Review Article

NLRP3 Inflammasome in Autoinflammatory Diseases and Periodontitis Advance in the Management

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Abstract

Inflammatory chemicals are released by the immune system in response to any perceived danger, including irritants and pathogenic organisms. The caspase activation and the response of inflammation are governed by inflammasomes, which are sensors and transmitters of the innate immune system. They have always been linked to swelling and pain. Research has mainly concentrated on the NOD-like protein transmitter 3 (NLRP3) inflammasome. Interleukin (IL)-1 and IL-18 are pro-inflammatory cytokines that are activated by the NOD-like antibody protein receptor 3 (NLRP3), which controls innate immune responses. The NLRP3 inflammasome has been associated with gum disease and other autoimmune inflammatory diseases in several studies. Scientists' discovery of IL-1's central role in the pathophysiology of numerous autoimmune disorders has increased public awareness of these conditions. The first disease to be connected with aberrant inflammasome activation was the autoinflammatory cryopyrin-associated periodic syndrome (CAPS). Targeted therapeutics against IL-1 have been delayed in development because their underlying reasons are poorly understood. The NLRP3 inflammasome has recently been related to higher production and activation in periodontitis. Multiple periodontal cell types are controlled by the NLRP3 inflammasome. To promote osteoclast genesis, the NLRP3 inflammasome either increases receptor-activator of nuclear factor kappa beta ligand (RANKL) synthesis or decreases osteoclast-promoting gene (OPG) levels. By boosting cytokines that promote inflammation in the periodontal ligament fibroblasts and triggering apoptosis in osteoblasts, the NLRP3 inflammasome regulates immune cell activity. These findings support further investigation into the NLRP3 inflammasome as a therapeutic target for the medical treatment of periodontitis. This article provides a short overview of the NLRP3 inflammatory proteins and discusses their role in the onset of autoinflammatory disorders (AIDs) and periodontitis.

Keywords: *Autoinflammatory disease, IL-1, NLRP3 inflammasome, periodontitis*

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Introduction

The body's built-in immune system is in charge of quickly identifying possible risks, such as pathogen incursions and shifts in the equilibrium, to the host. A few receptors expressed in the germline equip the myeloid effector lymphocytes that make up this immune system with the ability to recognize these dangers. These permanent receptors carry out their duties by recognizing characteristic patterns and components of harmful microbes. The adaptive immune response is reliant on the initial antimicrobial response, which is orchestrated by the innate immune system.

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The only innate immune receptors identified so far are pattern recognition receptors (PRRs). Potentially dangerous molecular trends (DAMPs) and molecular patterns linked to pathogens (PAMPs) might be recognized by PRRs. Examples of PRR families include the retinoic acid-inducible gene I (RIG-I) receptors in the body toll-like receptors (TLRs), C-type glycoprotein receptors in the body, and nucleotide oligomerization domain (NOD)-like receptors (NLRs).[1]

As part of the innate immune system, receptors containing a nucleotide-binding region and a leucine-rich repeat (NLR) play a significant role in host defense. These chemicals play a crucial role in setting off the inflammatory response in response to abnormal cellular conditions. The inflammasome is a multi-subunit complex of proteins that is NLR-rich.[2] The inflammasome consists of three molecules: the NLR, the adaptor apoptosis-associated speck-like proteins (ASC), and the effector caspase-1. Most research has been done on inflammasomes NLRP1, NLRP3, and NLRC4.[2]

Cytokine (IL)-1 and IL-18 are examples of pro-inflammatory cytokines that are processed and released by the inflammasome.[3,4] Widespread acknowledgment of the key relevance of NLR molecules in these illnesses may be traced back to the discovery of IL-1's function in the etiology of many autoinflammatory disorders (AIDs). The first disease to be connected with aberrant inflammasome activation was the autoinflammatory cryopyrin-associated periodic syndrome (CAPS). Subsequent research has linked NLR activity at the inflammasome level to inflammatory disorders.[3,4]

Autoinflammatory diseases are characterized by systemic inflammation in the absence of a clear trigger.[4] AIDs are characterized by periods of abnormal activation that do not include T and B cells, but there are no underlying infections or inflammatory symptoms present in these patients. The innate immune system's functions range from tissue protection to pathogen recognition. Several disorders caused by the nuclear factor B and influenza are now recognized as AIDS,[5] although AIDS characterized by irregular inflammasome activation is much more prevalent.

