

The Progress in the Occurrence and Treatment of NLRP3 Inflammasome in Bone and Joint Diseases

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Abstract. Inflammasomes play a pivotal role in the innate immune system, which regulates the activation and expression of inflammatory factors, has a profound impact on the occurrence and expression of various inflammatory diseases. In recent years, studies have demonstrated that the NLRP3 inflammasome is closely associated with many fields, such as cardiovascular diseases, metabolic disorders, and chronic diseases. Moreover, inflammatory diseases of bone and joints, which are more prevalent in the population, such as osteoarthritis and rheumatoid arthritis, can cause substantial damage to bone and cartilage, trigger pain and even dysfunction, and reduce the quality of life. Numerous studies have shown that the pathogenesis of multiple bone diseases and arthritic diseases, including osteoarthritis and rheumatoid arthritis, is closely associated with the NLRP3 inflammasome. Some progress has been made in the targeted treatment of the NLRP3 inflammasome, especially for small-molecule inhibitors. These inhibitors have potential therapeutic value by inhibiting the activation of the NLRP3 inflammasome, thereby reducing the inflammatory response. However, the research on the feasibility, safety, and drug metabolism of these small-molecule inhibitors in clinical application is still in the exploratory stage, and further research is urgently needed. This paper aims to review the NLRP3 inflammasome structure, function and its progress in bone-related diseases and treatment. Through this paper, we hope to improve the understanding of the NLRP3 inflammasome in the development and treatment of bone diseases, so as to provide a theoretical basis for clinical practice.

Keywords: NLRP3 inflammasome; bone and joint diseases; treatment.

1. Introduction

Inflammasomes are multi protein complexes within cells that can respond to various stimuli, including invading pathogens, danger signals from host cells, and environmental stimuli. The first line of defense against internal or external pathogen invasion is PRRs-recognition receptors which initiate the innate immune response and maintain homeostasis in the body [1].

NLRP3, the full name nod-like receptor thermoprotein domain-associated protein3, is an inflammasome that plays an important role in numerous physiological and pathological processes. Inflammasomes are a class of intracellular sensors capable of detecting abnormal intracellular changes, such as cellular damage, pathogen infection, or genetic variation. The activating signaling pathways of NLRP3 are extensive, including various mechanisms such as pathogen recognition, DNA damage, mitochondrial dysfunction and so on. NLRP3 plays a vital role in inflammatory and autoimmune diseases. When aberrant signals are detected by the cells, NLRP3 is activated, which recruits and activates caspase-1, leading to the release of inflammatory cytokines, such as IL-1 β and IL-18. These inflammatory factors have a positive effect on resisting pathogen invasion and maintaining organismal homeostasis. However, hyperactivated NLRP3 causes an uncontrolled inflammatory response, which triggers a range of inflammatory diseases [2]. NLRP3 expresses in immune cells, which makes NLRP3 widely influential in immune system regulation. Researchers are trying to explore the mechanisms of activation and inhibition of NLRP3 in the hope of finding more effective ways to intervene in the onset and progression of inflammatory diseases. When activating NLRP3, its activation pathways and regulatory mechanisms must be fully understood to avoid the inflammatory response caused by overactivation.

In this review, the composition and the activation mechanism of the NLRP3 will be described. In addition, the essential role of the NLRP3 plays in inflammation-related diseases will be highlight in

this essay. At last, with further investigation in NLRP3, this therapeutic target is expected to show its vital status in treating various diseases by more and more experts.

2. The Activation of NLRP3 Inflammasomes

The NLRP 3 inflammasome is an important intracellular sensor. Its main structure includes a central nucleotide-binding domain (NACHT), the LRR (Leucine-Rich Repeat) domain at the C terminus, and the PYD (Pyruvate Dehydrogenase) domain at the N terminus. This unique structure enables the NLRP 3 inflammasome to identify pathogen-associated molecular patterns (PAMP) and risk-associated molecular patterns (DAMP) within the cell. Two key activation steps in the NLRP 3 inflammasome, are 'initiation' and 'activation'. The initiation signal is mainly achieved through the NF- κ B pathway in pathogen-associated molecular patterns (PAMP) or risk-associated molecular patterns (DAMP). In this process, the NLRP 3 inflammasome binds to the pattern recognition receptor (PRR) located in the cell membrane, including toll-like receptors (TLR), interleukin receptor (IL-1R), and tumor necrosis factor receptor (TNFR). Upon binding, NF- κ B can be separated from its inhibitor I κ B and further relocalized within the nucleus, thereby activating the encoding expression of the inflammasome, pro-IL-1 β , pro-IL-18, and tumor necrosis factor- α . Activation signals are achieved by the expression of multiple PAMP or DAMP, a process involving crosstalk or independent regulation of multiple signaling pathways. These signals include the disruption of potassium, chloride, calcium ions, and lysosomes, etc. The involvement of these activating signals allows the NLRP 3 inflammasome to exert more efficient roles in response to changes in the cellular internal and external environment. Overall, the NLRP 3 inflammasome acts as an intracellular sensor to maintain intracellular homeostasis by recognizing PAMP and DAMP molecules to initiate and activate the inflammatory response [2].

