR-107 has a protective effect against KOA [127]. Similarly, miR-140-5p was found to be downregulated in expression in a rat model of knee OA. Increased levels of miR-140-5p ameliorated the inflammatory response resulting from chondrocyte pyroptosis, mainly achieved through the inhibition of NLRP3 inflammasome activation by miR-140-5p, which further reduced the secretion of IL-1β/18 [128].

5.1.4. Cellular therapy

Cellular therapy, an emerging treatment for repairing and replacing damaged tissues or organs by utilizing the body's own cells, has shown encouragingly positive results in clinical trials [129,130]. Xu et al. found that the soluble TNF-α receptor 1 (TNFR1) secreted by human adipose-derived mesenchymal stem cells (hAD-MSCs) exhibits highly specific TNF-α neutralizing activity, which can form a complex with TNF-α outside the cell that inhibits the interaction between TNFR1 receptor and TNF-α in CC. Consequently, this process indirectly inhibits the pyroptosis signaling pathway mediated by TNFR1, resulting in effects comparable to those of TNFR1 knockdown. Moreover, it was verified by in vivo test that hAD-MSCs could also inhibit cartilage matrix degradation and reduce cartilage damage [131].

5.1.5. Other ways of inhibiting CC pyroptosis

A recent investigation carried out by Li et al. revealed the potential of Monotropein in effectively alleviating CC inflammation and pyroptosis induced by IL-1β in OA, achieved through its specific intervention on the NF-κB signaling pathway [132]. In addition, Jiang and colleagues provided evidence of the significant therapeutic potential of PD0325901, an extracellular regulated protein kinases (ERK) inhibitor, in treating OA. By suppressing IL-1β-induced CC pyroptosis, PD0325901 effectively protects the CC and exhibits a protective effect against the induction of knee OA in vivo through destabilization of the medial meniscus (DMM) [133]. Zheng et al. discovered that PD184352 effectively inhibited the production of nitric oxide and inducible prostaglandin E2 in ATDC5 cells when exposed to il-1β. Furthermore, it was observed to mitigate pyroptosis by activating the nuclear factor NF-E2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) signaling pathway [134]. Furthermore, inhibition of P2X7 has been observed to attenuate the occurrence of OA. This phenomenon may arise from inhibiting the inflammatory response induced by chondrocyte pyroptosis and reducing the breakdown of extracellular mechanisms in CC [135] (see Table 1).

5.2. Regulation of fibroblast-like synoviocytes pyroptosis

The onset of FLS pyroptosis exacerbates synovial fibrosis, leading to further deterioration of knee OA [13]. The regulation of NLRP3 inflammasome, a crucial mediator in FLS pyroptosis, has been extensively investigated in the context of OA research [68]. Zhu et al. discovered that Ghrelin has the ability to significantly enhance cell migration and reduce the expression levels of cellular proteins associated with cellular pyroptosis. They hypothesized that Ghrelin may inhibit pyroptosis of FLS by suppressing the expression of NF-κB p65/NLRP3 [136]. Furthermore, there is experimental evidence that inhibition of FBXO3 down-regulation significantly affects the release and synthesis of IL-18 and IL-1β during the onset of cellular pyroptosis through a complex set of mechanisms [137]. The down-regulation of miR-219a-5p was observed in FLS affected by OA. Further investigations revealed that miR-219a-5p has the potential to impede the progression of knee OA both in laboratory settings and living organisms by suppressing the expression of F-box protein 3 (FBXO3), thereby inhibiting pyroptosis [138]. Zhang and colleagues provide evidence that upregulation of HIF-1α in FLS and induction of pyroptosis may cause synovial fibrosis, while inhibition of HIF-1α or GSDMD may improve the marker of FLS fibrosis [13]. We summarized the relevant studies on the regulation of FLS pyroptosis in OA (Table 2).