A hereditary predisposition and recurrent systemic inflammatory flare-ups are two of the clinical and etiopathogenetic criteria that distinguish autoinflammatory illnesses from autoimmune diseases. The TLR stimulation, autoantigen appearance, and early stages in dementia (ADs) that include immunity from within include recruiting B and T cells and producing autoantibodies. The second stage sees the establishment of adaptive immunity, a self-maintaining mechanism. At this time, the self-directed inflammation is caused by antibodies and immune system complexes containing nucleic acids. IL-1ß links the innate immune response induced by NLR activity to the progressive immunological responses of T and B cells, making it a key mediator of autoimmunity and inflammation.[6] AIDs, which are distinguished by a deficiency in either inhibitory antibodies or autoreactive T lymphocytes, are suspected to be caused by abnormalities in proteins of the innate immune system.[7]

Periodic fever with aphthous, pharyngitis, and adenitis (PFAPA) is a syndrome often seen in clinical practice that is hypothesized to be an autoinflammatory illness comparable to familial Mediterranean fever (FMF). However, they demonstrate the significance of regulatory mechanisms of the innate immune system in the control of inflammation. Similar but somewhat distinct processes are hypothesized to underlie the emergence of other, much more prevalent diseases.[8]

Inflammasome-Associated Autoinflammatory Diseases

Three separate periodic syndromes result from mutations in the NLRP3 gene that are collectively known as CAPS or cryopyrinopathies. Mutations cause elevated IL-1 production and constant activation by the NLRP3 inflammasome [Figure 1].[9,10] As one example, consider this. From the relatively benign familial cold autoinflammatory illness to the life-threatening neonatal-onset multisystem inflammatory disorder, CAPS covers a broad spectrum of inflammatory diseases. Inflammatory symptoms are common across many disorders and include fever, rash, conjunctivitis, and arthralgia. Leukocytosis and neutrophilia are frequent laboratory results, and acute phase reactants such as C-reactive protein tend to be elevated.[3,11] Certain mutations in the inflammasome genes NLRP3 have been associated in mice studies with illnesses such as complicated or congenital inflammasomopathies, suggesting a role for inflammasome activity in these disorders. Diseases like crystalline arthritis may develop when the inflammatory protein NLRP3 is triggered by external risk signals.[3,4]

The acute form of gouty arthritis is brought on by the accumulation of crystals of monosodium urate, or MSU, in the joint and surrounding tissue. Similarly, the deposition of calcium pyrophosphate dihydrate (CPPD) crystals causes inflammatory joint disease pseudogout.[12]

Elevated IL-1 release and damage to tissues have been linked to MSU and CPPD crystals within the joint cavity.[13,14] There is an immediate inflammatory response [Figure 1]. As one example, consider this.

Type II diabetes has been associated with the natural immune system and the NLRP3 inflammasome. Interleukin-1 (IL-1) production by human pancreatic cells in response to high levels of glucose is associated with cell dysfunction and mortality.[15]

Hyperglycemia increases and the inflammatory cycle persists when cell activity decreases. Glyburide, a sulfonylurea used in the management of Type II DM, requires activation of the NLRP3 inflammasome to exert its therapeutic benefits. Activation of the NLRP3 inflammasome, and hence IL-1 production, was found to be suppressed by glyburide.[16]

All the aforementioned autoinflammatory illnesses have one thing in common: an increase in IL-1 and IL-18 production. Furthermore, independent of genetic alterations, the precise mechanism responsible for the increased activity of the NLRP3 inflammasome remains unknown.[17]

Some studies[18,19] suggest that autophagy, the cell's waste disposal system, is responsible for regulating inflammation by removing damaged mitochondria. Chronic inflammatory diseases like periodontitis are a newer medical category. Periodontitis is characterized by low-grade chronic inflammation, although it does not exhibit overt inflammatory symptoms and does not respond consistently to non-specific anti-inflammatory drugs.[20] Disease prevention and treatment, however, are shifting their focus to these underlying causes.

