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Role of Pyroptosis in Osteoarthritis and Its Therapeutic Significance

Xiaosheng Chen, Zhenyu Yang, Qingqi Meng, Siming Li*

Department of Orthopedics, Guangzhou Red Cross Hospital, Jinan University, Guangzhou, China

Email address:

859202828@qq.com (Xiaosheng Chen), drsmli@163.com (Siming Li)

*Corresponding author

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Abstract: Osteoarthritis is a chronic inflammatory joint disease characterized by cartilage degradation, synovial inflammation, and subchondral bone remodeling, and its development may be influenced by multiple factors such as genetics, environment, metabolism, and mechanical stress, with a complex pathogenesis. Clinically, osteoarthritis seriously affects the life of patients with clinical manifestations such as pain, swelling, and joint movement disorders. With the aggravation of the aging population in China, patients with osteoarthritis are on the rise. Therefore, the study of OA pathological mechanism has drawn much more concerns. Pyroptosis is a proinflammatory programmed cell necrosis mediated by inflammasomes that depends on Gasdermin family proteins and it is closely related to the development and progression of a variety of diseases. Statistics showed that pyroptosis plays an important role in the development and progression of osteoarthritis. By reviewing the latest research on the molecular mechanism of pyroptosis and its effect in treating osteoarthritis, the important role of pyroptosis activation pathway in the process of osteoarthritis is revealed, focusing on the related signaling molecules, signaling pathways, targets of pyroptosis, and targeted drugs that inhibit pyroptosis. It provides new ideas for the mechanism study of osteoarthritis and also new targets for the treatment of osteoarthritis.

Keywords: Pyroptosis, Osteoarthritis, Caspase-1, NLRP3, Gasdermin-D, IL-1β

1. Introduction

Osteoarthritis (OA) is the most common joint disease in the elderly population. According to studies, about 1/3 of people at the age of over 65 suffer from OA [1], of which knee OA is the most common. The prevalence of knee OA in the elderly population aged 55 worldwide is as high as 44% to 70% [2]. The prevalence of KOA in China ranges from 20.0% to 23.9% [3]. According to epidemiological survey [4], with the aggravation of the aging population in China, patients with osteoarthritis are on the rise, and with age, the condition gradually aggravates, ultimately leading to joint deformity, seriously affecting the life quality of patients.

As a chronic inflammatory joint disease, OA is typically characterized by cartilage degradation, synovial inflammation, and subchondral bone remodeling. Chondrocytes are a cell type in cartilage tissue, and aging or death of chondrocytes leads to imbalance of cartilage metabolism, which results in cartilage matrix degradation [5]. Synovial tissue contains synoviocytes, which can further separate synovial macrophages and synovial fibroblasts [6]. Pathological alterations in these cells is one of the main triggers of OA. At the same time, synovial fibrosis can deposit excessive extracellular matrix, usually leading to joint pain and stiffness in OA patients [7].

Cell death is one of the basic physiological processes used by multicellular organisms to maintain homeostasis. According to information published by the Cell Death Nomenclature Committee in 2018, we divide cell death into ACD and RCD. The former refers to passive cell death caused by various physicochemical factors and mechanical stimuli, and the latter refers to cell death that depends on specialized molecular mechanisms and can be intervened by drugs or genetics, in which cell regulatory death occurring under physiological conditions is also called programmed cell death. Programmed cell death includes three major types: apoptosis, autophagy, and programmed necrosis[8].

Programmed cell necrosis includes, mitochondrial phosphate transporter-driven necrosis, necroptosis, iron death and pyroptosis. Pyroptosis, as a proinflammatory programmed cell death mode, is most significantly characterized by its destruction of cell membrane structural integrity and release of intracellular substances into the extracellular space, which in turn triggers inflammation [9]. This feature is different from apoptosis that maintains cell membrane structural integrity and forms apoptotic bodies [10]. Studies have shown that pyroptosis may be closely related to OA progression by linking pyroptosis with risk factors for OA development, OA cartilage degeneration and chronic synovial inflammation [11]. In this paper, Study review the research progress related to pyroptosis in OA synovium and chondrocytes, summarize the role of key signaling targets in the process of pyroptosis related to OA, and deeply study the mechanism of pyroptosis and its relationship with OA, which is helpful to elucidate the pathological mechanism of OA and provide new drug targets and new ideas for the treatment of OA.

