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Role of Inflammasomes in Periodontitis

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Abstract: ***Periodontitis is a chronic inflammatory disease characterized by the destruction of periodontal tissues, primarily driven by a dysregulated host immune response to subgingival biofilm. Recent advances in molecular immunology have highlighted the critical role of inflammasomes-intracellular multiprotein complexes-in orchestrating innate immune responses in periodontal disease. Among these, the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome has garnered significant attention due to its ability to activate caspase-1, leading to the maturation and secretion of interleukin (IL)-1β and IL-18, pivotal cytokines in periodontal inflammation and tissue breakdown. Dysregulated activation of inflammasomes contributes to excessive inflammatory cytokine release, increased osteoclastogenesis, and progressive alveolar bone loss. Additionally, microbial components such as lipopolysaccharides and danger-associated molecular patterns (DAMPs) act as potent triggers for inflammasome activation in gingival tissues. Understanding the role of inflammasomes provides novel insights into the immunopathogenesis of periodontitis and presents potential therapeutic targets for modulating host response. Targeted inhibition of inflammasome components or downstream cytokine pathways may offer promising adjunctive strategies in periodontal therapy. This review highlights current evidence on the involvement of inflammasomes in periodontitis and underscores their potential as biomarkers and therapeutic targets in the management of periodontal diseases.***

Keywords: Periodontitis, Inflammasome, Innate Immunity, Interleukin-18, DAMPS

1. Introduction

Periodontitis is a chronic, multifactorial inflammatory disease affecting the supporting structures of the teeth, leading to connective tissue attachment loss and progressive alveolar bone resorption. It results from a complex interplay between the subgingival microbiota and the host immune response. While microbial dysbiosis acts as the initial trigger, it is the dysregulated and exaggerated host inflammatory response that determines the severity and progression of the disease process [1,2]. In recent years, increasing attention has been given to the molecular mechanisms that regulate innate immunity in periodontal tissues, among which inflammasomes have emerged as critical components.

Inflammasomes are cytosolic multiprotein complexes that function as intracellular pattern recognition platforms. They are primarily responsible for sensing pathogenic microorganisms and endogenous danger signals, leading to the activation of caspase-1 and subsequent processing and secretion of key inflammatory cytokines, particularly interleukin-1 beta (IL-1β) and interleukin-18 (IL-18) [3]. These cytokines are central mediators in periodontal inflammation, with IL-1β in particular known to drive osteoclastogenesis, matrix metalloproteinase activation, and connective tissue degradation [4].

Several types of inflammasomes have been described in the literature, including the NOD-like receptor family pyrin domain-containing 3 (NLRP3), NOD-like receptor family CARD domain-containing 4 (NLRC4), and the Absent in Melanoma 2 (AIM2) inflammasomes. Among these, AIM2 has gained prominence in the context of periodontitis due to its role in recognizing cytosolic double-stranded DNA from periodontal pathogens and initiating inflammatory signalling cascades [5]. Studies have demonstrated elevated expression of AIM2 and its downstream effectors in gingival tissues from patients with chronic periodontitis compared to healthy controls [6].

Activation of inflammasomes not only leads to cytokine maturation but also induces a specific form of programmed cell death known as pyroptosis, which contributes to epithelial barrier breakdown and perpetuation of the inflammatory cycle [7]. The chronic activation of these pathways, particularly in the presence of persistent microbial stimulation, can result in sustained inflammation, alveolar bone destruction, and progression of periodontal disease.

Recent research also points to the role of inflammasomes as potential biomarkers for disease activity and severity, and as promising therapeutic targets. Modulating inflammasome activity through pharmacological inhibitors or gene silencing strategies has shown encouraging results in preclinical models of periodontitis [8].

Given their central role in coordinating innate immune responses and influencing periodontal tissue homeostasis, a deeper understanding of inflammasome biology is essential. This review aims to explore the current evidence on the role of inflammasomes in the pathogenesis of periodontitis and discusses their potential utility in diagnostic and therapeutic strategies.

2. History of Inflammasomes

The concept of inflammasomes was first introduced in 2002 by Jürg Tschopp and colleagues, who identified a cytosolic protein complex responsible for the activation of caspase-1, leading to the maturation and secretion of the pro-inflammatory cytokines interleukin (IL)-1β and IL-18 [8]. In this pioneering study, the NLRP1 inflammasome was described as a multiprotein complex composed of a nucleotide-binding domain and leucine-rich repeat receptor

(NLR), the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD), and pro-caspase-1.

This discovery was soon followed by the identification of other sensor proteins, most notably NLRP3, which was shown to be activated by a diverse array of pathogen-associated and danger-associated molecular patterns (PAMPs and DAMPs), including ATP, urate crystals, and bacterial toxins [9,10]. The NLRP3 inflammasome became the most extensively studied, particularly for its role in sterile inflammation.

Over the next decade, additional inflammasome sensors were identified. The NLRC4 inflammasome, which detects bacterial flagellin and components of the type III secretion system, was characterized in 2006 [11], while the AIM2 inflammasome, activated by cytoplasmic double-stranded DNA, was described in 2009 [12]. The Pyrin inflammasome, implicated in the sensing of microbial modifications to Rho GTPases, was also recognized as a critical player in innate immune signalling and autoinflammatory conditions [13].

By the early 2010s, inflammasome research had expanded to include links to numerous disease states. Gain-of-function mutations in the NLRP3 gene were shown to cause cryopyrin-associated periodic syndromes (CAPS), while aberrant inflammasome activation was implicated in conditions such as gout, atherosclerosis, type 2 diabetes, Alzheimer's disease, and periodontitis [14]. This era also saw the identification of non-canonical inflammasome pathways, particularly involving caspase-11 in mice (caspase-4/5 in humans), which are activated directly by cytoplasmic lipopolysaccharide independent of classical NLRs [15].