Due to the inflammatory nature of periodontitis, monocytes and polymorph nuclear leukocytes produce more prostaglandin E 2 (PGE2), tumor necrosis factor- (TNF-), interleukin-1 beta (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and interleukin-1. Loss of periodontal tissue results from an abnormal immune response, which is characterized by the synthesis of these cytokines incorrectly, either of the wrong kind or in an inappropriate amount. These circulating cytokines generated locally may keep an inflammatory response continuing for some time. That is why periodontitis is a major risk factor for the development of non-communicable diseases such as diabetes, osteoporosis, hypertension, and coronary artery disease.[21-24]

CRP plasma levels are greater in periodontitis patients compared to periodontally healthy people, with values ranging from 2 to 10 mg/L, corresponding with a condition of systemic low-grade chronic inflammation. In addition, compared to healthy persons, periodontitis patients have somewhat increased leukocyte counts and IL-6 levels. Similar findings are seen in the review by Santos Tunes *et al*., which found that periodontal patients had higher levels of CRP, IL-1, IL-6, TNF-, PGE2, and fibrinogen. According to Shrihari, periodontitis decides the status of LGI with a little rise in CRP levels, and as a result, it may be a covert risk factor for cardiovascular disorders. Sima *et al*. also indicate that periodontitis increases the amounts of circulating pro-inflammatory mediators, which is consistent with these results.[21,22,24] Periodontitis, according to Endo et al., can induce an increase in the number of polymorphonuclear leukocytes, as well as increased gene expression of IL-6, TNF-, and CRP in the liver and adipose tissue, as well as higher blood levels of TNF- and CRP. Del Pinto *et al*. and Gurav discuss how periodontitis induces the release of pro-inflammatory markers in the circulation and, as a source of systemic LGI, can impact systemic disorders such as CVD, endothelial dysfunction, and Alzheimer's disease.[25-28] The severity of periodontitis appears to be proportionately correlated with systemic levels of inflammatory markers.[29,30] The work by Gocke *et al*. in particular draws attention to the clear correlation between LGI indicators like fibrinogen and WBC levels and increasing pocket depth and clinical attachment loss scores.[31] Furthermore, Nibali *et al*. demonstrate a correlation between an increase in periodontal pockets and a rise in WBC levels.[30] On the other hand, it has been demonstrated that periodontal treatment results in improved periodontal health and repair of periodontal tissues, which in turn lowers levels of inflammatory markers like CRP, E-selectin, and TNF- and aids in the management of systemic diseases including hyperglycemia and stroke.[27,32]

Role of NLR3 in the Pathogenesis of Periodontitis

Plaque bacteria may contribute to periodontitis, an inflammation of the bone and gums that support the teeth. About 11.2% of the global population has it.[33,34] The effects of periodontitis extend beyond the mouth.[35] Periodontitis has been associated with a wide range of serious diseases,[36-40] including cancer, dementia, type 2 diabetes, rheumatoid arthritis, and cardiovascular disease.

Periodontitis is caused by a chain reaction of inflammatory gene transcription factors, inflammatory cytokines, and tissue-destructive chemicals that are triggered by the intricate interplay of several cell types.[41,42] Pathological alterations in periodontitis tissues are dependent on intracellular signaling, which was created by these substances.[43-54] Inflammasomes are critical regulators of the innate immunological response to pathogens in chronic illnesses.[46,47]

Recent studies have shown the importance of the "inflammasome" complex of nucleotide-binding

polymerization domain-like receptors (NLR) combinations in the immunological response in periodontal tissues. Restoring a healthy equilibrium between inflammasome-mediated inflammation and cell death promotes tissue regeneration. Accumulation and activation of inflammasomes often lead to unchecked inflammation, increased cytokines, tissue damage, and autoinflammatory and autoimmune diseases.[48,49] Multiple inflammasomes have been identified. Pathogenic inflammation generated by periodontitis-causing bacteria begins in part at the inflammasome (NLRP3), which has been the subject of most research.[50,51]