2. Pyroptosis

2.1. Concept and Morphological Characteristics of Pyroptosis

Pyroptosis was first discovered in 1992, and researchers found a lytic death in macrophages infected with S. flexneri, with morphological features distinct from apoptosis [12]. In 2001, scientists proposed the term pyroptosis to describe programmed necrosis of proinflammatory cells [13]. Until 2015, researchers discovered a protein called gasdermin D (GSDMD), which plays an important role in pyroptosis by releasing its N-terminal domain after cleavage by caspase-1 and caspase-4/5/11 through GSDMD, which has attachment to the cell membrane and forms pores on the cell membrane. This leads to changes in cell osmotic pressure and swells until the cell membrane ruptures, thus in turn promoting the development of pyroptosis [14].

2.2. Mechanisms of Pyroptosis

According to the mechanism of pyroptosis, it can be divided into caspase-1-dependent and caspase-1-independent modes, also known as classical pathway and non-classical pathway; the latter mode of cell death is induced by caspase-4 and caspase-5 in humans or caspase-11 in mice [15]. Pyroptosis is triggered by stimulation of pathogen-associated molecular patterns, damage-associated molecular patterns, or homeostasis-altering molecular processes [16], and like most inflammation, inflammasomes are important components of pyroptosis. Inflammasomes are intracellular pattern recognition receptors (PRRs) that play an important regulatory role in immune and inflammatory responses [17]. Toll-like receptors activate NLRP3 bodies when they recognize pathogen-associated molecular patterns (PAMPs) and endogenous damage-associated molecular patterns (DAMPs). Notably, when inflammatory mediators such as PAMP and IL-1β as well as tumor necrosis factor-α (TNF-α) bind to their corresponding receptors, they induce nuclear transcription factor-κB (NF-κB) activation, thereby promoting the transcription of their downstream genes to produce NLRP and caspase family members as pro-IL-1β and pro-IL-18 [18]. Among them, pro-caspase-1 is released and activated to form caspase-1 after cleavage by NLRP inflammasomes, and activated caspase-1 promotes the formation of proinflammatory cytokines IL-1β and IL-18 from pro-IL-1β and IL-18 through proteolysis [19]. Meanwhile, caspase-1 is able to cleave GSDMD, release the N-terminal domain and transport to the plasma membrane to oligomerize to form a pore with a diameter of 10 ~ 15 nm, thereby releasing pro-inflammatory cytokines such as IL-1β and IL-18 into the extracellular environment and inducing pyroptosis [20]. Eventually, it causes cell swelling and lysis. Although DNA fragmentation is present during pyroptosis, its nucleus remains, which is different from apoptosis [21]. In addition, unlike the classical pyroptosis pathway, pyroptosis initiates an activation program by directly sensing the expression of lipopolysaccharide (LPS) in the cytoplasm through caspase-4/5 in humans or caspase-11 in mice, forming pores on the cell membrane by GSDMD cleavage and promoting pyroptosis [22].