More recently, a major advance was the discovery of gasdermin D (GSDMD) as the terminal effector of pyroptosis, a form of programmed lytic cell death associated with inflammasome activation [16]. Additional findings have clarified the roles of mitochondrial dysfunction, ionic fluxes (e.g., K^+ efflux), reactive oxygen species (ROS), and post-translational modifications in the fine regulation of inflammasome assembly and activation [17].

From its discovery in 2002 to its current role as a pivotal component of immune homeostasis and disease, the history of inflammasomes reflects a trajectory of continuous scientific progress and growing translational significance.

3. Classification of Inflammasomes

Inflammasomes are classified based on the nature of their sensor molecules, which detect specific pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs). These sensors typically belong to the pattern recognition receptor (PRR) families, including NOD-like receptors (NLRs), AIM2-like receptors (ALRs), and Pyrin. Accordingly, inflammasomes are broadly classified into canonical and non-canonical types, with further subclassification based on the identity of the sensor.

1) Canonical Inflammasomes

These inflammasomes activate caspase-1, leading to the cleavage of pro-IL-1β and pro-IL-18 and the induction of pyroptosis via gasdermin D.

a) NLR family-based inflammasomes

- NLRP1 Inflammasome: First discovered inflammasome; activated by *Bacillus anthracis* lethal toxin and muramyl dipeptide (MDP) [18]. Unique among NLRs due to its FIIND (function-to-find domain) and CARD domain.
- NLRP3 Inflammasome: The most extensively studied; responds to a wide range of stimuli including ATP, uric acid crystals, amyloid-β, and pathogens [19]. Requires a priming (NF-κB activation) and activation step (ion flux, ROS, lysosomal damage).
- NLRC4 Inflammasome: Activated in response to bacterial components like flagellin and type III secretion system proteins [20]. Interacts with NAIPs (NLR apoptosis inhibitory proteins) for ligand specificity.
- NLRP6 and NLRP12 Inflammasomes: Involved in maintaining gut homeostasis and mucosal immunity [21,22].
  Less understood; implicated in colitis and tumorigenesis.

b) ALR family-based inflammasome

- AIM2 Inflammasome (Absent in Melanoma 2) Recognizes double-stranded DNA (dsDNA) in the cytosol from viruses, bacteria, or damaged host cells (6). Functions through a HIN-200 domain and recruits ASC for caspase-1 activation.

c) TRIM family and Pyrin Inflammasome

- Pyrin Inflammasome
  Senses pathogen-induced inactivation of Rho GTPases via bacterial toxins like *Clostridium difficile* TcdB [23]. Mutations are linked to familial Mediterranean fever (FMF) and autoinflammatory disorders.

2) Non-Canonical Inflammasomes

These inflammasomes do not rely on classical PRRs. Instead, they are activated directly by cytosolic LPS and function through caspase-11 in mice and caspase-4/5 in humans [24]. Their activation leads to:

- Cleavage of gasdermin D, inducing pyroptosis.
- Indirect activation of NLRP3 inflammasome via K^+ efflux and cell lysis.

3) Functional Classification Based on Ligands

Inflammasomes may also be functionally classified based on the nature of the stimuli:

- PAMP-activated: e.g., NLRC4, AIM2 (bacterial and viral components).
- DAMP-activated: e.g., NLRP3 (crystals, ROS, mitochondrial DNA).
- Homeostasis-perturbation sensors: e.g., Pyrin (detects changes in cytoskeletal integrity).

4) Species-Specific Inflammasomes

Certain inflammasomes are species-specific:

- NLRP1 isoforms vary between humans and rodents.
- NAIP proteins differ in number and specificity between species.

4. Structural components of inflammasomes

1) Pattern Recognition Receptors (PRRs):

- NOD-like Receptors (NLRs): These include NLRP1, NLRP3, NLRC4, and others. NLRs are cytosolic receptors

that detect intracellular PAMPs (pathogen-associated molecular patterns) and DAMPs (damage-associated molecular patterns) [23].
- AIM2-like Receptors (ALRs): AIM2 (Absent in Melanoma 2) detects cytosolic double-stranded DNA [23].
- Pyrin: Recognizes alterations in the host cell cytoskeleton induced by bacterial toxins and effector proteins [23].

2) **Adapter Protein:** ASC (Apoptosis-associated Speck-like protein containing a CARD) is an essential adaptor protein that bridges the receptor proteins and pro-caspase-1. ASC contains a pyrin domain (PYD) and a caspase recruitment domain (CARD), facilitating the formation of the inflammasome complex [9].