2.1. The Role of NLRP3 Inflammasome Activation in OA

Osteoarthritis (OA) is the most common joint disease in the world, with a population incidence of about 10%. The characteristic structural changes include synovial inflammation, articular cartilage loss, subchondral bone changes, meniscal injury, tendon and ligament degeneration. OA is the most important cause of joint pain, loss of function and disability in the elderly. The pathogenesis of OA has not been clarified clearly, but existing studies indicate that inflammation, pyroptosis and apoptosis play vital roles in the disease progression of OA [3].

Recent studies found that NLRP3 inflammasome is widely activated in OA so that make deep effects in OA. This particular tissue undergoes important changes in OA that promote the degenerative process throughout the joint through the production and release of inflammatory effectors. Moreover, the synovial tissue is also involved in the overproduction of ROS and the reduction of antioxidant enzymes, leading to oxidative stress. These changes not only affect the normal function of the joints but may also lead to pain and other symptoms. Therefore, an intensive study of this tissue will help researchers to understand the pathogenesis of osteoarthritis well and search for more effective treatments. It has been shown that the protein of synovium in OA patients, the content of NLRP3 and mediators associated with inflammation such as IL-1 are more than about 5 times than that in normal joints. A large amount of literature shows that inhibiting the expression of NLRP3 inflammasome could reduce the production of inflammatory mediators to inhibit the inflammatory response of OA effectively and relieve the pain symptoms of OA. For example, Agnuside (Agnuside, AGN, a natural herbal small molecule substance) can reduce synovitis of knee OA by inhibiting hypoxia-inducing factor and NLRP3 inflammasome [4].

Higher reactive oxygen species (ROS) and lower proliferation enzyme activity was reported in the serum of patients with knee osteoarthritis (KOA), suggesting that the activity of the enzyme and disease was caused because of the absence of collagen recycling. However, expression of proliferative enzymes in synovial tissue in KOA has not been investigated clearly and proliferative enzyme activity was significantly elevated in synovial tissue in hip OA patients. Meanwhile, in the report, the

investigators demonstrated an increased content of proliferative enzymes in the synovium of KOA patients which suggested that proliferative enzyme-mediated collagen degradation injury in joint may be involved in the overproduction of ROS in KOA disease. The current evidence clearly indicates that proinflammatory cytokines are key factors that cause the pathologica tissue to undergo catabolic processes. In KOA, the synovium is important in the production of pro-inflammatory effectors. Once these effectors spread into cartilage, which produces more pro-inflammatory cytokines by activating chondrocytes. These pro-inflammatory cytokines further initiate and exacerbate the inflammatory response, which lead to breakdown and destruction of joint tissue.

As a result, pro-inflammatory cytokines play a crucial role in the pathogenesis of KOA. There are many data using the important means of correlation analysis, which are designed to dig deeper association between the pro-oxidant enzymes and NLRP3 inflammasome in KOA patients. The results of the data analysis show a significant positive relationship between the inflammasome NLRP3 and ROX. This finding agrees with the data [5] reported in previous studies, strongly proving that ROS production plays a key role in NALP 3 activation, thus leading to an inflammatory state in osteoarthritic joints. This finding provides important clues to the understanding of OA and provides new ideas for future therapeutic strategies.

2.2. The Role of NLRP3 Inflammasome Activation on RA

Rheumatoid arthritis (RA) is an autoimmune disease, and the main lesion is joint synovitis. As the disease progresses, the cartilage and bone may be invaded, leading to irreversible joint deformity and dysfunction. The pathogenesis of RA mainly involves rheumatoid factor and anti-citrullinated peptide antibody [6]. Higher NLRP3 mRNA levels were found in the synovium of RA patients and NLRP 3 and ASC were expressed in myeloid, endothelial and B cells, but no elevated NLRP3 inflammasome were detected in fibroblast-like synoviocytes.