2.3. Pyroptosis Plays a Role in Other Diseases

In recent years, it has been continuously found that pyroptosis is closely related to different diseases in different systems, and studies have found that pyroptosis is the main mechanism of bacterial clearance [23]; CD4 + T cells uninfected with HIV can undergo pyroptosis, which in turn aggravates the condition [24]. Pyroptosis has also been shown to play an important role in endocrine system diseases, causing NLRP3 activation by stimulating sensitized bone marrow-derived dendritic cells and macrophages, which in turn activates caspase-1, thereby causing pyroptosis and promoting the progression of type 2 diabetes [25]. At the same time, the expression of NLRP3 inflammasome is increased in adipose tissue and liver, which is directly related to the severity of type 2 diabetes, and reduction of inflammasome expression in adipose tissue improves insulin resistance [26]. Inflammasomes play a key role in the pathogenesis of gout, and inhibition of IL-1B expression significantly reduces the degree of gout [27]. Scientists in the nervous system have found that neurologic-related diseases such as cerebral ischemia-reperfusion injury, Alzheimer's disease, parkinsonism, and amyotrophic lateral sclerosis are associated with pyroptosis [28]. In the cardiovascular system, increased expression of NLRP3, ASC, caspase-1, IL-1 B, and IL-18 has been found in cervical atherosclerotic plaques [29]. Pyroptosis of vascular smooth muscle cells affects the healing of vascular injury inducing acute cardiovascular disease [30]. Cardiovascular diseases, such as diabetic cardiomyopathy [31], cardiomegaly [32], and ischemic heart disease, may be associated with pyroptosis [33]. In addition, pyroptosis of monocytes or macrophages in the cardiovascular system may also be a cause of acute

cardiovascular events [34]. Available evidence suggests that inflammasome activation such as NLRP3 is also involved in the development of chronic intestinal inflammation [35] and colorectal cancer [36]. Pyroptosis can also trigger autoimmune diseases, such as systemic lupus erythematosus (SLE) [37]. Gram-negative bacterial infections leading to infectious diseases such as sepsis have also been associated with activation of caspase-4/5/11-induced coking [38]. Pyroptosis also plays a role in inflammatory joint diseases, such as rheumatoid arthritis (RA) [39]. Researchers have also found high expression of caspase-1, IL-1 B, and IL-18 in degenerated discs [40].

3. Relationship in Pyroptosis and OA

3.1. Mechanisms of Pyroptosis in Osteoarthritis

At present, OA, as a chronic inflammatory joint disease, the occurrence of inflammation is its essence. Cytokines related to the pathogenesis of OA, such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), can stimulate chondrocytes to release cartilage degrading enzymes, resulting in the digestion of proteoglycans and type II collagen (Col II), which allows cartilage matrix degradation and lead to inflammatory chondrocyte death. Scientists using caspase inhibitors and other methods to inhibit apoptosis can effectively control the progression of OA [41], which indicates that the occurrence of OA is closely related to apoptosis. Similarly, Study noticed that pyroptosis was also a programmed cell death mode dependent on caspase-1. Compared with normal cartilage tissues, the expression of caspase-l in OA cartilage is significantly increased [42], in addition, a large number of studies have shown that NLRP3-related synoviocyte or chondrocyte pyroptosis plays a central role in promoting the development of OA [43]. NLRP3-related synoviocytes play an important role in promoting the development of OA, inhibiting the expression of NLRP3 in synoviocytes and reducing the occurrence of pyroptosis [17]. This indicates that pyroptosis occurs in synoviocytes and is involved in the development of OA. Researchers have found that by inhibiting LPS-induced expression of pyropsis-related proteins such as caspase-1, IL-1β and IL-18 in chondrocytes is reduced, and thus inhibiting the occurrence of pyroptosis [44]. They inferred that chondrocyte pyroptosis occurs and is involved in the occurrence of OA, but it has also been shown that IL-1β and IL-18 inflammatory factors secreted by cartilage and synovium in OA mainly come from synoviocytes, rather than chondrocytes in cartilage [45]. Pyroptosis does exist in OA synoviocytes, while chondrocyte pyroptosis may require more and more rigorous experiments to further confirm [10].

