AMJ
ISSN: 0005-2523

ISSN: 0005-2523
Volume 62, Issue 08, October 2022

NODE LIKE RECEPTOR PYRINE-3 INFLAMMASOME: FUNCTION AND MECHANISM IN PERIODONTITIS

Mohammed Jasim AL-Obaidi[1*], Batool Hassan Al-Ghurabi[2]

[1] Master student, Department of basic science of Oral Microbiology, College of Dentistry, University of Baghdad/ Baghdad, Iraq.

[2]Professor, PhD in Microbiology/Immunology, Department of basic science College of Dentistry, University of Baghdad/ Baghdad,Iraq.

*Correspondence:alobaidi.Mohammed1984@gmail.com

: batoolamms@codental.uobaghdad.edu.iq

*ORCID: 0000-0002-7369-4272

Abstract:

Periodontitis is an inflammatory condition associated with bacterial overgrowth, and Gram-negative bacteria within the periodontal pockets have been shown to raise inflammatory markers. The NLRP3inflammasome is a vital elements of the innate immune system that activates and secretes pro-inflammatory cytokines in response to microbial (viral, bacterial. etc.) infections. Chronic inflammation brought on by host immunological responses is a common feature of periodontitis. The purpose of this review is to outline the function of the NLRP3 inflammasome in periodontal disease.

Keywords: *periodontal diseases, innate immunity, inflammasomes.*

Introduction:

Periodontal diseases include a lot of inflammatory situations that influence the gingiva, periodontal ligament and bone, that eventually cause tooth loss and involved in systemic inflammation. Oral microbita (dental plaque) cause initiation and proliferation of periodontal disease, later on inflammation and disease occur because of interaction between these microbiota and immune defenses (1). The pathophysiology of the disease has been characterized in its key molecular pathways and ultimately leads to activation of host-derived mediators that enable loss of marginal periodontal ligament fibers, apical migration of the junctional epithelium and allows apical spread of the bacterial biofilm along the root surface (2).

The pathogenesis of periodontal disease includes a complicated interplay between periodontal pathogens and the host immune response (3). Induction of the innate immune response is closely associated with the activation of the adaptive side. Several investigations have demonstrated that inflammasome plays a pivotal function in affecting this relationship. Cytoplasmic multiprotein complexes called inflammasomes include a sensor protein, inflammatory caspases, and, in some situations, an adapter protein that connects the two proteins. A wide variety of endogenous and exogenous triggers can set them off, resulting in the enzyme activation of caspases such canonical caspase-1 and non-canonical caspase-11, (or even the human equivalents caspase-4 and caspase-5) or caspase-8, leading to the release of IL-1 and IL-18 as well as apoptotic and pyroptotic induce apoptosis (4). Nod-like receptor protein 3 (NLRP3) is one of the effectively inflammasomes and a

member of the NLR protein family, which has twenty- two members in humans (5, 6). NLRP3 interacts to a wide variety of inflammatory infectious and endogenous ligands, including such PAMPs and/or DAMPs; as a result, the dysregulation of NLRP3 function is linked to the pathogenesis of various inflammatory illnesses (7, 8).

Material and methods:

To perform this research, relevant articles were searched in the scientific databases Scopus, Google Scholar, PubMed and Web of Science using keywords like periodontal diseases, innate immunity, inflammasomes, and NLRP3.

Innate Immunity in Periodontal Disease:

A select group of endogenous Gram-negative periodontal bacteria are responsible for the onset of periodontal disease, which trigger the immune system's defense mechanisms (both innate and adaptive). These processes lead to the breakdown of the tissues that surround and support the teeth, resulting in eventual tissue, bone, and tooth loss (9, 10, 11). The innate immune response is a homeostatic mechanism that is the initial line of defense and is able to distinguish invading germs as non-self, hence generating immunological responses to remove them. The adaptive immune system improves the effector mechanisms of the innate immune system through the formation of an efficient microbial clearance loop, where activation of the appropriate innate pathways ensures an efficient adaptive immune response, whose actions against periodontopathic bacteria are enhanced by these innate effectors. The innate immune system's basic reaction to infections is initiated by pattern recognition receptors (PRRs) that bind pathogen-associated molecular patterns (PAMPs) found in a wide variety of organisms. These receptor types include toll-like receptors, cluster of differentiation 14 (CD14), nucleotide-binding oligomerization domain (NOD) proteins, complement receptor-3, lectins and scavenger receptors (12, 13).