Studies [7] have shown that the expression of NLRP 3 is higher in the serum and synovium than in normal people, and the expression of NLRP 3 in the joint synovium is positively correlated with imaging and clinical symptoms. Through the application of the NLRP3-specific inhibitor MCC950, the expression of NLRP 3 in the synovial membrane can be significantly inhibited, thus alleviating the clinical symptoms of patients and reducing synovial inflammation and cartilage damage. In addition, related reports [8] have shown that, as a form of autoantibodies, ACPA plays an important role in the pathogenesis of rheumatoid arthritis. The mechanism may lie in ACPA enhancing the expression of CD147 and integrin β 1, thus promoting the expression of NLRP 3 and the activation of pro-IL-1 β , through the activation of the protein kinase / NF- κ B signaling pathway. Moreover, ACPA also activates ubiquitin channels, releasing extracellular ATP and promotes efflux of K⁺, which cause the activation of NLRP3 inflammasome. A20 gene-deficient mice will exhibit spontaneous erotic arthritis [2] associating with NLRP3 expression and increasing secretion of IL-1 β . A20-deficient bone marrow-derived macrophages present the inflammatory factor secretion and pyroptosis associated with NLRP3 hyperactivation, suggesting that A20 exerts an inhibitory effect on RA by attenuating NLRP3 activation. IL-18 is also an important inflammatory factor in RA, which is significantly higher in the serum, and suggests the positive correlation of IL-18 with RA acute phase-protein C-reactive protein (CRP). Some reports [9] found that IL-18 was an inducer of CD4⁺ T cells in the synovial tissue of RA patients and promoted the migration and activation of neutrophils and monocytes in the peripheral blood and synovial of RA patients. And IL-18 can directly bind and stimulate IL-18 receptors on lymphocytes, macrophages and fibroblast synoviocytes. The response is the key of the participation of IL-18 in the development of RA. Fibroblast-like synoviocytes in the presence of IL-18 can increase the expression of adhesion molecules, inflammatory factors, monocyte chemotaxis protein1, macrophage inflammatory protein 3 and vascular endothelial growth factor, which are important molecules involved in the progression of RA. In addition, IL-18 cooperates with IL-12 leading to joint inflammation and IL-1 β causing cartilage destruction.

Although the role of IL-1 β and IL-18 in damaging cartilage and bone tissue in RA has been affirmed, the function of the upstream regulatory molecule NLRP3 inflammasome in RA is still

controversial. In recent years, the inflammasome of NLRP3, as a research hotspot, its composition and structure has been basically clarified, but its activation pathway and regulation mechanism is not clear thoroughly. Especially in RA, research on NLRP3 inflammasome are still in its infancy, and more theoretical basis for the diagnosis and treatment of RA is deeply needed.

3. Current Therapeutic Strategies for NLRP3-related Diseases

Current therapeutic strategies for NLRP3-related diseases are mainly targeting the product of NLRP3-inflammasome activation, IL-1 β , IL-1 β neutralizing antibodies, and IL-1 β receptor antagonists which get positive clinical results in the treatment of relevant diseases. However, this method IL-1 β has some drawbacks. IL-1 β is produced in the activation of other inflammasomes, it will affect other normal physiological functions of the body and produce side effects. Specific targeting of NLRP3 inflammasome is used in treating NLRP3-related diseases, and good progress have been made, many NLRP3 inflammasome inhibitors show good therapeutic effects in NLRP3-related diseases and can be used as candidates for treating NLRP3-related diseases. According to the source of NLRP3 inflammasome inhibitors [10], they are divided into four categories: endogenous small molecules, small molecule compounds, natural products and clinical drugs, which will be introduced separately below.

3.1. The Endogenous Small Molecules of the Organism

β -Hydroxybutyrate (BHB), used as a ketone body and generated in the mammalian liver, can serve as an alternative energy source for the brain, heart and skeletal muscle under nutritional imbalance or low carbohydrate diet. According to a report in the literature, BHB has a specific inhibition of NLRP3 inflammasome activation but has no effect on the activation of AIM2, NLRC4 inflammasome. For the mechanism exploration and discovery, BHB inhibits K⁺ efflux during inflammasome activation, and then inhibits the NLRP3 inflammasome activation, In the animal experiment, MWS/ FCAS caused by the NLRP3 mutation, BHB has a good protective effect, and it was able to alleviate the MSU-induced acute peritonitis, which suggests that increasing the amount of BHB in the body by changing the diet or exogenous supplementation can treat NLRP3-related disease [11].