3.2. Mechanisms of Pyroptosis in Osteoarthritis

At present, there have been a large number of studies on the effect of pyroptosis on OA, which centered on the inflammasome, targeting each component of the inflammasome and providing a new target for the treatment of OA. The active ingredient Loganin extracted from Hedgehog signaling pathway inhibitor GANT-61 and cyclooxygenase 2 (COX2) inhibitor Corni Fructus (CF) can significantly inhibit NF-κB signaling pathway [46]. In addition, Morroniside extracted from it can also inhibit NLRP3 expression and activation by inhibiting NF-κB signaling transduction pathway [47]. Indomethacin combination was able to synergistically inhibit pyroptosis in OA chondrocytes [44]. Icariin (ICA), extracted from Epimedium, was used to reduce chondrocyte pyroptosis and cellular inflammation by inhibiting NLRP3 expression [48]. Lico A (licochalcone A) phenolic compounds extracted from Glycyrrhiza uralensis could down-regulate LPS-induced inflammatory factors in chondrocytes of OA mice [49]. Objective To investigate the effect of Guizhi Fuzi Decoction (GZFZD) on inhibiting chondrocyte pyroptosis by regulating thioredoxin-interacting protein (TXNIP)/(NLRP3)/caspase-1 pathway [50]. This revealed that loganin inhibited NF-κB signaling and attenuated cartilage matrix catabolism and pyrophosphorylation of chondrocytes in articular cartilage. Lomanin can be used as a potential therapeutic agent for OA treatment [51]. P2X7 (P2X purinoceptor 7) is a purinergic receptor, and P2X7 mediates pyroptosis in OA chondrocytes through the NF-κB signaling pathway. Injecting monosodium iodoacetate (MIA) into the articular cavity and prompting chondrocytes to produce high concentrations of ATP activates P2X7, can result in OA chondrocyte pyroptosis [51]. Knockdown of Nrf2 by using siRNA increases ROS levels and upregulates NLRP3 expression in cells [52]. It has been shown that hypoxia-inducible factor 1-alpha (HIF-1α) silencing significantly decreased LPS + ATP-induced pyroptosis in synovial fibroblasts 53]. Moxibustion down-regulates p38 MAPK signaling pathway to inhibit NLRP3 inflammasome-mediated chondrocyte pyroptosis, effectively reduces the degradation of cartilage extracellular matrix, and exerts a chondroprotective effect 54]. Studies have shown that experimental OA activates NLRP3, and pharmacological inhibition of NLRP3 inflammasome activation by CY-09 (a selective and direct inhibitor of NLRP3) protects chondrocytes from inflammation and attenuates OA development [55]. Stromal cell-derived factor-1 (SDF-1) is a homeostatic CXC chemokine, and SDF-1 treatment of synoviocytes and collagenase-induced OA results in a significant down-regulation of NLRP3 inflammasome and synoviocyte pyroapoptosis biomarker expression. Inhibition of AMPK signaling significantly inhibited the inhibitory effect of SDF-1 on NLRP3 inflammasome expression in OA synoviocytes [56].

4. Conclusion

Our current understanding of the pathogenesis of OA is still incomplete, but it is clear that different tissue components in OA may undergo pyroptosis through experimental studies, and it is found and confirmed that damaged chondrocytes and synoviocytes show morphological changes consistent with pyroptosis, which

suggests that this programmed cell death mode dependent on caspase-1 is inseparable from the occurrence and development of OA, contributing significantly to the development of new therapeutic targets by inhibiting the mechanism of pyroptosis, and then inhibits or slows down the occurrence of OA.

In summary, by verifying the relationship between OA and pyroptosis, and listing the relevant new targets that may be used to treat OA, Study can directly target each component of the inflammasome, or target upstream modulators or downstream targets of the inflammasome and regulate chondrocyte or synoviocyte pyroptosis, thus exerting effect in the prevention and treatment of OA. In addition, OA is recognized as a chronic inflammatory disease involving articular cartilage and subchondral bone, as well as total joint lesions of the joint synovium. At present, no study has shown whether pyroptosis has an effect on the subchondral bone in the joint. Scientist also noticed that most of the current studies are validating the effect of pyroptosis on OA. However, in combination with the characteristics and pathological characteristics of OA, Study found that OA has different pathological characteristics in different periods, of which whether pyroptosis is positively correlated with the severity of osteoarthritis, or the expression of pyroptosis varies in different periods. For these parts, further experiments are still needed to verify, and it is also an important future research direction.

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