5.3. Regulation of macrophages pyroptosis

Lipoxin A4 (LXA4) is an eicosanoid that is rapidly synthesized and metabolized during exercise therapy, produced by capillaries and subpatellar fat pads through cell–cell interactions [92,139]. Shen and colleagues made an interesting finding that moderate physical activity induces the production of LXA4, which regulates MC polarization from M1 to M2 in the synovial membrane, ultimately preventing the onset of CC pyroptosis [140]. Zhang et al. transfected MC with siRNA GSDMD and observed a significant reduction in synovial fibrosis markers when co-cultured with FLS [70]. We summarized the relevant studies on the regulation of MC pyroptosis in OA (Table 3).

6. Conclusion and perspective

MC, FLS and CC play a crucial role in ensuring the balance of the homeostatic microenvironment within the joint and in the pathogenesis to OA. The pro-inflammatory factors generated during pyroptosis in these three cell types can directly contribute to synovial inflammation and cartilage matrix degradation, thereby promoting the progression of OA. Therefore, therapeutic strategies targeting the initiation of pyroptosis may be a hopeful method to impede the progression in OA.

Numerous studies have documented in vivo or in vitro experiments involving diverse compounds that disrupt pyroptosis; however, no clinical trials have been conducted on humans. Future research should focus on how intra-articular multicellular pyroptosis interactions contribute to the development of OA and its symptoms, as well as on the development of new drugs that can modulate pyroptosis occurrence and conduct rigorous clinical trials for OA treatment. Safety is one of the key challenges in modulating pyroptosis-related modalities in clinical trials. Based on the current research, a viable and safe approach may involve moderate exercise or consumption of omega-3 PUFA-rich foods. For other biologics, it is essential to thoroughly evaluate the safety and potential risks of the treatment before entering the clinical trial stage to ensure that the patients' health and safety are not compromised.

Due to the potential for multi-cellular interactions within the joint, treatment of OA should not solely focus on targeting one specific site or cell. Instead, integrated treatment strategies and a focus on intercellular synergy are necessary. Furthermore, investigating the crosstalk between MC-FLS-CC and pyroptosis will advance our comprehension of OA pathophysiology and refine current treatment strategies. Notably, while most studies have reported that the onset of pyroptosis promotes the development of OA, a few studies remain skeptical about the beneficial effects of inhibiting pyroptosis in OA mainly due to the fact that many details in the specific role and molecular mechanisms of the pyroptosis in OA are still unknown [12,141]. In addition, the interplay between MC, FLS, and CC in relation to pyroptosis may collectively or individually contribute to the progression and growth of OA at different stages, whether in its early, progressing, or concluding phases. It is not known for certain which subtype of OA is predominantly influenced by pyroptosis-related crosstalk between MC, FLS, and CC, and there are no conclusions regarding the specific of cellular pyroptosis that controls OA at each stage. At this point, it is imperative to acquire a holistic comprehension of the distinct pathways involved in the intercommunication of cells during different stages and types of OA, with a view to expediting the formulation of more precise interventions for arresting or reversing OA pathology.

In addition to MC, FLS, and CC, subchondral bone cells also play an irreplaceable role in the progression of OA, making it an effective approach to improve OA by modulating the subchondral bone microenvironment [142,143]. In the future, more focus should be placed on

Table 1
Summary of the regulation of chondrocyte pyroptosis in osteoarthritis.