Dopamine (DA) plays an important role in regulating body behavior, movement, endocrine, et al. In addition, DA also plays certain functions in immune regulation. DA deficiency is closely related to systemic inflammation in the pathogenesis of Parkinson's disease. Studies have found that DA specifically inhibited NLRP3 inflammasome activation, but for other inflammasomes such as AIM2, NLRC4 will not be impacted. DA promotes intracellular cAMP production through the DRD1 receptor, which can promote NLRP3 ubiquitination and degradation, and inhibit NLRP3 inflammasome activation. At the same time, some experiments showed that DA can relieve the neuroinflammation induced by MPTP [12].

3.2. Small Molecule Compounds

INF39 is a modified small-molecule compound based on acrylate. Through a series of chemical structural modifications, it enhanced the inhibitory effect and reduced the cytotoxicity of the NLRP3 inflammasome. It is achieved by inhibition of NLRP3 ATP enzyme activity and activation of the NLRP3 inflammasome. Moreover, INF39 can also be absorbed by the small intestine against colitis induced by DNBS. However, an excessive inflammatory response often leads to tissue damage, which then triggers a series of diseases, such as inflammatory bowel disease and autoimmune diseases. Therefore, the search for compounds that can effectively inhibit NLRP3 inflammasome activation has important implications for treating these diseases. Back to INF39, it reduces the inflammatory response by its inhibition of NLRP3 ATP enzyme activity and activation of the NLRP3 inflammasome. After entering the cell, INF39 can bind to the NLRP3 protein, preventing it from forming an activated state. In this way, NLRP3 could not induce intracellular production of inflammatory factors, which reduce the inflammatory response. Moreover, INF39 can also further

reduce the inflammation response by regulating other intracellular signaling pathways, such as the NF- κ B pathway. It is worth mentioning that INF39 not only has NLRP3 inflammasome inhibition, but also has good biocompatibility. During the experiment, the researchers found that INF39 could be absorbed into the small intestine, meaning that it could enter the blood circulation and then act on all parts of the body. INF39 shows a significant protective effect in the DNBS-induced colitis model [13].

MCC950 is a selective NLRP3 inhibitor [14]. It attenuates joint inflammation by inhibiting NLRP3 inflammatory activation in monocytes and macrophages, inhibiting inflammatory responses and bone destruction. Moreover, MCC950 is also able to modify cysteine residues to reduce the NLRP3 inflammation. In the treatment of RA, the mechanism of MCC950 is mainly manifested in many aspects: 1. Inhibition of inflammatory response: MCC950 inhibits the activation of NLRP3 inflammasome, thus reducing the inflammatory state. This is crucial for the treatment of RA because the inflammatory response is a key factor in the deterioration of RA. 2. Reducing bone destruction: MCC950 can inhibit the activation of macrophages and reduce the generation of osteoclasts, thus reducing bone destruction. In RA patients, the inflammatory response leads to the destruction of the articular cartilage and bone, which leads to joint dysfunction. The role of MCC950 helps to protect the joint structure and function. 3. Protecting articular cartilage: MCC950 can reduce the IL-1 β and IL-18 and other inflammatory factors, thus reducing the destruction of articular cartilage. This helps to slow the progression of RA and reduce the risk of joint damage. 4. Regulation of the immune system: MCC950 can modify cysteine to reduce the inflammatory state. This helps to regulate the immune system to restore its normal balance.

2ABP is a small molecule compound whose main mechanism of action is to inhibit the activation of the NLRP3 inflammasome by affecting the flow of calcium ions (Ca^{2+}). The balance of calcium ions is crucial for the homeostasis of the organism. In the study, the 2ABP was modified in a series to retain its function. The experimental results show that these modified compounds can significantly reduce the systemic inflammation induced by lipopolysaccharide (LPS), suggesting that they are promising candidates for the treatment of NLRP3-related diseases [15].

Calcium ions play key roles in organisms, and they are involved in many cellular signaling processes that regulate biological functions inside and outside cells. In physiological conditions, the NLRP3 inflammasome is important for maintaining body immune homeostasis. However, under certain pathological conditions, hyperactivation of the NLRP3 inflammasome leads to inflammatory diseases.

The experiment results showed that the modified 2ABP compound significantly reduced the systemic inflammation induced by LPS. Therefore, regulatory strategies targeting the NLRP3 pathway have broad applications. Future studies are expected to explore the role of 2ABP and its modified compounds in the treatment of NLRP3-related diseases, with a view to providing new therapeutic approaches for clinical practice [15].