The possible role of NLRP3 in gingivitis has been the subject of much clinical research. Compared with healthy gingival samples, NLRP3 mRNA expression was shown to be four to five times higher in patients with chronic periodontitis,[52,53] and seven times higher in patients with advanced periodontitis. Gingival NLRP3 mRNA levels are positively correlated with IL1B mRNA levels.[53] Periodontitis has been related to an unfavorable microbial imbalance in the mouth. However, periodontium loss is caused by an immune system's deregulated response to microbial infections.[54]

Most immune system damage results from infections of host cells, which trigger inflammatory and cellular aging. The secretory phenotype associated with senescence (SASP) is characterized by the random secretion of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and TNF-alpha by senescent cells. The production of pro-inflammatory cytokines near the gum line is linked to a more severe type of periodontitis.[55,56] For lipopolysaccharides (LPS) produced by gram-negative bacteria, TLR4 is the main receptor. Periodontitis is difficult to manage without the TLR4 protein, which controls cell signaling, apoptosis, and the strength of immunological responses.[57]

When the TLR4 pathway is triggered, the NLRP3 inflammasome is activated, which is composed of the protein receptor, NLRP3, Caspase-1, and apoptosis-associated speck such as molecule containing a CARD domain (ASC). Caspase-1 and IL-1 are both secreted when the activated NLRP3 assembles at the inflammasome, which is a crucial step in the development of periodontal disease [Figure 1].[58,59] The inflammasome NLRP3 plays a role in the development of IL-1 and IL-18, which is essential for the pathophysiology and progression of periodontitis.[60]

As a result, the initiation of NLRP3 inflammasomes has both positive and negative effects on the host's defense system.[61,62] Periodontitis is a condition that affects the periodontal ligaments and alveolar bone.[63]

Studies of periodontal disease have focused heavily on alveolar fractures and the functions of osteoclasts and osteoblasts.[64] Numerous studies[65,66] have examined the function of osteoclasts and osteoblasts in gingivitis. Multiple cell types (osteoclasts, bone marrow cells, gingival fibroblast ligament cells, and immune cells) have been linked to NLRP3 inflammasome activity in periodontitis development.[35] Bone resorption due to periodontitis is greatly aided by osteoclasts.[67]

Osteoclastogenesis relies heavily on the receptor-activator of nuclear factor kappa beta (RANK), receptor-activator of nuclear factor kappa beta ligand (RANKL), and osteoclast-promoting gene (OPG) axis. Osteoclasts, a kind of multinucleated cell responsible for breaking down the tissue of bones as required to maintain a healthy rate of bone turnover, develop from immature myeloid progenitors under normal conditions. Alternatively, substantial bone loss is associated with harmful illnesses. The cytokines interleukin-1 (IL-1) and interleukin-18 (IL-18), which are processed by caspase-1, may have both direct and indirect effects on osteoclasts.[68] According to a study by Yamaguchi *et al*., the NLRP3 inflammasome has mediated the release of inflammatory cytokines and significantly affects bone loss caused by P. gingivalis. Additionally, they discovered that NLRP3-KO mice had considerably higher levels of OPG and lower levels of RANKL, indicating that NLRP3 inflammasomes may have contributed to the enhancement of osteoclastogenesis in periodontitis animals.[69]

According to a periodontitis-based model of aging, NLRP3 has a role in osteoclastogenesis as individuals age.[70] Periodontitis has been associated with a decrease in bone production, differentiation, and proliferation; an increase in pyroptosis in osteoblasts; and an increase in bone resorption.[35]

Osteoblasts, the cells responsible for making bone, contain the inflammasome protein NLRP3.[71] Infection by periodontal pathogens triggers IL-1 and IL-18 secretion and death in osteoblastic cells. The NLRP3 inflammasome plays a key role in this process. Because of the inflammation that they trigger, these[72] may have a long-term impact on bone resorption and bone turnover. The fibroblasts found in human periodontal tissue (hPDLFs) secrete cytokines and chemokines that promote the development of periodontitis. Previous studies have shown that the levels of NLRP3 and ASC in both human and mouse PDLFs are consistent. When the NLRP3 inflammasome is active, pro-inflammatory cytokines like IL-1 and IL-6 are produced in large quantities, and the periodontal ligament is damaged. The NLRP3 inflammasome in periodontal ligament fibroblasts has been largely overlooked.[73,74]