3) **Effector Proteins:** Caspase-1 is a crucial protease that, when activated, processes pro-inflammatory cytokines pro-IL-1β and pro-IL-18 into their active forms. Caspase1 also induces pyroptosis, a form of programmed cell death associated with inflammation [23]

5. Activation mechanism of inflammasomes

Inflammasomes are pivotal components of the innate immune system, acting as cytosolic sensors that detect both pathogen-associated molecular patterns (PAMPs), such as bacterial lipopolysaccharides and viral RNA, and danger-associated molecular patterns (DAMPs), including extracellular adenosine triphosphate (ATP) and uric acid crystals. Upon recognition of these stimuli, inflammasomes initiate potent inflammatory cascades aimed at eliminating pathogens and restoring tissue homeostasis

1) Assembly of the Inflammasome Complex

Several types of canonical inflammasomes have been implicated in periodontal pathogenesis, each with distinct ligand specificity and activation mechanisms:
- *NLRP3 Inflammasome*: The nucleotide-binding domain and leucine-rich repeat-containing protein 3 (NLRP3) inflammasome is the most extensively studied. It is activated in response to a wide spectrum of stimuli, including bacterial infection, metabolic stress, and environmental irritants. Upon stimulation, NLRP3 oligomerizes and recruits the adaptor protein apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) via pyrin domain (PYD) interactions. ASC then binds pro-caspase-1 through caspase recruitment domain (CARD) interactions, facilitating the formation of the inflammasome complex [24].
- *AIM2 Inflammasome*: The absent in melanoma 2 (AIM2) inflammasome responds to cytosolic double-stranded DNA from viral or bacterial sources. Binding of DNA triggers AIM2 oligomerization and subsequent recruitment of ASC and pro-caspase-1, assembling a functional inflammasome complex [24].
- *NLRP1 and NLRC4 Inflammasomes*: The NLRP1 inflammasome is activated by bacterial toxins and intracellular stress signals, whereas the NLRC4 inflammasome responds to bacterial flagellin and structural components of type III and type IV secretion systems. Both receptors undergo oligomerization and ASC-mediated recruitment of pro-caspase-1, culminating in caspase-1 activation [24].

2) Caspase-1 Activation and Cytokine Maturation

The formation of the inflammasome complex leads to the autoproteolytic cleavage of pro-caspase-1 into its active form, caspase-1. Active caspase-1 is essential for the proteolytic processing of the inactive precursors of interleukin-1 beta (IL-1β) and interleukin-18 (IL-18) into their mature, biologically active forms. These cytokines are then secreted into the extracellular environment, where they function to amplify and sustain the inflammatory response in periodontal tissues [24].

3) Pyroptosis: Inflammatory Cell Death

In addition to cytokine maturation, activated caspase-1 induces **pyroptosis**, a pro-inflammatory, lytic form of programmed cell death characterized by cellular swelling, membrane rupture, and release of intracellular contents. This process not only eliminates infected or damaged cells but also exacerbates inflammation by releasing DAMPs and inflammatory mediators into the surrounding tissues. Pyroptosis contributes to the disruption of epithelial integrity and accelerates periodontal tissue destruction in chronic periodontitis [24].

6. Types of Inflammasomes Relevant to Periodontitis

a) *NLRP1 Inflammasome:* The initial NLR known to create an inflammasome complex was NLRP1. This gene, present as a singular copy in humans, encodes proteins with a PYD (pyrin) domain, FIIND (function-to-find domain), and CARD domain. Studies indicate that NLRP1 signalling is triggered by muramyl dipeptide (MDP), a peptidoglycan component found in bacterial cell walls, as well as anthrax lethal factor (LF) from the Bacillus anthracis lethal toxin (LeTx) [11]. This toxin includes protective antigen (PA) and lethal factor (LF), which together form pores in the host cell membrane. This action then leads to the activation of NLRP1β, prompting the assembly of inflammasomes. Reduced levels of NLRP1 were detected in samples from healthy, chronic, and aggressive periodontitis gums, with higher expression typically observed in the epithelium and connective tissue of individuals with aggressive periodontitis [25].

b) *NLRP3 Inflammasome:* The NLRP3 inflammasome is one of the most extensively studied inflammasomes in periodontitis. It consists of NLRP3 as the sensor protein, ASC as the adaptor protein, and caspase-1 as the effector protein. Activation of NLRP3 inflammasome occurs in response to a variety of stimuli, including microbial components, ATP, and environmental stressors [26].

c) *AIM2 Inflammasome*: The AIM2 inflammasome is activated by cytosolic double stranded DNA (dsDNA), typically released during cell damage or infection. AIM2 binds to dsDNA, recruits ASC, and activates caspase-1, leading to IL-1β and IL-18 maturation [27].

d) *NLRC4 Inflammasome*: The NLRC4 inflammasome responds to intracellular pathogens, particularly bacteria, by sensing bacterial flagellin and type III secretion system (T3SS) proteins. NLRC4 forms a complex with

ASC and caspase-1 to initiate the inflammatory response [27]

7. Role of inflammasomes in periodontal pathogenesis

Periodontal pathogens can trigger inflammasome activation through various mechanisms. Inflammasomes play a crucial role in the innate immune response by activating proinflammatory cytokines like interleukin-1β (IL-1β) and interleukin-18 (IL-18). Periodontal pathogens, such as Porphyromonas gingivalis (P. gingivalis) and Aggregatibacter actinomycetemcomitans (A. actinomycetemcomitans), are recognized by PRRs like Toll-like receptors (TLRs) and NOD-like receptors (NLRs) on host cells. TLRs recognize pathogen associated molecular patterns (PAMPs) present on these bacteria, while NLRs can detect intracellular pathogens or danger signals [28]. One of the well-studied inflammasomes in the context of periodontal pathogens is the NLRP3 (NOD-like receptor family, pyrin domain-containing inflammasome. P. gingivalis and other periodontal pathogens can activate the NLRP3 inflammasome through various mechanisms [28]. For example, they can release virulence factors like lipopolysaccharides (LPS), gingipains, and outer membrane vesicles (OMVs), which are sensed by NLRP3. Periodontal pathogens can induce ion fluxes such as potassium efflux and calcium influx, leading to cellular stress and activation of the NLRP3 inflammasome. These pathogens may also cause mitochondrial dysfunction, reactive oxygen species (ROS) generation, and endoplasmic reticulum stress, all of which contribute to inflammasome activation. Upon NLRP3 inflammasome activation, pro-caspase-1 is cleaved into its active form, caspase-1 [29]. Caspase-1 then cleaves pro-IL-1β and pro-IL-18 into their active forms (IL-1β and IL-18), which are released from the cell to initiate inflammatory responses and recruit immune cells. The activation of the inflammasome and subsequent release of IL-1β and IL-18 lead to inflammation within the periodontal tissues. This inflammatory response can contribute to tissue damage, bone loss, and the progression of periodontal disease [29]