Toll-like receptor and neutrophils have been the primary focus of studies on the innate immune response and periodontitis in Latin America. South American countries including Brazil, Chile, and Mexico are developing such research, table (1.1) (14, 15, 16, 17, 18). Nucleotide like receptors (NLRs), Nucleotide-binding and oligomerization domain (NOD) are a part of intracellular (PRRs) which serve essential roles in pathogen detection and upregulation of innate immune signal transduction. These receptors were activated through variety of ligands, including (LPS), polyinosinic-polycytidylic acid and peptidoglycans (19).

Inflammasomes:

Inflammasomes are caspase-1-dependent and -independent multiprotein platforms which nucleate around an intracellular receptor that typically belong to the family of nucleotide binding leucine-rich repeat containing proteins (NLRs). Inflammasome components are principally expressed in innate immune cells such as monocytes and macrophages (20), but also in dendritic cells and neutrophils (21,22), as well as in certain non-immune cells, such as keratinocytes (23).

Inflammasome association and activity is triggered upon detection of microbial products, sterile endogenous danger signals or upon alterations in homeostasis, known under the names of

pathogen- or danger-associated molecular patterns or homeostasis-altering molecular processes (PAMPs or DAMPs or HAMPs, respectively) (24, 25). Inflammasomes, play major roles in host defense against intracellular bacteria and viruses (26) and in the regulation of inflammation (27, 28) through pro-inflammatory cytokine secretion. Mutations in inflammasome genes are causal for an increasing number of self-directed inflammatory diseases termed auto-inflammatory diseases (29). A deregulated inflammasome activity has also been reported in common metabolic, immune and inflammatory disorders (27, 30, 31, 32, 33).

Node Like Receptor Pyrine-3 (NLRP3) inflammasome is a critical component of the innate immune system that mediates caspase-1 activation and the secretion of proinflammatory cytokines IL-1 and IL-18 in response to microbial infection and cellular damage. However, the aberrant activation of the NLRP3 inflammasome has been linked with several inflammatory disorders, which include cryopyrin-associated periodic syndromes, Alzheimer's disease, diabetes and atherosclerosis (34). The activation of the NLRP3 is caused by bacterial stimuli, as LPS from bacteria and bacterial RNA or by endogenous ones, as extracellular ATP, uric acid, or cholesterol crystals (34).

Mechanism of NLRP3 inflammasome Activation:

The activation of the NLRP3 inflammasome requires a two-step signal. Signal 1 is priming, which is mainly mediated by TLRs and TNF-α and aims to upregulate pro- IL-1β, pro-IL-18 and NLRP3 in an NF-κB-dependent manner. Caspase-8 and Fas-associated protein with death domain (FADD) are engaged in the NF-κB signalling pathway. Inflammasome priming also occurs via non-transcriptional pathways. Signal 2 is triggering, which involves the recruitment and assembly of NLRP3, Apoptosis-Associated speck-like protein containing a Caspase-recruitment domain (ASC) and pro-caspase-1 to form the active NLRP3 inflammasome complex.

Three models have been proposed to lead to Signal 2: (1) eATP induces K+ efflux via a purogenic P2X7-dependent pore; (2) PAMPs /DAMPs lead to mitochondrial dysfunction, Reactive Oxygen Species (ROS) production, and oxidative stress; and (3) lysosomal rupture induced by phagocytosed crystalline or particulate structures releases lysosomal contents, such as cathepsin B. In addition, Nucleoside diphosphate kinase (NDK) induces the expression of ecto-ATPases, resulting in the cleavage of eATP, which prevents P2X7 receptors activation. The inflammasome self cleaves and activates caspase-1, which in turn contributes to the production and secretion of bio-active IL-1β and IL-18, figure (1) (35).

After that, the activated NLRP3 inflammasome catalyzes procaspase-1 to become mature caspase-1, resulting in an even greater increase in the amount of IL-1 β and IL-18 that is secreted (36). IL-1 β incites the expression of genes that regulate fever, pain threshold, vasodilation, and hypotension, and its reception results in an endothelial cell response that facilitates immune cell infiltration into infected or damaged tissues (37). Inflammasome formations is a response to cellular infections, cellular stress or damage of the cells (38). Particularly, IL-1 β and IL-18 activities is central to the immune response of the host in periodontitis (39). Many studies have shown that caspase-1-processed IL-1β and IL-18 promote IL-17 secretion and mediate autoimmunity by CD4 T cells (40, 41). The NLRP3 inflammasome plays a role in mediating host

metabolic responses, and the dysregulation of inflammasome components is associated with various inherited chronic inflammatory and immune disorders, such as diabetes and obesity (42).

