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The role of inflammasomes in periodontal disease and pathogenesis

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ABSTRACT

Inflammasomes are complex cellular structures that play crucial roles in the pathogenesis of periodontal disease. Inflammasomes are proteins that sense microbial pathogens in the host and trigger an inflammatory response. This response is vital for combating infection but can also damage tissue if inflammation is not controlled. Several studies have reviewed the role of inflammasomes in periodontal disease. In periodontal disease, inflammasome activation has been linked to the release of pro-inflammatory cytokines, which can lead to tissue destruction and periodontal damage. The term "inflammasome" was coined by Jurg Tschopp in 2002. Recently, significant research has focused on activating inflammasomes and their roles in disease processes. The NLRP1, NLRP3, NLRC4, and AIM2 inflammasomes have been identified as essential. Inflammasomes are a group of proteins that are part of the innate immune system and play a role in the pathogenesis of periodontal diseases. They are activated by bacteria, which leads to the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6). Periodontitis is triggered by these cytokines, leading to increased inflammation and tissue destruction. This review aimed to examine how these inflammasomes contribute to periodontitis pathogenesis.

Keywords: *Inflammasome, NLRP3, periodontal disease, periodontal pathogen, IL-1β*

BACKGROUND

Periodontitis is a complex inflammatory infection with various elements regulated by genetics and environmental factors that results in a damaging inflammatory response against microbial biofilms. (1). The condition is identified by the escalating loss of tooth-supporting structures and has been connected

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to dysbiotic plaque biofilms. Periodontitis is the sixth-most common disease in the world, accounting for 11.2 percent of cases and being the primary cause of tooth loss worldwide (2-4). It is more than simply a localized oral disease; it also impacts an individual's systemic health and is a risk factor for several systemic disorders (5,6). As a result, understanding the causes of periodontitis onset and progression is crucial for developing effective treatment and preventative interventions.

Inflammasomes

Inflammasomes are a group of intracellular molecules responsible for activating an inflammatory response in the body. Recently, research has started investigating the part of inflammasome periodontal disease'sdisease's pathogenesis. The analysis suggests that inflammasomes play an important role in periodontal disease, activating a pro-incendiary response and increasing the destruction of periodontal tissue. The body's innate immune system first defends itself against infections. Pattern Recognition Receptors (PRRs) in the innate immune system oversee identifying specific patterns—pathogens, including bacteria and viruses. PRRs can detect various microbial components, often called Pathogen Associated Molecular Patterns (PAMPs). A Damage Associated Molecular Pattern (DAMP), a part of, is active every second the host cell a certain originates during inflammation or is derived from the surroundings (7).

Cells, each innate, both the immunological system epithelial, endothelial, and immune system systems all express PRRs, despite innate immunity cells expressing PRRs more frequently. When a PRR is activated by its ligand, subsequent signaling cascades are triggered, which have a variety of effects. One of these effects is the innate immune cells' activation. Another is cytokine and chemokine production, which draws immune cells to the infection site (7).

Activating inflammatory caspases because of the innate immune system is a mechanism for activating cysteine proteases. These caspases cleave several cellular substrates during the immunological response (8,9).

Procaspase-1, a member of the NLR family, is assembled into the multimeric inflammasome. Procaspase-1 zymogen is an inactive enzyme stored in the immune system's cells. It is an essential inflammasome component, a molecular complicated that controls each production of IL-1 and IL-18, two examples of cytokines, response to infections. Autoproteolysis is a process by which the procaspase-1 zymogen is activated, resulting in each production proscribing in favor of IL-1 and IL-18. Each activation of procaspase-1 zymogen occurs in two steps. First, the enzyme undergoes cleavage to create Pro-IL-1, and pro-IL-18 precursors are cleaved into their mature forms by active caspase-1. This process is essential for producing these cytokines, which are crucial in immunological reactions to infections. The action of procaspase-1 is controlled by various proteins, including NLRP3, which is found in the inflammasome. Activation of NLRP3 leads to reactive oxygen species generation and the cleavage of procaspase-1 (9,10).

