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Inflammasomes Role in the Pathogenesis of Periodontal Disease -A Review

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Abstract:- Inflammasome is a multiprotein complex that consists of a PRR- an adaptor protein or ASC [apoptosis-related speck-like protein containing a CARD (caspase activation and recruitment domain)] an active form of caspase-1.Active caspase-1 subsequently processes the leaderless proinflammatory cytokines pro L-1b and pro-IL-18, which are unconventionally secreted on caspase-1 cleavage. Therefore, inflammasome-mediated processing and secretion of pro-IL-1b and pro-IL-18 enables a rapid, yet tightly regulated and highly inducible proinflammatory response. In addition to cytokine secretion, inflammasome activation can also trigger an inflammatory cell death dubbed pyroptosis, which serves to blunt intracellular pathogen replication.

Keywords:- *Inflammasomes, Caspase, Pyroptosis.*

I. INTRODUCTION

The innate immune response provides the first line of defense against pathogens. The innate immune system recognizes pathogens, by engagement of the germline encoded pattern recognition receptors (PRR)[1]. PRRs that are able to sense a vast array of microbial components, referred to as pathogen-associated molecular patterns (PAMP) and damage-associated molecular patterns (DAMP).They are found in bacteria, viruses, fungi etc. Examples of PAMPs found in bacteria are flagellin, bacterial DNA and RNA, Lipopolysaccharide, toxins. DAMPs are normally self derived,when there is cell injury or damage to cell there is release of host DNA / RNA, ATP, Uric acid. Both PAMPs and DAMPs can initiate innate immune system. PRR engagement by its ligand induces downstream signaling cascades can induce multiple effects, including activation of innate immune cells and cytokine/chemokine production for the recruitment of immune cells to the site of infection or tissue damage[1].

When pathogen approaching the cell ,it can be sensed by Membrane bound receptor i.e Toll like receptor present in cytoplasm forming pathogen contained vacuole, where transcriptional regulation of inflammatory cytokines, Type 1 interferons(IFNs) antimicrobials that can clear the infection. Sometimes these vacuole is lysed and pathogen is set free into cytoplasm , some host cells are equipped with several family of cytoplasmic receptors ,they help to defend against pathogens such as Retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs), Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs),which are equally capable of transcriptional regulation of Inflammatory cytokines and interferons. Certain member of NLR and ALR's also initiate the formation of inflammasome .

Inflammasome is a relatively new concept introduced by Tschopp et al. in 2002.It is a multiprotein complex that consists of a PRR- an adaptor protein or ASC [apoptosis-related speck-like protein containing a CARD (caspase activation and recruitment domain)] an active form of caspase-1.Active caspase-1 subsequently processes the leaderless proinflammatory cytokines pro L-1b and pro-IL-18, which are unconventionally secreted on caspase-1 cleavage[2]. Therefore, inflammasome-mediated processing and secretion of pro-IL-1b and pro-IL-18 enables a rapid, yet tightly regulated and highly inducible proinflammatory response. In addition to cytokine secretion, inflammasome activation can also trigger an inflammatory cell death dubbed pyroptosis, which serves to blunt intracellular pathogen replication (Miao et al. 2011).

Pyroptosis occurs when the cytoplasmic protein gasdermin D, is cleaved by caspase-1,inducing the N-terminal gasdermin D fragment to oligomerize and insert into the plasma membrane forming pores. Cell lysis and the release of intracellular components (DAMPS) into the intracellular milieu, perpetuating inflammation.

Although insufficient inflammation can lead to persistent infection of pathogens, excessive inflammation can cause chronic or systemic inflammatory diseases. Therefore, it is important that the host balances inflammasome activation.Because inflammasome activation is highly inflammatory, it is tightly regulated to prevent aberrant activation.

Recognition of mature interleukin-1β and interleukin-18 by their receptors has following actions:
(a) neutrophils and other innate immune cells recruitment,
(b) B cells activation and antibody production and
(c) T cells differentiation[1]

II. ROLE OF INFLAMMASOMES IN PERIODONTAL DISEASE

Periodontal disease is an inflammatory and infectious disease characterized by the destruction of the tooth's supporting tissues.[3] This tissue destruction is initiated by an excessive inflammatory host response to periodontal pathogens**.** The host response to periodontal pathogens are characterized by the production of key pro-inflammatory cytokines, such as interleukin-1beta (IL-1β),which is produced by various immune and tissue-resident cells, including macrophages, oral fibroblasts, oral epithelial cells, and osteoblasts. The release of IL-1β is a major step in the immune response due to its ability to induce the expression of a range of other inflammatory cytokines[4].

IL-1β activates endothelial cells and enables the adhesion of eosinophils, thereby increasing the inflammatory response. IL-1β also will regulates the destruction of the alveolar bone by promoting osteoclast formation and activity[5]. The monitoring of IL1β levels in GCF has been proposed as a useful approach for evaluating the host response during disease initiation, progression, and for determining therapeutic outcomes[6]. Clinical studies shows that IL-1β levels are higher in the gingival crevicular fluid (GCF) of periodontitis patients compared with controls, and there is also a correlation between IL-1β gingival tissue levels and severity of periodontal disease[7.8].