8. Consequences of Inflammasome Activation

1) Tissue Destruction and Periodontal Breakdown

Inflammasome activation not only initiates inflammatory responses but also plays a pivotal role in the degradation of periodontal tissues. The inflammasome-mediated release of proinflammatory cytokines, particularly interleukin-1 beta (IL-1β) and interleukin-18 (IL-18), amplifies the local inflammatory milieu and promotes the production of matrix metalloproteinases (MMPs), which degrade extracellular matrix components within the gingival connective tissue and periodontal ligament [30].

IL-1β, a key effector cytokine downstream of caspase-1 activation, has been shown to directly stimulate osteoclastogenesis through the upregulation of receptor activator of nuclear factor kappa-B ligand (RANKL) expression on osteoblasts and stromal cells. This results in enhanced differentiation and activity of osteoclasts, leading to increased bone resorption at the alveolar crest, a hallmark of progressive periodontitis. The cumulative outcome is loss of periodontal attachment, alveolar bone destruction, and eventual tooth mobility or loss [30].

2) Chronic Inflammation and Disease Progression

The persistent activation of inflammasomes in response to microbial dysbiosis and host-derived danger signals contributes to the chronicity of periodontal inflammation. Unlike acute inflammation, which is typically self-limiting and resolves upon removal of the initiating stimulus, inflammasome-driven inflammation in periodontitis becomes self-perpetuating. This dysregulated immune response impairs resolution and tissue regeneration, promoting a cycle of destruction, impaired healing, and further microbial colonization [30].

Clinically, this manifests as chronic periodontitis—a progressive condition marked by continued attachment loss, alveolar bone resorption, and systemic inflammatory burden. Furthermore, chronic inflammasome activation may compromise host defense by disrupting epithelial barriers and promoting pyroptotic cell death, which in turn facilitates deeper microbial invasion and further exacerbates tissue breakdown [30].

Understanding these mechanisms underscores the importance of inflammasome regulation in maintaining periodontal tissue homeostasis and identifies inflammasome components as potential therapeutic targets for halting or reversing disease progression.

9. Correlation between Inflammasome Activity and Periodontitis

Severity Periodontitis is intricately linked to the activity of inflammasomes, multiprotein complexes that regulate the inflammatory response. The correlation between inflammasome activity and the severity of periodontitis has garnered significant attention in recent years, shedding light on the underlying mechanisms driving disease progression and providing potential avenues for therapeutic interventions. As periodontitis progresses from a reversible gingivitis stage to irreversible tissue destruction, the activity of inflammasomes escalates, fuelling a cascade of inflammatory events [31]. Experimental studies using animal models and human samples have demonstrated a positive correlation between the expression levels of inflammasome components (e.g., NLRP3, ASC, caspase 1) and the severity of periodontal lesions. Histological analyses reveal heightened inflammasome activation in advanced periodontitis characterized by extensive connective tissue loss, alveolar bone resorption, and periodontal pocket formation [31]. Moreover, the dysregulated release of pro-inflammatory cytokines such as interleukin-1β (IL-1β) and interleukin-18 (IL-18) due to inflammasome activation contributes to tissue damage and amplifies the local inflammatory milieu within periodontal tissues [31]. This sustained inflammatory response perpetuates a vicious cycle of tissue destruction, recruitment of immune cells, and matrix metalloproteinase-mediated degradation of extracellular matrix components, further exacerbating periodontitis severity [31].

10. Biomarkers for assessing inflammasome activation in periodontal disease

Inflammasome-related biomarkers emerge as promising tools for assessing disease activity, predicting disease progression, and monitoring therapeutic outcomes in periodontal patients. Notable biomarkers include IL-1β, IL-18, caspase-1, ASC specks, and markers of cellular stress and inflammation (e.g., reactive oxygen species, cytokines [32]. Biomarker profiling in gingival crevicular fluid (GCF), saliva, and serum offers valuable insights into the inflammatory status of periodontal tissues and the systemic implications of periodontitis-associated inflammasome activation [32]. Elevated levels of IL-1β and IL-18 in GCF correlate with periodontitis severity and serve as indicators of active inflammation and tissue destruction. Furthermore, the presence of ASC specks, a hallmark of inflammasome activation, in GCF samples is associated with more aggressive forms of periodontitis and a poorer response to conventional periodontal therapies [33]. Advancements in molecular techniques, including enzyme-linked immunosorbent assays (ELISA), polymerase chain reaction (PCR), and immunofluorescence microscopy, enable sensitive and specific quantification of inflammasome-related biomarkers in clinical settings [33]. These biomarkers not only aid in diagnosis and prognostication but also guide personalized treatment strategies tailored to the inflammatory profile of individual patients. In addition to their diagnostic utility, inflammasome-related biomarkers hold promise as therapeutic targets in the management of periodontitis. Strategies aimed at modulating inflammasome activation pathways, such as pharmacological inhibitors targeting NLRP3 or upstream signalling molecules, represent novel therapeutic avenues for mitigating periodontal inflammation and halting disease progression [33].