Inflammasomes are intracellular proteins that respond to various stimuli and significantly contribute to the body'sbody's immune response. The activation of inflammasomes often depends on danger signs like bacterial contamination or viral particles, toxic molecules, or changes in temperature or pH. When inflammasomes are activated, they release pro-inflammatory cytokines, which help the immune system combats infection. Additionally, each activation of inflammasomes can trigger pyroptosis, an instance of planned cell death that produces inflammation. Pyroptosis is a self-destructive process that helps the body to remove damaged or infected cells. Activating inflammasomes is vital for the body's ability to defend itself from infection and disease. However, when inflammasomes are activated inappropriately or without an appropriate stimulus, they may cause severe inflammation and tissue damage (10). Pyroptosis is a bacterial clearance mechanism generated by the innate immune mechanism. It describes the extraordinary pro-inflammatory process that occurs during the death of cells (9).

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Caspases are involved in cellular self-destruction, so it was initially mistaken for traditional apoptosis. While pyroptosis and apoptosis share many characteristics, the main difference is that inflammatory reactions characterize the process. Furthermore, pyroptosis is accompanied by the release of many pro-inflammatory molecules (11).

Pyroptosis results from multiple signaling pathways, each activating the downstream signaling pathways of GSDMD. The cytoplasmic interleukin-1 (IL-1) and IL-18 release (IL-18) through each hole caused by GSDMD is one crucial step in inducing a significant inflammatory response. GSDMD is a crucial protein that helps to regulate inflammation and is primarily found in neutrophils. When GSDMD is activated, it forms holes IL-1 and IL-18 permitted in a cell membrane to escape the cell and enter the surrounding tissue. Once IL-1 and IL-18 have become available, they begin to activate other key inflammatory molecules, such as TNFα and IL-6, which are recognized as responsible for the body's inflammatory response. This cascade of events results in a significant inflammatory response, helping to protect the body from harmful pathogens. Also, IL-1 and IL-18 can activate other immune cells, such as macrophages, which can help clear away infection and promote tissue repair. Overall, the escape of both IL-1 and IL-18 through each hole caused by GSDMD is crucial in triggering a substantial inflammatory response. The receptor - RANKL (receptor activator of p-NF-B ligand) is one of several genes that can be expressed as a result of activated IL-1. The presence of pyroptosis may therefore be determined by signals which include Caspase 1 activation, GSDMD cleavage, IL-1, and IL-18 development and secretion (8). (Figure 1). Four key inflammasomes have been best characterized, namely NLRP1, NLRP3, NLRC4, and AIM2 (12).

NLRP1 is known for being the first protein to form an inflammasome, as well as its probable function in host innate immunity and inflammatory disorders. The NLRP3 gene on human chromosome 1 encodes NLRP3, which is mostly expressed in macrophages (7,13).

Inflammasome assembly is distinctive in that it is brought about by both external and endogenous stimuli. The NLRP3 protein, a member of the family of NOD-like receptors, is one major component of the innate immune system responsible for identifying pathogens and responding to potential infections. It has a broad spectrum of signal detection capabilities, including Pathogen-Associated Molecular Patterns (PAMPs) and Damage-Associated Molecular Patterns (DAMPs), as well as bacterial toxins. PAMPs are molecules found on the surfaces of bacteria and other pathogens that act as a warning signal to the immune system. NLRP3 recognizes these molecules and can activate an inflammatory response to eliminate the threat. DAMPs are molecules released from damaged and dying cells that can activate NLRP3 and result in an inflammatory response. In addition, NLRP3 can detect bacterial toxins and activate an immune response (14). As these inflammasomes are activated, inflammatory cytokines, including IFN- and IL-18, are secreted. The release of these cytokines can trigger both periodontal disease and inflammation in the body (15,16).

How inflammasomes contribute to periodontitis pathogenesis

Inflammasomes are protein complexes that play significant roles in the pathogenesis of periodontitis. Inflammasomes are activated in response to inflammatory cues such as bacterial strains or other irritants. Once activated, they begin producing pro-inflammatory cytokines, which are proteins that promote inflammation. These cytokines lead to the infiltration of immune cells into the surrounding tissue, which can further aggravate the inflammatory response. In addition, a type of planned cell death known as apoptosis may also be induced by inflammasomes. This can help remove damaged or infected cells from the tissues. Inflammasomes can also activate other enzymes and pathways that contribute to periodontitis pathogenesis. For example, they can induce the production of matrix metalloproteinase (MMP), which is an enzyme involved in tissue degradation. Inflammasomes play an essential role in the

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pathogenesis of periodontitis (1-3). Increased immune and inflammatory responses are linked to bacteria that cause periodontitis (1,6).