III. INFLAMMASOME ACTIVATION

The first step is CELL PRIMING,priming causes transcriptional and translational upregulation of inflammasome components, including the sensing PRR, caspase-1 and interleukin-1β.The secondly priming causes the post-translational modification of the PRR and adaptor molecule, ASC[9]**.** Inflammasome priming occurs through recognition of various PAMPs or DAMPS that engage a subset of multiple toll-like receptors, NOD1 or NOD2, or by the cytokines, tumor necrosis factor and interleukin-1β, that lead to transcriptional upregulation of inflammasome components mostly through the activation of the transcription factor nuclear factor-Kb[1].The second step is recognizing a PAMP or DAMP specific to each inflammasome, which then induces inflammasome formation and activation.

It is still not clear how many sensors are capable of forming inflammasomes, with strong literature support for over 10 different inflammasomes, including NLRP1, NLRP3, NLRP6, NLRP12, pyrin, NAIP/NLRC4, RIG-I AIM2, IFI16, NLRC3, NLP6, are recently studied[10].

- *NLRP1*

Of the NLRPs, the first discovered was the NLRP1 inflammasome, which is activated primarily by the lethal toxin from Bacillus anthracis[11]. Although NLRP1 was the first inflammasome described, exactly how it is activated is still unclear[12,13]. The role of the NLRP1 inflammasome has been evaluated in periodontal disease,[14,15] and similar expression levels have been reported in chronic periodontitis (CP), aggressive periodontitis (AgP), and periodontally healthy controls. Yilmaz et al reported that infection with Porphyromonas gingivalis (Pg) of human gingival epithelial cells did not significantly activate the NLRP1 inflammasome, and Bostanci et al [16]also reported no differences in NLRP1 activation in gingival fibroblasts infected with either subgingival or supragingival biofilms. Similarly, Belibasakis et al[17] found that NLRP1 was also not effected by Aggregatibacter actinomycetemcomitans (Aa) in human mononuclear leukocyte cells. Huck et al[18] reported no differences in NLRP1 inflammasome activity in human umbilical vein endothelial cells exposed to Pg or Pg lipopolysaccharide (LPS). Notably, Guo et al [19] reported a downregulation of NLRP1 in human gingival epithelium infected with Pg.

- *NLRP2*

The NLRP2 inflammasome inhibits NF-κB activation[20] .[21]The gingival levels of the NLRP2 inflammasome in patients with CP, AgP, and gingivitis (G) were reportedly significantly higher compared with healthy controls.[22] Pg challenge induced a downregulation in the NLRP2 inflammasome in a human monocytic cell line. However, no effect was reported ofNLRP2 in human oral epithelial cells infected with Pg.[23] In addition, no NLRP2 expression was reported in human gingival fibroblasts infected with subgingival or supragingival biofilms.[17] Lastly, Aa infection did not effect NLRP2 inflammasome activity in human mononuclear leukocytes.[18]

- *NLRP3*

NLRP3 is one of the best-studied inflammasome complexes. NLRP3 expression has been detected at higher levels in the gingiva of patients with CP [24,25]Aggressive periodontitis [26] when compared with periodontally healthy participants. Pg upregulates NLRP3 expression in human gingival epithelial cells[27] and mouse osteoblasts[28.]In addition, another periodontal pathogen, Aa, reportedly also mediates NLRP3 activation in human mononuclear leukocytes,[29] human osteoblastic cell lines[30], THP-1 cell lines [31] and murine macrophage-like cell lines.Treponema denticola (Td), a member of the red complex of bacteria, can also activate the NLRP3 inflammasome in THP-1 cells[32.]Being the most studied inflammasome in clinical diseases, NLRP3 has been implicated as having a role in several inflammatory and autoimmune diseases, including atherosclerosis, diabetes mellitus, obesity and rheumatoid arthritis,all of which are diseases known for their clinical association with periodontal disease.[33,34,35]The data indicate that in these four conditions there is a dysregulation of the inflammatory response that is partly driven by NLRP3.In diabetes mellitus type 2, endogenous and exogenous stimulators of NLRP3 inflammasome have been shown to accumulate in the

pancreas, including glucose, islet amyloid polypeptides, reactive oxygen species, neuro modulatory lipids and saturated fatty acids that arise from a high-fat diet.The accumulation of these stimulators can induce NLRP3 activation and subsequent cytokine expression.