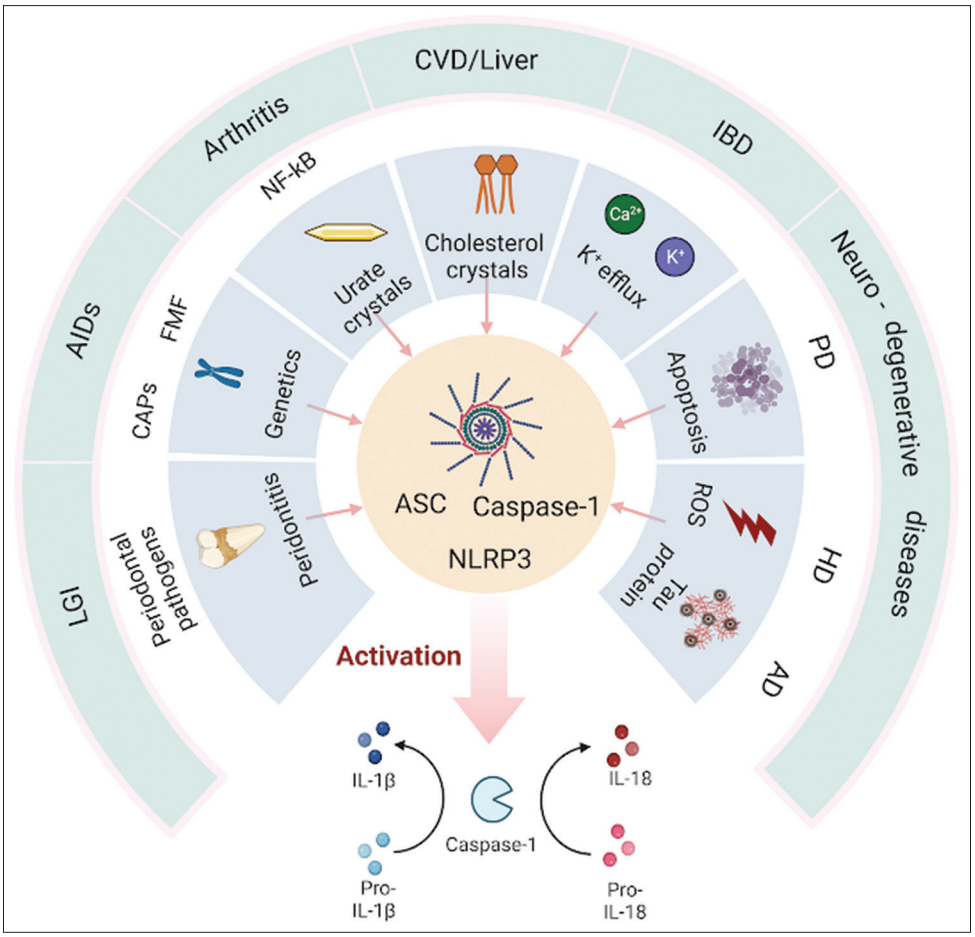

Figure 1: The NOD-like receptor protein 3 (NLRP3) inflammasome regulates innate immune reactions by turning on caspase-1 and the inflammatory cytokines interleukin (IL)-1 and IL-18. As a result, the NLRP3 inflammasome is crucial for the emergence of certain systemic diseases. Created with BioRender.com

Management

Every treatment for an autoinflammatory disease has as its main objective the reduction of that disease's unique inflammatory mechanism. Biologic medicines that inhibit certain cytokines are being used to treat autoimmune inflammatory disorders. Glucocorticoids and non-steroidal anti-inflammatory medications (NSAIDs) are two examples of potential alternative therapies. The patient's inflammation must be monitored both when symptoms emerge and as they subside.

Due to their consistent efficacy, anti-IL-1 medications have become the standard treatment for numerous autoinflammatory diseases.[75] Diseases mostly mediated by IL-1-beta respond well to interleukin (IL) 1 blockade. Successful treatment of NLRP3-associated autoimmune illnesses may one day be possible thanks to novel targeted therapies based on an improved knowledge of NLRP3 inflammasome activation and control.[76] The host's response to periodontitis maintains an inflammatory and dysbiotic condition, both of which contribute to tissue loss. However, most efforts in the field of biology have focused on altering bacteria (with antibiotics) instead of the immune system of humans to improve periodontal therapy.