Name	Description	Source	Experimental model	Involved mechanism	Reference
Monotropein	The main active ingredient of Morinda officinalis F.C	*Morinda officinalis* F.C.	DMM-induced mice in vivo and IL-1β-induced mice chondrocytes in vitro	Inhibition of the NF-κB signaling pathway, inhibited pyroptosis	[132]
PD0325901	A specific inhibitor of ERK	Shanghai, China	IL-1β-induced ATDC5 in vitro and DMM-induced mice in vivo	Inhibited the MAPK and NF-κB pathway, inhibited pyroptosis	[133]
PD184352	A selective MEK inhibitor	HY-50295, NJ, USA	DMM-induced mice in vivo and IL-1β-induced ATDC5 in vitro	Activation of Nrf2/HO-1 signaling pathway, inhibited pyroptosis	[134]
CY-09	A selective direct small-molecule inhibitor of NLRP3	Selleck, Shanghai, China.	DMM-induced mice in vivo and TNF-α-induced mice chondrocytes in vitro	Prevented the activation of NLRP3, inhibited pyroptosis	[109]
Metformin	The first-line medication for diabetes treatment	Sino-American Shanghai Squibb Pharmaceuticals Ltd.	DMM-induced mice in vivo	Inhibited the activation of NLRP3 inflammasome, inhibited pyroptosis	[110]
Ginsenoside compound K	A metabolite of ginseng	The root of *Panax ginseng* C. A. Meyer	MIA-induced rat OA model in vivo and IL-1β-induced rat chondrocytes in vitro	Inhibiting the ERS-IRE1α-TXNIP-NLRP3 axis, inhibited pyroptosis	[111]
Icariin	An extract from Epimedium	Epimedium	MIA-induced rat OA model in vivo and LPS-induced rat chondrocytes in vitro	Inhibiting NLRP3-mediated pyroptosis	[112]
CF101	The specific adenosine A3 receptor agonist	MedChemExpress	ACLT-induced rat OA model in vivo and H2O2-induced rat chondrocytes in vitro	Inhibiting ROS initiated NLRP3 inflammasome activation, inhibited pyroptosis	[115]
Moderate-intensity exercise	—	—	MIA-induced rat OA model in vivo	promoted autophagy through the P2X7/AMPK/mTOR signaling axis, inhibited pyroptosis	[118]
Rapamycin	A mTOR inhibitor	Sigma; cat. no. V900930	BzATP-induced rat chondrocytes in vitro	Inhibiting mTOR promoted autophagy, inhibited pyroptosis	[118]
A-769662	the AMPK activator	Sigma; cat. no. SML2578	BzATP-induced rat chondrocytes in vitro	Activation of AMPK promoted autophagy, inhibited pyroptosis	[118]
A740003	An P2X7R antagonist	Sigma–Aldrich	MIA-induced OA model in vivo and MIA induced rat chondrocytes in vitro	Inhibiting P2X7, inhibited pyroptosis	[135]
AICAR	An AMPK activator	A9978-5 MG, Sigma, USA	ACLT-induced rat OA model in vivo and LPS-induced human chondrocytes in vitro	Activation of LKB1/AMPK signaling pathway, inhibited pyroptosis	[117]
Ad-sh-IRF7	IRF7 knockdown adenovirus	Gene pharma	MMTL-induced mice OA model in vivo and LPS- induced C28/I2 chondrocytes in vitro	Upregulation of FGF21, inhibited pyroptosis	[116]
Pioglitazone	A therapeutic agent for treating type 2 diabetes	PHR1632, Sigma	ACLT + MCLT + DMM-induced rat OA model in vivo and LPS/ATP-induced rat chondrocytes in vitro	Activating Nrf2 and PGC-1α, inhibited pyroptosis	[114]
metrnl	Adipomyokine produced by adipose tissue and skeletal muscle during exercise	CSB-EP719323RA, CUSABIO, Wuhan, China	MIA-induced rat OA model in vivo and IL-1β-induced rat chondrocytes in vitro	Inhibiting PI3K/Akt/NF-κB and NLRP3/caspase-1/GSDMD signaling, inhibited pyroptosis	[121]
hAD-MSCs	Human adipose-derived mesenchymal stem cells	Bopin biopharma Co., Ltd	ACLT + MCLT + DMM-induced rat OA model in vivo and TNF-α-induced rat chondrocytes in vitro	Inhibit pyroptosis signaling pathway by secreting sTNFR1 binding to TNF-α, inhibited pyroptosis	[131]
AgomiR-124-3p	miR-124-3p agonists	GenePharma Co, Ltd	DMM-induced mice OA model in vivo and LPS-induced mice chondrocytes in vitro	Reduced MALAT1 stability and inhibited the binding of MALAT1 and KLF5 to downregulate CXCL11, inhibited pyroptosis	[125]
miR-155 inhibitor	Inhibition of miR-155	Biomics Biotech, Nantong, Jiangsu, China	DMM-induced mice OA model in vivo and LPS-induced mice chondrocytes in vitro	Inhibited the NLRP3/Caspase-1 pathway by targeting SMAD2, inhibited pyroptosis	[126]
miR-107 mimic	—	Nvitrogen, Shanghai, China	LPS/ATP-induced rat chondrocytes in vitro	Downregulating caspase-1 expression, inhibited pyroptosis	[127]
AgomiR-140-5p	miR-140-5p agonists	GenScript, Nanjing, Jiangsu, China	MMTL-induced mice OA model in vivo and LPS-induced mice chondrocytes in vitro	suppressed the binding of CTSB and NLRP3 protein by targeting CTSB, inhibited pyroptosis	[128]
n-3 PUFA and MUFA	Dietary fatty acid	—	DMM-induced mice OA model in vivo and LPS-induced mice chondrocytes in vitro and	reduced NLRP3, GSDMD, and caspase-1 expression via TLR4, inhibited pyroptosis	[122]