Dysregulation of pro-inflammatory and anti-inflammatory cytokines is one of the molecular mechanisms that destroy periodontal tissues. It has long been established that cytokines are crucial for maintaining tissue homeostasis, controlling immunological responses, and communication between cells. As a result of inflammation, Gram-negative bacteria release LPS and pro-inflammatory cytokines, which trigger the release of pro-inflammatory cytokines. Alveolar bone loss has consistently been associated with higher cytokine levels (17).

The cytokine interleukin-1 (IL-1) is crucial in the human body and is a significant factor in periodontitis. IL-1β is primarily secreted, and macrophages actively participate in the inflammatory response. In periodontitis, IL-1β is believed to play a role in controlling the production of pro-inflammatory cytokines, which induce inflammation and remove periodontal tissue. IL-1β has been identified as a crucial mediator of each inflammatory reaction in the periodontal tissue. It has also been shown to increase the expression of matrix metalloproteinases. It contributes to the degeneration of periodontal tissue and increases the production of pro-inflammatory mediators, including TNF- and IL-6. IL-1 is also believed to be crucial for stimulating bone growth and resorption by osteoclasts. IL-1β is an essential target for therapeutic interventions in periodontitis because of its role in an inflammatory response and bone resorption. The administration of IL-1 β inhibitors caused relative to the control locations resulted in a 50% decrease in radiographic bone loss, indicating that IL-1 may contribute to periodontal disease (18,19). High levels of inflammation are linked to inflammasome triggering; therefore, it must be tightly controlled to avoid abnormal activation. The host regulates inflammation under normal and healthy conditions by activating inflammasomes (20).

Numerous earlier studies have emphasized the significance of the proper activation of inflammasomes in the etiology of periodontal disease. Inflammasomes play a role in the control of inflammation in both healthy and diseased individuals. A better understanding of the various methods that can be employed to control excessive inflammatory responses at the cellular and molecular levels may help develop treatments and preventative measures that are more successful in treating periodontal and systemic diseases linked to it (21-23).

Inflammasomes and Periodontal Pathogens

Changing the symbiotic relationship to dysbiosis and causing periodontal damage is primarily a result of Porphyromonas gingivalis, the keystone pathogen (22).

A key indicator for maintaining periodontal homeostasis is activation of the NLRP3 inflammasome. Different immune responses may be launched during microbial invasion as a result of recognizing commensal and pathogenic strains.

It has also been found that activation of NLRP3 inflammasomes during periodontal infection with P. gingivalis increased Caspase-1 activation and released mature IL-1, thereby promoting cytotoxicity (22).

Among the bacteria that cause periodontitis are Porphyromonas gingivalis, Tannerella denticola, and Treponema forsythia. These bacteria have been found to activate caspase-1 and caspase-4, two important proteases that are involved in the inflammatory response. Caspase-1 and caspase-4 are critical components of the immune system's response to inflammation. They are activated by various pro-inflammatory mediators, including the three periodontitis-causing bacteria. When activated, these caspases induce the formation of inflammatory cytokines, which mediate the local inflammatory response in periodontitis. Recent evidence suggests that Porphyromonas gingivalis, Tannerella Caspase-1, and Caspase-4 are activated by denticola and Treponema forsythia through different mechanisms. In particular, P. gingivalis has been shown to activate these caspases. This may enhance the immune and inflammatory response to periodontitis (24).

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Clinical relevance of inflammasomes with periodontal disease

Autoinflammatory disorders are linked to inappropriate caspase-1 activation, which is brought on by inflammasome mutations (25).

Additionally, caspase-1 has a role in the development of several disorders. Caspase-1 a crucial an integral part of the innate resistant system which plays a crucial part in periodontitis. Caspase-1 is a protein that acts as an enzyme in the inflammation operation of the body and does responsible for each production of inflammatory cytokines. It is suspected of being engaged in the production of pro-inflammatory cytokines, such as IL-1 and IL-18, linked to periodontal diseases. Caspase-1 expresses itself mostly in monocytes and macrophages, which are a part of the inflammatory process of the periodontium. It is activated by mediators of inflammation like lipopolysaccharide and interleukin-1. Upon activation, it triggers the cleavage of pro-inflammatory cytokines which contributes to the progression of periodontitis. Each role of caspase-1 in periodontitis is also linked to the activation of matrix metalloproteinases (MMPs). MMPs are in charge of connective tissue deterioration and are involved in the destruction of the periodontal ligament (26). Caspases-1 are also important components of the immune system, which allows the body to defend itself from virulent organisms.