11. Potential inhibitors of the NLRP3 inflammasome in the treatment of periodontitis:

The NLRP3 inflammasome is activated in the periodontal tissues of individuals with periodontitis. Targeting the negative regulation of this inflammasome presents a promising therapeutic approach for diseases associated with NLRP3. Several inhibitors of NLRP3 possess the capability to block its activation, with some demonstrating therapeutic promise in addressing periodontitis [33]

- **MCC950** has demonstrated therapeutic effects in addressing periodontitis. It significantly reduces the number of osteoclasts and inhibits their differentiation, leading to decreased alveolar bone loss in mice with periodontitis [34].
- **Glyburide**, also known as glibenclamide, serves as an orally active inhibitor of the ATP-sensitive K+ channel. Glyburide has demonstrated its ability to prevent NLRP3 inflammasome activation and decrease the release of IL-1β in inflammation induced by periodontal pathogens. Furthermore, administration of glyburide orally has been shown to mitigate alveolar bone resorption and osteoclastogenesis caused by traumatic occlusion in a rat model [34].
- **Tranilast** inhibits the activation of nuclear factor-κB and reduces the induction and nuclear translocation of nuclear factor of activated T cells, ultimately leading to the inhibition of osteoclastogenesis by RANKL signalling [34].
- **Irisin** promotes the proliferation of primary hPDLCs and enhances osteogenic potential by increasing extracellular matrix formation. Under P. gingivalis-triggered inflammation, irisin facilitates the osteogenic/cementogenic differentiation of hPDLCs, partly through the p38 signalling pathway [34]

12. Inflammasomes and Periodontal Microbiota:

Inflammasomes play a critical role in the immune response to periodontitis. In periodontitis, pathogenic bacteria in the oral microbiota can activate inflammasomes, leading to the production of inflammatory cytokines like IL-1β. This inflammation contributes to the destruction of gum tissue and bone. Dysbiosis, or an imbalance in the oral microbiota, exacerbates inflammasome activation, driving the progression of the disease.

A study by Padial-Molina [35] collected soft tissue samples from around the implant and studied the relative abundance of bacteria and alpha-diversity after analysing the 16S rRNA gene using next-generation sequencing. The soft-tissue samples were processed for evaluation of the inflammasomes NLRP3 and AIM2 as well as caspase-1 and IL-1β and it was found that a cluster of variables were formed by NLRP3 in the lamina propria and AIM2, caspase-1, and IL-1β in the lamina propria and the epithelium with Prevotella dentalis, Prevotella tannerae, Tannerella forsythia, or Selenomonas timonae. Thus, concluding that inflammasomes NLRP3 and AIM2 and their downstream effectors caspase-1 and interleukin1β were significantly associated with specific bacteria. A study by Lee et al., [36] examined the anti-inflammatory effects of catechin in THP-1-derived macrophages infected with P. gingivalis and found that catechin inhibited the activation of inflammasomes induced by P. gingivalis, suggesting that it can potentially be used for the prevention and treatment of periodontal inflammation caused by P. gingivalis [36].

13. Inflammasomes in periodontal disease

In periodontal disease, inflammasomes are pivotal in mediating the immune response to bacterial infection in the gums. These multi-protein complexes detect periodontal pathogens, triggering the release of inflammatory cytokines such as IL-1β and IL-18. This inflammatory response, while protective, can become chronic and lead to the destruction of gum tissue and supporting bone structures [36]. Excessive activation of inflammasomes due to dysbiosis in the oral microbiota further exacerbates tissue damage. Thus, targeting inflammasome pathways holds potential for therapeutic strategies in managing periodontal disease.

A study [37] found that polymorphisms in NLRP3, IL1B and IL2 genes were associated to periodontal disease susceptibility. Men carrying the NLRP3, IL1R, IL6, TNF, IL2, TGFB1, IL4RA and IL4 polymorphisms had greater susceptibility than women for developing periodontal disease. A study has analysed the expression of proteins that regulate the inflammasome in periodontitis and found that NLRP3 and

IL-1β were upregulated in the periodontally compromised groups when compared to healthy individuals. AIM2 was found to be downregulated in the chronic periodontitis group when compared with the gingival disease and healthy group. TRIM20, TRIM16, and CARD18 were downregulated in the gingival and periodontally compromised group, thus highlighting the fact that active periodontal disease may result in downregulation of inflammasome regulators that may increase the activity of NLRP3 and IL-1β in periodontal disease.

In a study by [38] a quantitative real-time polymerase chain reaction (PCR) was done to find the mRNA expression of NALP3, its effector molecule apoptosis associated speck-like protein (ASC), its putative antagonist NLRP2, IL-1b and IL-18 in gingival tissues from patients with gingivitis, chronic periodontitis, generalized aggressive periodontitis, as well as in healthy subjects in response to P. gingivalis challenge for 6 hours, wherein it was found that in comparison to healthy tissues,NALP3 expression was significantly ($P < 0{\cdot}05$) higher in either of the periodontitis groups or gingivitis groups. In particular, NALP3 expression was higher by 7·4-fold in G-AgP, 4·3-fold in CP and 7·7-fold in gingivitis, respectively. A study by [39] has also found that higher levels of NLRP3, ASC, and IL-1b were detected in periodontitis groups in comparison to the periodontally healthy group.