Abbreviations: DMM, destabilization of the medial meniscusin; IL-1β, interleukin-1β; NF-κB, nuclear factor-κ-gene binding; ERK, extracellular regulated protein kinases; MAPK, mitogen-activated protein kinases; MEK, mitogen-activated extracellular signal-regulated kinase; DMM, destabilization of the medial meniscus; Nrf2, nuclear factor erythroid-2-related factor; HO-1, heme oxygenase-1; NLRP3, NOD-like receptor protein 3; TNF-α, tumor necrosis factor-α; MIA, monoiodoacetate; ERS, endoplasmic reticulum stress; IRE1α, inositol-requiring enzyme 1 α; TXNIP, thioredoxin interacting protein; LPS, lipopolysaccharide; ACLT, anterior cruciate ligament transection; ROS, reactive oxygen species; AMPK, adenosine 5'-monophosphate-activated protein kinase; mTOR, mammalian target of rapamycin; BzATP, 2'(3)-O-(4-Benzoylbenzoyl) adenosine-5'-triphosphate; P2X7R, P2X7 receptor; LKB1, linear ubiquitination modification of liver kinase B1; IRF7, interferon regulatory factor 7; MMTL, medial meniscotibial ligament; FGF21, fibroblast growth factor 21; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator-1α; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; GSDMD: gasdermin D; sTNFR1, soluble TNF-α receptor 1; MALAT1, metastasis associated in lung denocarcinoma transcript 1; KLF5, kruppel-like factor 5; CXCL11, chemokine ligand 11; CTSB, Cathepsin B; Metrnl, the myokine meteorin-like; MCLT, medial collateral ligaments transection; hAD-MSCs, human adipose-derived mesenchymal stem cells; MUFAs, monounsaturated fatty acids; PUFAs, polyunsaturated fatty acids; TLR4, toll-like receptor 4.

Table 2
Summary of the regulation of FLS pyroptosis in osteoarthritis.

Name	Description	Source	Experimental model	Involved mechanism	Reference
Ghrelin	The only endogenous ligand of the growth hormone secretagogue receptor	prospec, Hamada, USA	ACL partial injury-induced rat in vivo and TNF-α-induced human FLS in vitro	Suppressing NF-κB p65/NLRP3 signaling pathway, inhibited pyroptosis	[136]
AgomiR-219a-5p	miR-219a-5p agonists	GeneChem, Shanghai, China	MIA-induced rat model in vivo and LPS/ATP-induced rat FLS in vitro	Inactivating the NLRP3 signaling via targeting FBXO3, inhibited pyroptosis	[138]
HIF-1α siRNA	—	Invitrogen, CA, USA)	LPS/ATP-induced rat FLS in vitro	Reduce both gene and protein levels of caspase-1, ASC, NLRP3, GSDMD, IL-1β, and IL-18, inhibited pyroptosis	[13]
GSDMD siRNA	—	Invitrogen, CA, USA)	LPS/ATP-induced rat FLS in vitro	Reduce both gene and protein levels of TGF-β, COL1A1, PLOD2, and TIMP1, inhibited pyroptosis	[13]