Several studies have suggested that the NLRP3 inflammasome is primarily responsible for caspase-1 activation. Therefore, caspase-1 plays an important role in modulating NLRP3 activation, thereby modulating the inflammasome function. Inflammasomes NLRP3 and NLRP4 are proposed to be key players in periodontal diseases because of their ability to respond to LPS, bacterial RNA, and peptidoglycans (PAMPs and DAMPs) (23,27). The inflammasome at NLRP3 plays a prominent role in periodontitis development. Many stimulating factors activate the NLRP3 inflammasome, including infections and inflammation. When NLRP3 is triggered, the enzyme caspase 1 is activated, which is accountable for processing, along with the activation of pro-inflammatory cytokines (such as IL-1 and IL-18). Through caspase 1 activation, caspase 3 is activated in response to a variety of cellular stresses in periodontitis, which increases the generation of inflammatory cytokines, causing an increase in inflammation and destruction of periodontal tissue. This increased inflammation leads to increased levels of tissue destruction, resulting in periodontal inflammation, dental plaque formation, and gingival recession (28,29).

NLRP3 and IL-1 expression levels were positively correlated in gingival tissues, according to a clinical investigation. It is also found that NLRP3 was significantly expressed more in patients with periodontal disease than in controls. In another clinical trial of the saliva of individuals with periodontitis, the outcomes of the study demonstrated decreased NLRP3 and IL-1 levels compared to those in the control group (30-32).

These findings suggest that the NLRP3 inflammasome and its etiology are vital in periodontal disease. Additionally, many NLRP3 inflammasome-related conditions, including rheumatoid arthritis (RA), diabetes, and Alzheimer's disease, are thought to be at risk because of periodontal disease. The activation of IL-1 and NLRP3 inflammasomes may be related to chronic inflammation and infection in periodontitis (33-35). A high level of NLRP3 activation is associated with type 2 diabetes, and metformin helps control inflammasome activation. Therefore, metformin may be an effective NLRP3 inhibitor (29). Furthermore, inflammasomes, including NLRP3, predominantly activate macrophage caspase-1 and increase IL-1 levels in the periodontal ligament and serum of aged mice with poor alveolar bone health. Mice that were administered the NLRP3-suppressing drug MCC950 showed significant reductions in alveolar bone loss as a result of treatment (36). Recent improvements have been made in understanding the critical role of NLRP3 inflammasomes during periapical inflammation. Therefore, it may be possible to target the NLRP3 inflammasome for anti-inflammatory treatment (37,38). In the future, inhibitors of the NLRP3 inflammasome signaling pathway may also help treat inflammatory diseases (39).

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Inflammasomes in Periodontal Disease: Key Players in Pathogenesis and Potential Therapeutic Targets

Periodontal disease affects a significant proportion of the population and can lead to tooth loss and other systemic complications. The pathogenesis of the periodontal disease is complex and involves an interplay between host immune responses and the oral microbiome. Inflammasomes are key players in the innate immune system, and their dysregulation has been implicated in the pathogenesis of many inflammatory conditions, including periodontal diseases [43].

Inflammasome activation in periodontal disease: The oral microbiome can activate inflammasomes via various mechanisms, including bacterial lipopolysaccharides and damage-associated molecular patterns (DAMPs) released during tissue damage. Inflammasome activation leads to the production of pro-inflammatory cytokines, such as interleukin (IL)-1β and IL-18, which drive the recruitment and activation of immune cells and contribute to tissue destruction [44]. Inflammasome activation has been linked to the progression of periodontal disease. Studies have shown that inflammasome activation is increased in patients with periodontitis and is correlated with disease severity. Inflammasome-mediated inflammation can exacerbate tissue damage by promoting bone resorption and inhibiting bone formation.