Many diseases have been related to the inappropriate activation of inflammasomes and the persistent generation of pro-inflammatory cytokines. Medications that block or block off the inflammasome's ability to produce inflammatory cytokines are being studied for use in the treatment of periodontal disease.[77] An overactive NLRP3 inflammasome boosts osteoclasts' bone resorption capacity in several ways, including by restoring the actin cytoskeleton, activating autophagy, and enhancing ubiquitination. The NLRP3 inflammasome has been proposed as a therapeutic target for periodontitis because of its potential to modulate osteoclast activity and differentiation.[49]

NLRP3 inhibitors are being studied as a possible therapy for periodontitis along with other inflammatory diseases. For the treatment of inflammatory illnesses such as periodontitis and autoimmune disorders, several NLRP3 inflammasome inhibitors with potential for therapy have

been developed and have shown considerable promise. Whether or whether NLRP3 inflammasome inhibitors help with either disease treatment, how they operate, or if they have any adverse effects, remains unknown at this time. It is possible that periodontitis and other autoimmune inflammatory disorders may be treated more effectively if powerful but safe NLRP3 inflammasome inhibitors were developed.[35]

MCC950 has been shown effective in treating periodontitis. MCC950 prevents further osteoclast formation and greatly lowers osteoclast numbers in mice with periodontitis, resulting in less alveolar bone loss. Potentially ground-breaking therapy[78] for periodontitis is on the horizon. MCC950 has been shown to reduce NLRP3-mediated inflammation and prevent additional alveolar bone loss in animal models.

Treatment with the sulfonylurea glyburide is used for type 2 diabetes. Pancreatic cells' K+ (ATP) channels are targeted, making this therapy very effective. Glyburide reduced the activation of the cryopyrin inflammasome. Similar to cryopyrin, glyburide mitigated LPS-induced mortality in mice. In contrast to PAMPs, DAMPs, and crystals, glyburide was the first chemical demonstrated to suppress IL-1 synthesis.[16] By inhibiting the production of inflammatory molecules like TNFs, interleukin 1 (IL-1), and reactive oxygen species,[79] glyburide may halt the expansion of inflammatory cells. Glyburide has the potential to alleviate periodontal inflammation by inhibiting the NLRP3 inflammasome and reducing IL-1 production. Oral treatment of glyburide inhibits osteoclast generation and alveolar bone resorption in a rat model of traumatic occlusion. Evidence like this[80] shows that glyburide could potentially be useful in combating periodontal disease.

Many inflammasomes in macrophages are suppressed by parthenolide because of its direct inhibition of caspase-1 protease activity. Parthenolide inhibits the ATPase activity of NLRP3, which in turn decreases NLRP3 activity. Therapeutic promise exists for autoinflammatory illnesses due to parthenolide's anti-inflammatory characteristics, which target the inflammasome NLRP3.[81]

Several studies have examined parthenolide's potential as a therapy for periodontitis. The anti-inflammatory and anti-osteoclast genic effects of parthenolide have been found to aid in bone repair in individuals with periodontitis. Inhibition of RANKL-mediated osteoclast genesis[81] suggests that parthenolide may prevent the development of osteoclasts.

Table 1: NLRP3 inflammasome inhibitors in the therapy of autoinflammatory disease