Abbreviations: FLS, fibroblast-like synoviocytes; TNF-α, tumor necrosis factor-α; ACL, anterior cruciate ligament; NF-κB, nuclear factor-κ-gene binding; NLRP3, NOD-like receptor protein 3; MIA, monoiodoacetate; LPS, lipopolysaccharide; ATP, adenosine triphosphate; FBX03, F-box protein 3; GSDMD: gasdermin D; IL-1β, interleukin-1β; IL-18, interleukin-18; TGF-β, Transforming growth factor-β; COL1A1, Collagen type I α1 chain; PLOD2, procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2; TIMP1, tissue inhibitor of metalloproteinase 1.

Table 3
Summary of the regulation of macrophages pyroptosis in osteoarthritis.

Name	Description	Source	Experimental model	Involved mechanism	Reference
LXA4	An eicosanoid acid produced in the capillaries and infrapatellar fat pad during cell–cell interactions	—	Synovial macrophages were co-cultured with chondrocytes	Inhibit chondrocyte pyroptosis via synovial macrophage M2 subtype polarization	[140]
CTS	Similar conditions to that experienced in the joint	Flexcell International, McKeesport, PA, USA	Synovial macrophages were co-cultured with chondrocytes	Inhibit chondrocyte pyroptosis via synovial macrophage M2 subtype polarization	[140]
Moderate-intensity treadmill exercise	—	—	MIA-induced rat OA model in vivo	Promoted M2 subtype polarization of synovial macrophages	[140]
Ac-YVAD-CMK	Specific caspase1 inhibitor	Sigma–Aldrich, St. Louis, MO, USA	ACLT-induced rat OA model in vivo	Both mRNA and protein expressions of IL-1β, IL-18, and HMGB1 were decreased in synovium	[70]
siRNA GSDMD	GSDMD inhibitor	Invitrogen, CA, USA	LPS/ATP-induced macrophages were co-cultured with FLS	Both mRNA and protein expressions of TGF-β, PLOD2, COL1A1, and TIMP1 in FLS were significantly decreased, inhibit macrophages pyroptosis	[70]

Abbreviations: FLS, fibroblast-like synoviocytes; LXA4, lipoxin A4; CTS, cyclic tensile strain; TGF-β, Transforming growth factor-β; PLOD2, procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2; COL1A1, collagen type I α1 chain; TIMP1, tissue inhibitor of metalloproteinase 1. HIF-1α: hypoxia-inducible factors-1α; ATP: adenosine triphosphate; LPS: lipopolysaccharide; GSDMD: gasdermin D; HMGB1, high mobility group box 1.

the effect of pyroptosis occurring in subchondral bone cells on OA, in order to provide a more comprehensive understanding of the role that pyroptosis plays in OA. Furthermore, biomaterials with bone-targeted properties, serving as a novel therapeutic tool with a wide range of applications such as bone/cartilage targeted hydrogel, osteochondral scaffolds, and mesenchymal stem cell-derived extracellular vesicles, can be customized to cater to individual patient differences and specific needs in order to protect from healthy tissues [144–146]. Combining pyroptosis-targeted drugs with these novel biomaterials not only enables more precise therapeutic effects but also allows the biomaterials to play a more significant role in therapy.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This work was supported by the National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University (2021KFJJ06) and Hunan Provincial NaturalFoundation of China (2021JJ30040).

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