Therapeutic targets: Given the potential role of inflammasomes in periodontal disease pathogenesis, targeting inflammasomes may be a potential therapeutic strategy for managing periodontitis. Inhibition of inflammasome activation or downstream signaling pathways may reduce inflammation and tissue destruction. However, the efficacy and safety of inflammasome-targeted therapies require further evaluation in clinical studies [44,45]. Inflammasomes are essential players in the pathogenesis of periodontal disease and offer potential therapeutic targets for managing periodontitis. Future studies should focus on better understanding the role of inflammasomes in periodontal disease and evaluating the safety and efficacy of inflammasome-targeted therapies [46].

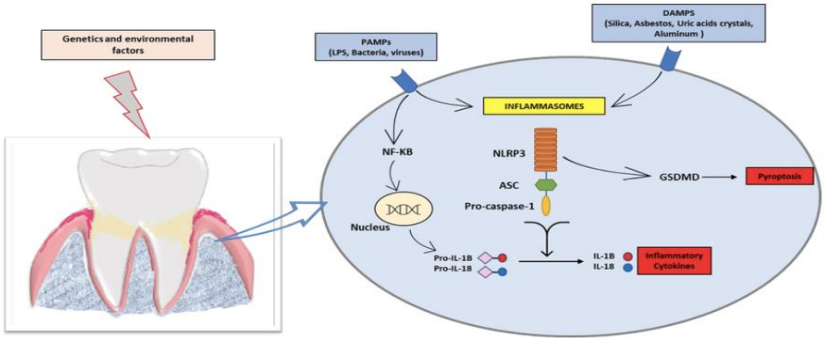

FIGURE 1. The pathophysiological pathway of NLRP3 inflammasomes activation by periodontitis. The NLRP3 structure contains three domains: NLRP3, adaptor apoptosis speck (ASC), and pro-caspase-1. Activation of the pathway results in binding of the three domains forming NLRP3 inflammasome complex. This activation is induced mainly by *Porphyromonas gingivalis* pathogens in periodontitis, which is influenced by genetics and environmental factors. The signals from pathogen-associated molecular patterns (PAMPs) or by damage-associated molecular patterns (DAMPs) which activates the NF-κB pathway to release pro IL-1β and IL-18 from nucleus into the cytoplasm. The activation and formation of NLRP3 inflammasome complex has two main effects: (i) activation of Gasdermin D GSDMD and inducing pyroptosis and/or (ii) active caspase-1 which then cleaves pro-IL-1β and pro-IL-18 into their active forms IL-1β and IL-18 as proinflammatory cytokines that released out the cell causing periodontitis.

TABLE 1: shows numerous works in the literature examining the impact of various inflammasome types on the pathogenesis of periodontal diseases.

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Authors and year	Investigated molecules	Study group (Animal/Human)	Results	Reference
Fernanda R G. Rocha, et al.2020.	NLRP3 inflammasome and of Caspase-1	Male adult mice (In vivo)	A pro-resorption effect of Caspase-1 was observed in experimental periodontal disease, and Nlrp3 inflammasome did not contribute significantly to inflammation.	(40)
Pei-Hui Ding, et al. 2020.	NLRPs inflammasome and IL-1β.	Patients with severe chronic Periodontitis	NLRP3 and IL-1 were found to be significantly expressed in chronic periodontitis gingival tissues.	(22)
Dan Zhao1, et al. (2016)	NLRP1 and NLRP3 inflammasomes	Human Periodontal Ligament CellsHPDLCs (In vitro)	The release of IL-1 was associated with cyclic stretch activating the NLRP3 and NLRP1 inflammasomes and pyroptosis in human periodontal ligament cells-related mechanism (HPDLCs).	(41)
Hou L, et al. (2022). .	NLRP3 inflammasome	Mice (In vivo)	THP-1 cells and mouse periodontal tissues expressed higher levels of the NLRP3 inflammasome pathway when A20 is knocked off. A20 overexpression, on the other hand, suppressed the NLRP3 inflammasome pathway. A20 reduces periodontal bone resorption as well as NLRP3-mediated M1 macrophage polarization.	(42)
Han Y, et al. (2022).	NLRP3 inflammasome	Mice (In vivo)	By skewing proinflammatory M1 macrophages, leptin accelerates the development of periodontitis, and inhibiting leptin/NLRP3 signaling may be a viable strategy for treating periodontitis.	(43)
Chen Y, et al. (2020).	NLRP3 inflammasome	Mice	A mouse lacking NLRP3 displays significantly reduced levels of alveolar bone loss, which suggests that NLRP3 plays an important role in the osteoclastic differentiation of periodontal tissues. In addition, the NLRP3 inflammasome also actively participate in the activation of pro-inflammatory cytokines. It includes IL-1β. The IL-1β	(44)