In a study by (Fernand) [40] bacterial-associated experimental periodontitis was induced in wild-type and Nlrc4-KO C57BL/6 mice and the relevance of NLRC4 for RANKL-induced osteoclastic differentiation and activity was investigated in vitro using bone marrow-derived macrophages. Bone resorption was significantly greater in Nlrc4-KO mice; In vitro, osteoclast activity was significantly enhanced in Nlrc4-deficient macrophages whereas RANKL-induced differentiation was not affected and showed that NLRC4 inflammasome had a protective role on inflammatory bone resorption. A similar study by Jayaprakash [41] assessed the role of NLRP3 in regulating gingival epithelial cell responses when evoked by Aggregatibacter actinomycetemcomitans. Here it was seen that a targeted protein analysis of inflammation-related proteins showed that the expression of 37 proteins were identified as being significantly altered after infection compared to unstimulated Cas9 and NLRP3-deficient cells. Of the 37 proteins, 23 of these inflammation-related proteins released by NLRP3-deficient cells differed significantly compared to Cas9 cells after infection suggesting that NLRP3 has a broad effect on the inflammatory response in gingival epithelial cells. In contrast a study by (Rocha et al) [42] also investigated the role of NLRP3 inflammasome and its main effector Caspase-1 in inflammation and alveolar bone resorption associated with periodontitis wherein heat-killed Aggregatibacter actinomycetemcomitans (Aa) was injected 3x/week (4 weeks) into gingival tissues of wild-type (WT), Nlrp3-KO and Caspase1-KO mice and it was found that bone resorption decreased in Casp1-KO mice but not in Nlrp3-KO mice and osteoclasts derived from Nlrp3-deficient macrophages exhibited increased resorbing activity in vitro suggesting that the Nlrp3 inflammasome does not play a major role in inflammation and bone resorption in vivo, whereas Caspase-1 appeared to have a proresorptive role in experimental periodontal disease. A similar study by (Cheat et al.) [43] it was found that in NLRP3 KO mice, mature IL-1b expression was lower and almost no neutrophils were mobilized highlighting the role of NLRP3 in periodontitis by highlighting the ambiguous role of neutrophils, and P. gingivalis which affected NLRP3 functions [43].

14. Inflammasomes in periodontitis associated systemic diseases

Inflammasomes are key players in the link between periodontitis and systemic diseases. In periodontitis, chronic activation of inflammasomes leads to sustained inflammation and release of cytokines like IL-1β into the bloodstream. This systemic inflammation can exacerbate conditions such as cardiovascular disease and diabetes. The interconnectedness of inflammasome activity in periodontitis and these systemic diseases highlights the importance of managing oral health to prevent broader health complications.

A study [44] sought to explore whether macrophage pyroptosis plays a role in the development of diabetes mellitus–periodontitis and found that hyperglycemia promoted IL-1_ production and pyroptosis in macrophages suffered by periodontal microbial stimuli. The study highlighted that MCC950, a potent and selective molecule inhibitor of the NLRP3 inflammasome, effectively inhibited macrophage pyroptosis and attenuated alveolar bone losses in diabetes mellitus–periodontitis. Similar studies by (Isola, Arunachalam, García-Hernández et al) [45,46,47] also studied the serum and salivary NLRP3 concentrations in patients with periodontitis and type-II diabetes mellitus and found that periodontitis and periodontitis + type-IIDM patients had higher serum and salivary NLRP3 concentrations. The correlation between NLRP3 inflammasome and chronic hepatitis C and periodontal diseases were examined in a study by (Surlin et al) [48] which found significant positive correlations between the GCF NLRP3 levels and the periodontal probing depth, clinical attachment loss, and gingival bleeding index ($r = 0.4$) thus highlighting the fact that chronic hepatitis C and periodontal disease could have a significant influence on the upregulation of NLRP3 inflammasome and its components, possibly contributing to an increased local inflammatory reaction and clinical periodontal consequences.

15. Discussion

The current body of evidence underscores the pivotal role of inflammasomes as central regulators of the innate immune response in periodontitis. Their activation by both pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) initiates a cascade of inflammatory events that ultimately contribute to periodontal tissue breakdown. Among the various inflammasome complexes, the NLRP3 and AIM2 inflammasomes have been most consistently implicated in periodontal pathology due to their broad activation profiles and downstream proinflammatory effects.

Activation of inflammasomes leads to caspase-1-dependent processing of interleukin-1 beta (IL-1β) and interleukin-18 (IL-18), which are key mediators of local tissue inflammation and destruction. IL-1β in particular has been shown to enhance

the expression of matrix metalloproteinases (MMPs) and promote osteoclastogenesis via the RANK/RANKL axis, thereby linking inflammasome activation directly to connective tissue degradation and alveolar bone resorption [16,10]. These findings are supported by histological and immunohistochemical studies showing elevated levels of inflammasome components and effector cytokines in gingival tissues from patients with chronic periodontitis compared to healthy controls [5].

Furthermore, the induction of pyroptosis—a lytic, caspase-1-mediated form of programmed cell death—by inflammasome activation represents another mechanism by which host cells contribute to disease progression. Pyroptosis results in the release of intracellular contents, amplifying inflammation and further disrupting the epithelial barrier, which facilitates microbial invasion and perpetuates the inflammatory cycle [49].

Importantly, persistent and dysregulated inflammasome activation appears to play a major role in the transition from acute inflammation to chronic periodontal disease. The chronic release of inflammatory mediators impairs normal tissue repair mechanisms and contributes to a microenvironment conducive to further microbial dysbiosis. This bidirectional relationship between inflammasome activation and microbial imbalance exemplifies the complexity of host-pathogen interactions in periodontal disease [50].