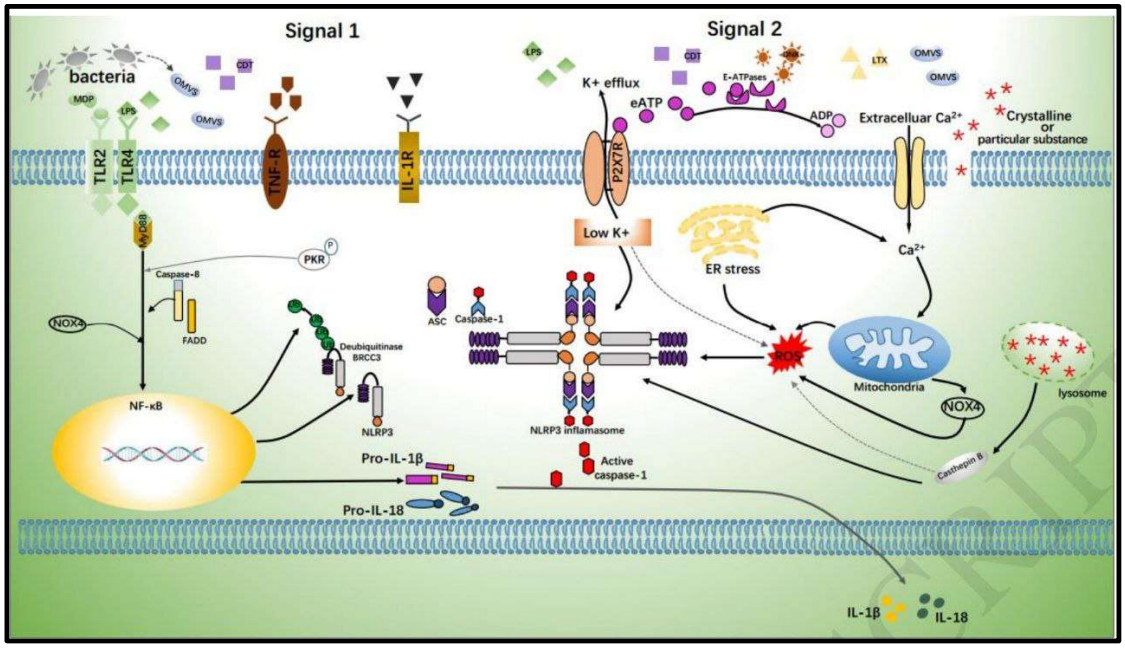

Figure 1: Inflamasome activation (35).

Role of Infammasome Pathogenesis of Periodontal Disease:

The gingival expression of NLRP2 and NLRP3 inflammasomes were increased in different types of periodontal disease, including periodontitis and gingivitis compared with healthy controls (43). The inflammasome is regulated by different proteins and processes, including pyrin domain (PYD)-only proteins (POPs) and CARD-only proteins (COPs), tripartite motif family proteins (TRIMs), autophagy and IFNs (44). POP1 and POP2 (pyrin only protien) inhibit inflammasome activation by interacting with ASC and NLRP3 and NLRP2 and AIM2, respectively (45). COPs, including CARD16 and CARD18 are upregulated by tumor necrosis factor alpha (TNF-α) and LPS (46). And inhibit the inflammasome through caspase-1 activity. TRIM20 and TRIM16 also inhibit inflammasome activation by interacting with both NLRPs and caspase-1 (44).

Inflammatory periodontal disease may cause a reduction in inflammasome regulators, including POPs, TRIMs, and some COPs which in turn promote the increased expression and activity of NLRP3 and IL-1β that trigger periodontal tissue breakdown (47). The NLRP3 inflammasome is activated by periodontal pathogen-associated or DAMP (48, 49). Particular, IL-1β and IL-18 activity represent a focus of the host immune response in periodontitis (50).

The NLRP3 inflammasome plays a significant role in regulating the innate immune system by interacting with thioredoxin-interacting protein (51). Moreover, activation of the NLRP3 inflammasome affects glucose tolerance, insulin sensitivity, and interactions with gut microbes (52, 53). The influential role of NLRP3 in insulin resistance has been studied in animal models and human adipose tissue samples. Such studies have found that NLRP3 mice have enhanced glucose tolerance and insulin sensitivity, which may be related to the involvement of TXNIP in inflammasome activation (51).

Conclusion:

The development of inflammatory and immune responses is significantly influenced by the NLRP3 inflammasome. The NLRP3 inflammasome may be involved in the abnormal regulation of inflammatory and immunological responses in periodontitis, NLRP3 inflammasome may be a viable therapeutic target for the treatment and prevention of periodontitis.

Competing interests:

Authors and planners have not indicated any potential monetary or other conflicts of interest.

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