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			has demonstrated inducing osteo clastogenesis.	
Surlin P, et al. (2021).	Inflammasome NLRP3, Caspase (CASP-1), and Interlukin (IL-18).	Patients with Periodontal disease and chronic hepatitis C.	When NLRP3 is activated, proinflammatory cytokines (IL-1β), are produced, which can cause inflammation and tissue damage. Furthermore, NLRP3 activation can lead to increased bone resorption, which is a hallmark of periodontal pathogenesis. In chronic hepatitis C, NLRP3 is found to be activated in the hepatocytes.	(45)
Bostanci N, et al. (2009).	NALP3, (ASC), NLRP2 (NLR family, PYD-containing protein 2), IL-1beta and IL-18.	In this study, gingivitis chronic periodontitis, generalized aggressive periodontitis, and healthy subjects were compared	A comparison of periodontitis samples with healthy gingival tissues revealed significantly increased expression of inflammasomes and other related molecules. This suggests that inflammasomes may be involved in the initiation and maintenance of periodontal inflammation. Furthermore, inflammasome expression was also regulated by proinflammatory cytokines and lipopolysaccharides, according to the study.	(31)

Exploring the Molecular Mechanisms of Inflammasomes in Periodontal Disease Pathogenesis

The immune response to periodontal pathogens plays a significant role in disease pathogenesis. Inflammasomes are intracellular multiprotein complexes that sense pathogen-associated molecular patterns (PAMPs) and danger-associated molecular patterns (DAMPs), triggering the activation of caspase-1 and the release of the pro-inflammatory cytokines IL-1β and IL-18. The inflammasome consists of a sensor protein, such as NLRP3, AIM2, or NLRC4, and an adaptor protein, ASC, and caspase-1. The sensor protein recognizes PAMPs or DAMPs and oligomerizes and recruits ASC and pro-caspase-1 to form the inflammasome complex. Pro-caspase-1 undergoes autocatalytic cleavage to form the active caspase-1, which cleaves pro-IL-1β and pro-IL-18 to generate the mature cytokines [47, 48].

Role of Inflammasomes in Periodontal Disease: Studies have shown that inflammasome activation increases in periodontal tissues and gingival crevicular fluid (GCF) in patients with periodontal disease. NLRP3 is the most widely studied inflammasome sensor in periodontal disease. NLRP3 inflammasome activation leads to the production of IL-1β, a potent pro-inflammatory cytokine involved in the recruitment and activation of immune cells. IL-1β is also involved in bone resorption, a hallmark of periodontal disease [47]. Inflammasomes are molecular complexes that play a crucial role in regulating innate immune response and have been implicated in the pathogenesis of several inflammatory diseases, including periodontitis. Inflammasomes are cytosolic multiprotein complexes that activate caspase-1, which in turn processes and activates the pro-inflammatory cytokines interleukin (IL)-1β and IL-18. In periodontal disease, inflammasomes are

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activated by the presence of bacterial components, such as lipopolysaccharides (LPS) and peptidoglycans (PGN), which are recognized by pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs). Activating inflammasomes leads to the production and release of IL-1β and IL-18, potent pro-inflammatory cytokines that promote tissue destruction and bone resorption in periodontitis [18]. Several studies have demonstrated the involvement of various inflammasome components in the pathogenesis of the periodontal disease. For example, NLRP3, a member of the NLR family, is upregulated in periodontitis, and its activation has been linked to increased IL-1β production and periodontal tissue destruction (1, 2). Another inflammasome component, AIM2, is upregulated in periodontitis, and its activation has been linked to increased IL-1β and IL-18 production (3, 4).

Furthermore, inflammasome activation has been linked to osteoclast formation, responsible for bone resorption in periodontitis. The activation of NLRP3 inflammasome leads to the production of receptor activators of nuclear factor kappa-B ligand (RANKL), a cytokine that induces osteoclastogenesis and bone resorption (5, 6). In addition, IL-1β and IL-18 have also been shown to promote osteoclast differentiation and bone resorption (7, 8).