From a therapeutic perspective, targeting inflammasome components offers a promising avenue for adjunctive periodontal treatment. Inhibitors of the NLRP3 inflammasome (e.g., MCC950) or caspase-1 have demonstrated efficacy in reducing inflammation and bone loss in preclinical models of periodontitis [51]. Additionally, modulating upstream signals such as oxidative stress or potassium efflux that trigger inflammasome activation may help to restore periodontal immune homeostasis. However, translating these findings into clinical therapies requires further investigation, including safety profiling and long-term outcome studies.

Despite significant progress, several questions remain unanswered. The precise triggers of different inflammasome subtypes in the periodontal niche, their interactions with other innate immune pathways, and the extent of their involvement in systemic inflammatory burden associated with periodontitis warrant deeper exploration. Moreover, individual genetic variations in inflammasome-related genes may influence susceptibility to periodontitis and treatment outcomes, suggesting a potential role for personalized therapeutic approaches in the future.

16. Future direction

Future studies should delve deeper into the intricate molecular mechanisms underlying inflammasome activation in periodontal tissues, elucidating the specific pathways through which inflammasomes contribute to inflammation and tissue damage [52]

Additionally, exploring the interactions between oral microbiota dysbiosis and inflammasome activity can provide crucial insights into disease progression. Developing targeted therapies that selectively modulate inflammasome activity without compromising overall immune function is another important avenue for future investigation [52].

Clinical trials evaluating the efficacy and safety of potential inflammasome inhibitors or modulators in periodontitis patients are essential to translate these findings into clinical practice [53].

Longitudinal studies assessing the long-term effects of inflammasome activation on periodontal health and systemic health outcomes would also be valuable. Furthermore, identifying and validating biomarkers associated with inflammasome activity could facilitate early diagnosis, monitoring disease progression, and assessing treatment responses [53].

Research should also be undertaken to understand the interplay between genetic factors, environmental influences, and inflammasome regulation in periodontitis as it can provide a more comprehensive understanding of disease pathogenesis and personalized treatment approaches. Integrating findings from cross-disease studies to explore common pathways between inflammasome activation in periodontitis and other inflammatory conditions can lead to innovative and holistic therapeutic strategies [53].

17. Conclusion

Inflammasomes are central regulators of the host innate immune response and play a critical role in the pathogenesis of periodontitis. Their activation by microbial and endogenous danger signals results in caspase-1-dependent maturation of proinflammatory cytokines and induction of pyroptosis, collectively contributing to connective tissue degradation and alveolar bone resorption. Among the various inflammasome complexes, NLRP3 and AIM2 have emerged as key mediators in periodontal inflammation. Persistent and dysregulated inflammasome activity not only drives chronic inflammation but also impairs tissue repair, exacerbating disease progression [54].

Understanding the molecular mechanisms underlying inflammasome signalling has opened new avenues for biomarker development and targeted host-modulation therapy. Selective inhibition of inflammasome pathways may offer a novel adjunctive strategy to conventional periodontal treatment, particularly in refractory or aggressive disease phenotypes. Further clinical research is warranted to elucidate inflammasome-targeted interventions and their potential to alter disease trajectory and improve periodontal outcomes [55].

18. Figures

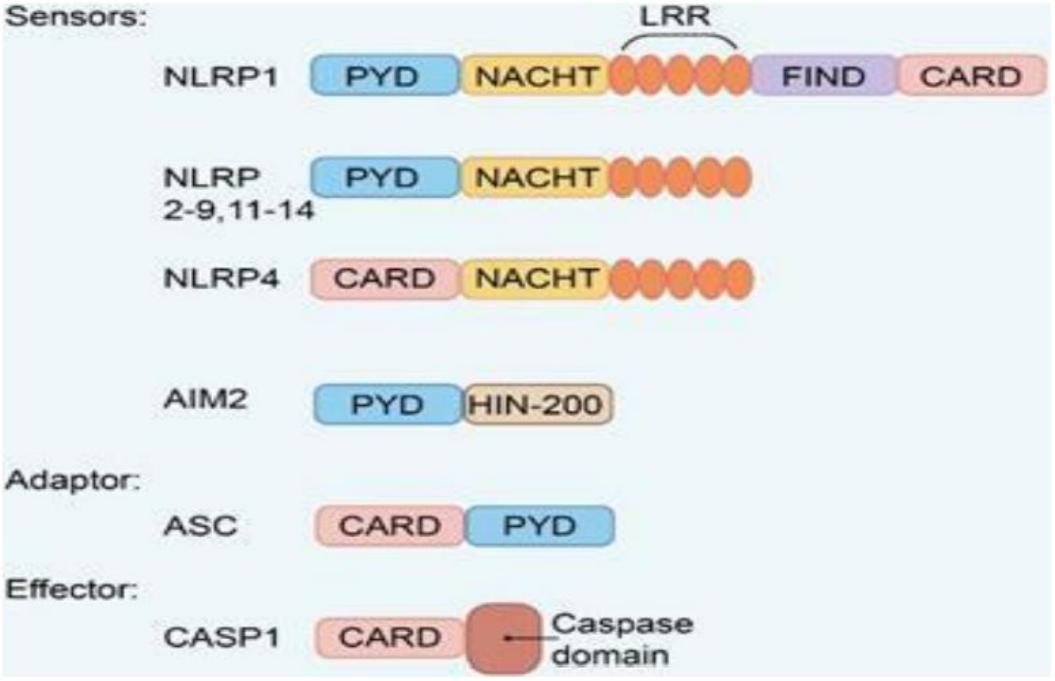

Figure 1: Domain architecture of representative inflammasome
Source: (Zhao et al., 2022)