Agent	Mechanism of inhibition	Benefit	Reference
MCC950	Inhibits both canonical and non-canonical NLRP3 activation. Blocks NLRP3 induced ASC oligomerization	Reduces interleukin-1p (IL-1β) production in vivo and attenuates the severity of experimental autoimmune encephalomyelitis (EAE).	Coll RC, Robertson AA, Chae JJ, Higgins SC, Muñoz-Planillo R, Inserra MC, Vetter I, Dungan LS, Monks BG, Stutz A, Croker DE, Butler MS, Haneklaus M, Sutton CE, Núñez G, Latz E, Kastner DL, Mills KH, Masters SL, Schroder K, Cooper MA, O'Neill LA. A small-molecule inhibitor of the NLRP3 inflammasome for the treatment of inflammatory diseases. Nat Med. 2015 Mar; 21 (3):248-55.[77]
Glyburide	Inhibits the cryopyrin inflammasome downstream of the $P2X_7$ receptor. Inhibits LPS+ATP-induced caspase-1 activation, IL-1β secretion	Prevents cryopyrin activation and microbial ligand-, DAMP-, and crystal-induced IL-1β secretion.	Lamkanfi M, Mueller JL, Vitari AC, Misaghi S, Fedorova A, Deshayes K, Lee WP, Hoffman HM, Dixit VM. Glyburide inhibits the Cryopyrin/Nalp3 inflammasome. J Cell Biol. 2009 Oct 5;187 (1):61-70.[78]
Parthenolide	Inhibits the ATPase activity of NLRP3. Inhibits the protease activity of caspase-1	Provides anti-inflammatory activity and potential therapeutics that target the NLRP3 inflammasome.	Zhang X, Chen Q, Liu J, Fan C, Wei Q, Chen Z. *et al*. Parthenolide Promotes Differentiation of Osteoblasts Through the Wnt/beta-Catenin Signaling Pathway in Inflammatory Environments. J Interferon Cytokine Res. 2017;37:406–14.[81]
Melatonin	Prevents inflammasome NLRP3 activation, inhibits NF-κB activation	Reduces the expression of the pro-inflammatory cytokines.	Rüdiger Hardeland. Journal of Pineal Research 2018; 65: e12525.[82]
Tranilast	Inhibits some key inflammation-associated transcription factors such as NF-κB and impeding NLRP3 inflammasome	Suppression of cytokine IL-13 and mucosal secretions.	Saeedi-Boroujeni A, Mahmoudian-Sani MR, Nashibi R, Houshmandfar S, Tahmaseby Gandomkari S, Khodadadi A. Tranilast: a potential anti-inflammatory and NLRP3 inflammasome inhibitor drug for COVID-19. Immunopharmacol Immunotoxicol. 2021 Jun; 43 (3):247-258.[92]

Table 2: NLRP3 inflammasome inhibitors in the therapy of periodontitis

Agent	Mechanism of inhibition	Benefit	Reference
MCC950	Could directly interact with the Walker B motif within the NLRP3 NACHT domain, and then blocking ATP hydrolysis and inhibiting NLRP3 activation and inflammasome formation	Significantly decreases the number and inhibits osteoclast differentiation, which ultimately results in the reduction of alveolar bone loss in mice with periodontitis	Zang Y, Song JH, Oh SH, Kim JW, Lee MN, Piao X. *et al*. Targeting NLRP3 Inflammasome Reduces Age-Related Experimental Alveolar Bone Loss. J Dent Res. 2020;99:1287–95.[70]
Dioscin	Reduces NLRP3 inflammasome activation	Enhances mouse pre-osteoblast osteogenesis	Cai J, Liu J, Fan P, Dong X, Zhu K, Liu X. *et al*. Dioscin prevents DSS-induced colitis in mice with enhancing intestinal barrier function and reducing colon inflammation. Int Immunopharmacol. 2021;99:108015.[88]
Parthenolide	Inhibits NLRP3 ATPase activity	Anti-inflammatory and anti-osteoclastogenic	Zhang X, Chen Q, Liu J, Fan C, Wei Q, Chen Z. *et al*. Parthenolide Promotes Differentiation of Osteoblasts Through the Wnt/beta-Catenin Signaling Pathway in Inflammatory Environments. J Interferon Cytokine Res. 2017;37:406–14.[81]
Tranilast	Resists lipopolysaccharide-induced oxidative stress, NLRP3 inflammasome production, and activation	Increases the production of primary hPDLCs, and encourages osteogenic differentiation of hPDLCs	Kawakami T, Fukai K, Sowa J, Ishii M, Teramae H, Kanazawa K. Case of cheilitis granulomatosa associated with apical periodontitis. J Dermatol. 2008;35:115–9.[87]
Irisin	Inhibits NLRP3 inflammasome formation and activation caused by lipopolysaccharides	Promotes osteogenesis Has a significant role in periodontitis' small alveolar bone defects	Pullisaar H, Colaianni G, Lian AM, Vandevska-Radunovic V, Grano M, Reseland JE. Irisin promotes growth, migration and matrix formation in human periodontal ligament cells. Arch Oral Biol. 2020;111:104635.[90]
Glyburide	Blocks NLRP3 inflammasome activation	Reverses inflammation. Lessens the alveolar bone resorption and osteoclastogenesis	Jiang M, Shang Z, Zhang T, Yin X, Liang X, Sun H. Study on the role of pyroptosis in bone resorption induced by occlusal trauma with or without periodontitis. J Periodontal Res. 2022;57:448–60.[80]
Melatonin	Exerts inhibitory function on NLRP3 inflammasome activation through inhibiting or activating several proteins and pathways	Promotes new bone regeneration and increases the number of osteoblast-like cells	Lu X, Yu S, Chen G, Zheng W, Peng J, Huang X, Insight into the roles of melatonin in bone tissue and bone-related diseases (Review) Int J Mol Med. 2021. 47.[85]