3.3. Natural Products

Licorice has a long history and can be used to treat type 2 diabetes, lung disease as well as cough. Isoliquiritigenin is the main ingredient of licorice which has a certain anti-inflammatory effect, but the mechanism is not clear. It was found [16] that Isoliquiritigenin affected NLRP3 inflammasome activation by inhibiting ASC polymerization, and significantly improved insulin resistance, metabolic disorders and inflammation in high-fat food-induced obesity model mice.

Resveratrol is a polyphenol which exists in grape and mulberry bark. Studies have found that resveratrol has anti-inflammatory and antioxidant functions, and it has a relieving effect on some diseases, but the anti-inflammatory mechanism is unclear. Articles reported that Resveratrol can inhibit the acetylation of α -tubulin during inflammasome activation and inhibit the NLRP3-ASC interaction. Subsequently, resveratrol was found to relieve the MSU-induced acute peritonitis, which suggested that resveratrol achieves anti-inflammatory function by inhibiting the NLRP3 inflammasome [17].

3.4. Clinical Drugs

Inflammation is a biological response of organisms to pathogens or damage signals. However, excessive inflammatory response may lead to the occurrence of a variety of diseases. In order to alleviate the damage brought about by inflammation, the research and development of clinical drugs are particularly important. Among many clinical drugs, many drugs can inhibit NLRP 3 inflammasome activation. According to this mechanism, people can inhibit NLRP3 inflammation through drugs, so as to achieve the purpose of anti-inflammatory and treat NLRP3-related diseases.

Fenamic-acid drug was found to inhibit the activation of NLRP 3 inflammasome. Some studies have reported that Fenamic-acid drug can inhibit the effects of nonsteroidal anti-inflammatory drugs in NSAIDs on NLRP 3, AIM 2 and NLRC 4 inflammasome, thus inhibiting inflammation. Through intensive investigation of this phenomenon, the scientists revealed that acid drugs can inhibit the activation of NLRP3 inflammasomes. It is worth mentioning that Fenamic-acid drug has shown remission effects on NLRP3-dependent peritonitis and Alzheimer's disease. This suggests that drug studies targeting VRAC have broad applications. Studies of VRAC channels and targeted interventions are expected to bring new treatments to patients with NLRP3 inflammasome-related diseases [18].

Tranilast is a drug that has been widely used in the treatment of asthma, atypical dermatitis, and allergic conjunctivitis. Several recent research reports have revealed the inhibitory effect of Tranilast on NLRP 3 inflammasome activation, providing new perspectives on our understanding of the mechanism of action. It was found that Tranilast can bind to NLRP 3 and inhibit the multimerization of NLRP 3, thus preventing the activation of the NLRP 3 inflammasome. This finding reveals the reason why Tranilast shows good protective of chronic inflammatory diseases and arthritis, and it is remarkable for the prevention and treatment of these diseases. Further studies show that Tranilast is able to inhibit the activation of the inflammasome in the joint fluid cells of gout patients, and this result indicates a high safety profile of Tranilast in clinical application. These findings provide us with a possible new therapeutic strategy for NLRP 3-related diseases, and Tranilast may be a boon for patients with such diseases [19].

4. Conclusion

As an important immune regulation mechanism in the human body, NLRP3 is closely linked with various diseases such as inflammation, autoimmune diseases and metabolic diseases. Although numerous studies have been devoted to find small molecule compounds that effectively inhibit NLRP 3 inflammasome activation with remarkable results at the cellular level, only some of the inhibitors showed promising prophylactic or therapeutic effects in related disease model animals. Drug development is a time-consuming process, requiring multiple factors, such as drug safety, efficacy, and targeted. In recent years, scientists have made breakthroughs in studying the NLRP3 inflammasome, laying the foundation for the development of clinical drugs that directly target the NLRP3 inflammasome. Future research will continue to focus on the following aspects: first, the activation mechanism and regulation pathway of NLRP3 inflammasome should be deeply explored to find more potential drug targets; second, the structure and activity of existing inhibitors should be optimized and improved as well as their stability and bioavailability in the body; finally, preclinical and clinical trials should be conducted to verify the actual effect of drugs targeting NLRP3 inflammasome in the treatment of related diseases.

In conclusion, the NLRP 3 inflammasome study has achieved some research results, which are expected to bring hope for the rehabilitation of many patients. In the future, it is expected to get the advent of clinical drugs that gets the NLRP3 inflammasome directly to revolutionize the treatment of NLRP3-related diseases. At the same time, researchers will also be encouraged to continue to explore other potential inflammasome targets, in order to provide more possibilities for future drug development.

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