Targeting inflammasomes has emerged as a potential therapeutic approach for treating periodontal diseases. Several inflammasome inhibitors have been developed and have been tested in preclinical studies. For example, MCC950, a selective NLRP3 inflammasome inhibitor, reduced inflammation, and bone loss in experimental periodontitis (9). Other inflammasome inhibitors, such as VX-765 and CY-09, have shown promising results in preclinical studies (10, 11).

Inflammasomes and Host-Microbial Interactions in the Pathogenesis of Periodontal Disease

Inflammasomes are molecular complexes that play a crucial role in regulating the innate immune response and have been implicated in the pathogenesis of several inflammatory diseases, including periodontitis.

Inflammasomes and host-microbial interactions (inflammasomes) are activated by the recognition of microbe-associated molecular patterns (MAMPs) and danger-associated molecular patterns (DAMPs) by pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs). In periodontal disease, bacterial biofilms on tooth surfaces are recognized by TLRs and NLRs, leading to the activation of inflammasomes and subsequent release of pro-inflammatory cytokines, such as interleukin (IL)-1β and IL-18. Inflammasome activation also leads to the formation of pyroptotic cells, which are involved in host defense against microbial invasion [1].

Inflammasome Components in Periodontal Disease: Inflammasome components have been implicated in the pathogenesis of periodontal disease. For example, NLRP3 inflammasome activation has been shown to promote IL-1β production and osteoclastogenesis, leading to tissue destruction and bone resorption in periodontitis [2, 3]. Activation of the AIM2 inflammasome has also been linked to IL-1β production and periodontal tissue destruction (4). In addition, activation of the NLRP6 inflammasome regulates the composition of the oral microbiota and prevents the development of periodontitis in mice [5].

Interactions Between Inflammasomes and Other Immune Pathways: Inflammasomes are not the only immune pathways involved in the pathogenesis of the periodontal disease. Other immune pathways, such as the complement system, cytokines, and chemokines, also play essential roles in the pathogenesis of periodontitis. Inflammasome activation leads to the production of pro-inflammatory cytokines such as IL-1β and IL-18, which in turn promote the production of other cytokines and chemokines involved in the recruitment of immune cells to the site of inflammation [6].

Therapeutic Implications: Targeting inflammasomes and other immune pathways involved in the pathogenesis of periodontal disease has emerged as a potential therapeutic approach. Several inflammasome inhibitors have

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been developed and tested in preclinical studies, including MCC950 and VX-765, which have shown promising results in reducing inflammation and bone loss in experimental periodontitis [7, 8]. In addition, targeting other immune pathways, such as the complement system and cytokines, has shown potential for treating periodontitis [9, 10]. Inflammasomes play a crucial role in host-microbial interactions and the pathogenesis of the periodontal disease. Targeting inflammasomes and other immune pathways involved in the pathogenesis of periodontitis may represent a promising therapeutic approach for treating this chronic inflammatory disease [49].

The role of inflammasomes in periodontitis and implications for novel therapeutic approaches

Inflammasomes are intracellular multiprotein complexes activated in response to various stimuli such as microbial pathogens, danger signals, and host-derived molecules. The canonical inflammasome pathway involves assembling a sensor protein, such as NLRP3, with an adaptor protein, ASC, and an effector protein, caspase-1. The activated inflammasome cleaves the precursor forms of proinflammatory cytokines, such as interleukin (IL)-1β and IL-18, into their active forms, leading to the initiation and amplification of the inflammatory response. Several studies have demonstrated that inflammasomes play a critical role in periodontitis pathogenesis. For instance, NLRP3 inflammasome activation is increased in the gingival tissues of patients with periodontitis compared to healthy controls, and its expression correlates with disease severity [1, 2]. Inflammasome activation is also associated with the release of proinflammatory cytokines such as IL-1β and IL-18, which are implicated in the destruction of periodontal tissues. Furthermore, animal studies have shown that genetic or pharmacological inhibition of inflammasome components attenuates periodontal inflammation and bone loss [15, 19]. Dysbiotic microbial communities in periodontitis trigger inflammasome activation through several mechanisms. Bacterial components such as lipopolysaccharides and extracellular DNA can activate the NLRP3 inflammasome through Toll-like receptor (TLR) signaling [11, 18]. The release of host-derived molecules, such as ATP, uric acid, and reactive oxygen species, can also activate the inflammasome through the purinergic receptor P2X7 and the NADPH oxidase complex [10]. Given the crucial role of inflammasomes in periodontitis, several novel therapeutic approaches have been proposed to target these pathways. One approach involves the use of small-molecule inhibitors targeting NLRP3 or caspase-1. Several compounds, such as MCC950 and CY-09, have shown promising results in preclinical studies [27]. Another approach involves using probiotics or commensal bacteria to modulate inflammasome activation and restore the microbial community balance [13]. Furthermore, strategies that target the upstream signaling pathways of inflammasome activation, such as TLR or P2X7, have also been proposed [14].