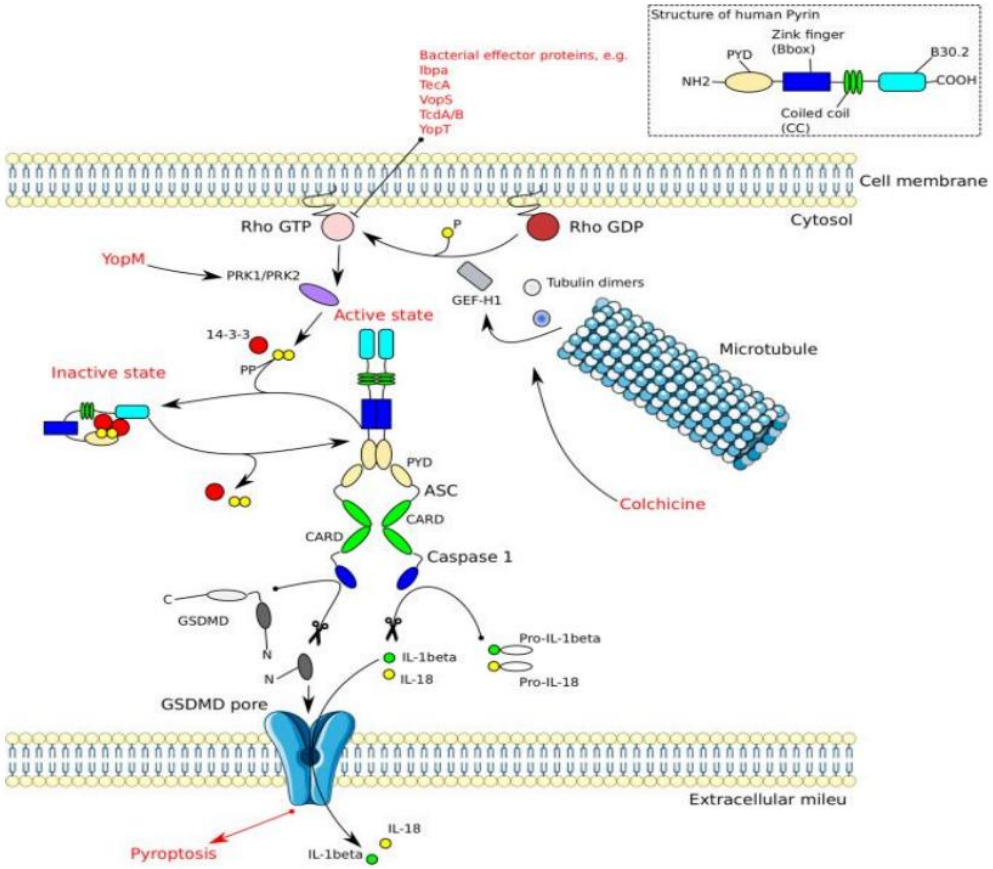

Figure 2: The inflammasome unit and its actions inside the cell
Source: (Zheng, Liwinski and Elinav, 2020)

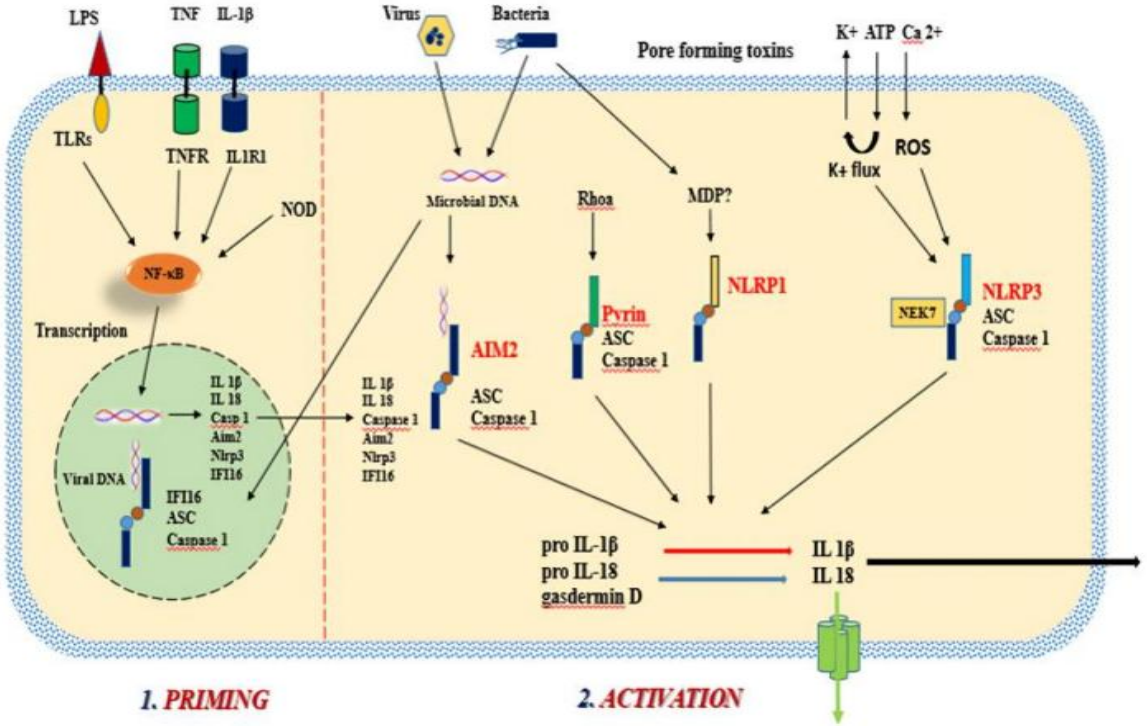

Figure 3: Inflammasome priming and activation
Source: (Ansari et al., 2020)

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