Melatonin

When it comes to the immune system, melatonin may have both pro-inflammatory and anti-inflammatory properties.[82] By modulating the expression of multiple proteins and the signaling processes that they engage in, melatonin suppresses the NLRP3 inflammasome. Levels of melatonin have been connected to the severity of periodontitis. Balaji, *et al*.[83] conducted a systematic review and found that melatonin levels drop early in the course of periodontitis and then rebound later in the disease. Researchers[84,85] found that melatonin stimulated the growth of cells that resemble osteoblasts, the cells responsible for the production of new bone.

Tryptophan may be replaced by N-[3',4'-dimetho xycinnamoyl]-anthranilic acid (tranilast). Significant protective or curative benefits against NLRP3-related human illnesses such as gout, cryopyrin-associated autoinflammatory syndromes, and type 2 diabetes have been seen in mouse models.[86]

By decreasing osteoclast genesis,[87] tranilast has a partial therapeutic impact on periodontitis, reducing apical periodontitis with its anti-inflammatory and anti-oxidative characteristics. Dioscin is a steroid saponin found in plants that has been shown to reduce inflammation. The NLRP3 inflammasome has been targeted to provide the desired results. Macrophage M2 polarization and inflammation are both dampened. Dioscin reduces NLRP3 inflammasome activation and induces the process of osteogenesis in mouse pre-osteoblasts,[88,89] which has a therapeutic impact on periodical periodontitis in mice. By blocking the formation and activation of NLRP3 inflammasomes in response to lipopolysaccharides,[90] irisin functions as an NLRP3 inhibitor.

Irisin stimulated the maturation of initial hPDLCs and osteogenesis by increasing extracellular matrix synthesis and decreasing osteoclast formation. Based on these findings, irisin seems to play a critical role in the repair

of alveolar bone lost to periodontal disease.[91] Both autoinflammatory diseases and periodontitis may be effectively treated with NLRP3 inflammasome inhibitors, as shown in Tables 1 and 2.

Conclusion

Pleiotropic involvement in inflammation and significant breakthroughs in functional characterization have made NLRP3 an attractive target for medicinal research. While selective NLRP3 inhibitors have enormous promise in terms of safety and effectiveness, more study is needed to completely grasp the complexity of the NLRP3 inflammasome. Recent research has shown a relationship between periodontitis and the inflammasome NLRP3 being overexpressed and activated. The NLRP3 inflammasome has a role in many regulatory mechanisms in periodontal tissue cells. This is achieved by increasing the production of cytokines that are inflammatory by periodontal ligament fibroblasts and encouraging the formation of osteoclasts. Based on these findings, the NLRP3 inflammasome seems to have great therapeutic potential for the treatment of periodontal and other autoimmune inflammatory diseases. Drugs that block the NLRP3 inflammasome may be useful in treating these conditions. However, it is still unclear how exactly NLRP3 inflammasome inhibitors affect autoinflammatory diseases and periodontitis. Therapy of NRLP3-associated autoinflammatory illnesses, such as periodontitis, may benefit by blocking the inflammasome's downstream responses and signaling pathways.

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Conflicts of interest

There are no conflicts of interest.

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