The NLRP3 inflammasome is activated in response to various periodontal pathogens, including Porphyromonas gingivalis, Aggregatibacter actinomycetemcomitans, and Tannerella forsythia. Activation of the NLRP3 inflammasome leads to the secretion of mature IL-1β and IL-18, which promotes inflammation and tissue destruction in the periodontium [32]. Furthermore, genetic studies have identified several polymorphisms in the genes encoding inflammasome components associated with an increased risk of periodontitis. Given the involvement of inflammasomes in periodontitis pathogenesis, they represent promising targets for novel therapeutic approaches. Several studies have investigated the use of inflammasome inhibitors in treating periodontitis. A recent study demonstrated that treatment with the NLRP3 inflammasome inhibitor MCC950 reduced bone loss and inflammation in a mouse periodontitis model [41]. Similarly, the use of IL-1β inhibitors such as anakinra and canakinumab is effective in reducing inflammation and improving clinical outcomes in patients with rheumatoid arthritis, which shares many pathogenic mechanisms with periodontitis [50].

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CONCLUSION

There are several families of inflammasomes, each with a unique set of functions, the majority of which are currently unknown. A key component of innate immunity, inflammasomes are important players in the inflammatory process, which opens up the prospect of novel targets for modulating host responses and enabling an effective response to bacterial challenges in the future.

Periodontal tissues, gingival crevicular fluid, and saliva contain higher levels of inflammasome components. Periodontal host responses may be affected by the molecular processes that activate abnormal inflammasomes in chronic conditions. The role of inflammasome pathways in the treatment of periodontal disease has gained significant attention in recent years.

OUTLOOK

Since Inflammasomes have been identified as protein platforms that regulate IL-1 and IL-18 processing, innate immunology has advanced significantly. P. gingivalis-treated THP-1 cells knocked out with siRNAs for NLRP3, Caspase-1, and Caspase-4 were shown to produce less IL-1 periodontitis and alveolar bone resorption, which are essential for the dysregulated immuno-inflammatory response associated with periodontal disease.

Inflammasomes have gained attention in recent years as a possible cause of periodontitis, due to their potential to provide light on the underlying causes of the disease. The inflammasome is a complex of proteins that serve as a contributing factor in the immune system's inflammatory response to pathogens and other triggers. It has been found that inflammasome activation is associated with periodontitis in several studies. Activation of the inflammasome produces pro-inflammatory cytokines, which are accountable for the inflammatory reaction to the disease. On top of that, studies have identified modification of inflammasome-related gene expression in periodontal tissues, indicating that the inflammasome has a role to play in the progression of periodontitis. In addition, the investigation into understanding the function of the inflammasome and the pathogenesis of periodontitis. These results might pave the way for a new therapeutic intervention that targets inflammasome-regulated pathways implicated in periodontal disease as well as a massive effort to find and develop small-molecule treatments that specifically suppress inflammasome activation.

Further investigation of the function of inflammasomes in periodontal disease. This could include exploring how certain lifestyle factors, such as smoking, can influence inflammasome activity and cause of periodontal disease. More research and in-depth analysis are needed to examine how therapeutic interventions might be used to target the reaction of inflammasomes to periodontal disease. In conclusion, the role of the inflammasome in periodontal disease and its pathogenesis is an evolving and rapidly expanding area of research. Further study in this area might lead to the development of novel treatments and therapies to better understand the role of inflammasomes in periodontal disease.

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