➢ *NOD1 AND NOD2*

NOD1 is ubiquitously expressed, whereas NOD2 is found in myeloid cells, as well as epithelial cells and osteoblasts. Although NOD does not activate its own inflammasome, activation of NOD has been shown to promote activation of both NLRP3 and NLRP1 inflammasomes[36,37].The importance of NOD2 in inflammatory diseases is most strongly supported by the association of mutations in NOD2 and the increased risk for developing Crohn's disease, an autoinflammatory disorder of the gastrointestinal tract[38,39]. It has been suggested that inflammatory bowel disease and periodontal disease share similar immunopathogenic pathways, in that both entities show tissue-destructive mucosal inflammation directed against commensal microbiota.

➢ *PYHIN inflammasomes*

The PYHIN inflammasomes contain PYHIN proteins encoded by four family gene members (IFI16, AIM2, MNDA, and IFIX) instead of NLRs. AIM2 and IFI16 form the caspase-1-activating inflammasomes. AIM2 is present in the cytosol and recognizes aberrant cytoplasmic dsDNA of viral or bacterial origin. AIM2 induces cytokine maturation, release, and pyroptosis and is therefore understood to provide defense against bacterial and viral DNA[40]. Gingiva of CP patients(Park et.al,2014)and AgP patients(Kim S,2016) were reported to express more AIM2 compared with healthy controls. AIM2 expression was upregulated in human gingival fibroblasts in response to both supragingival and subgingival biofilms.Similar to these findings, Pg and Aa triggered an increased AIM2 expression in THP-1 cells.

➢ *Periodontal pathogens and inflammasomes*

Many periodontal pathogens are seen to be involved in inflammasome signaling. Pg is a major Gram-negative bacteria that also creates an advantageous environment for its co inhabitants, such as Fusobacterium nucleatum (Fn) and Td[41]. Pg infection is also involved in inflammasome activation, through activation of TLR signaling via LPS, which subsequently activates NLRP3, pro-IL-1β, and pro-IL-18 expression and induces danger signals, such as ATP and ROS,which results in the secretion of several inflammatory cytokines.[42]Another Gram-negative anaerobic periodontal pathogen, Aa, is also involved in inflammasome activation[43,44,45]. Aa has virulence factors, such as LPS, leukotoxin, and cytolethal distending toxin, that can notably kill human leukocytes via caspase-1 activation and IL-1β release[41]. Td can also promote Pg's ability to modulate inflammasomes and enhance the colonization of other periodontal pathogens[46].Fn can also activate NF-κB and DAMP signaling to stimulate the NLRP3 inflammasome[41,47]. Tannerella forsythia (Tf), is reportedly capable of inflammasome activation[41,48].

IV. INFLAMMASOME-MEDIATED CYTOKINES AND ITS ROLE IN PERIODONTITIS

➢ *INTERLEUKIN-1β*

Interleukin-1 β has a main role in the host response as a mediator of local tissue destruction and bone resorption. In pathogenesis of periodontal disease, IL-1β activates endothelial cells and enables the adhesion of eosinophils, thereby increasing the inflammatory response. IL-1β also regulates the destruction of the alveolar bone by promoting osteoclast formation and activity[49,50].

In various studies the monitoring of IL1β levels in GCF has been proposed as a useful approach for evaluating the host response during disease initiation, progression, and for determining therapeutic outcomes[51,52].

➢ *Interleukin-18*

Interleukin-18 belongs to the interleukin-1 superfamily which was originally discovered as an interferon γ-inducing factor[53]. It is secreted by a variety of cell types and strongly influences interferon-γ production in natural killer cells and Th1 cells. Although it is also a cytokine produced through inflammasome activation, the role of interleukin-18 in diseases is significantly less explored as compared with interleukin-1β[54]

➢ *COVID-19*

Inflammasome activation and pyroptosis could be underappreciated events in the COVID-19 pathogenesis. Abnormalities in blood coagulation leading to thrombotic complications, including pulmonary embolism, are associated with poor prognosis in COVID-19 patients.The suppression of inflammasome-mediated pyroptosis in macrophages might mitigate anomalous blood clotting by preventing the release of tissue factor, which is an initiator of blood coagulation cascades.Many repurposed compounds with regulatory effects on inflammasome activity are currently being appraised in clinical trials as treatment for COVID-19.An example is tranilast, a tryptophan analogue that has a direct inhibitory action against NLRP3.Preventing gasdermin-D pore formation without disrupting inflammasome activation represents a promising approach, as one can restrict viral replication within cells by eliciting inflammasome mediated apoptotic cell death instead of pyroptosis and cytokine release, thus limiting widespread tissue inflammation.Clinically approved drugs such as nonsteroidal antiinflammatory drugs (NSAIDs) can also be repurposed to selectively inhibit NLRP3. NSAIDs of the fenemate type such as flufenamic acid and mefenamic acid were shown to inhibit NLRP3 inflammasome by reversibly blocking volume-regulated anion channels, which regulate Cl2 transport across plasma membrane . Additionally, it was suggested that NSAIDs also contribute to limiting the secretion of proinflammatory cytokines through their cyclooxygenase-1 (COX-1)–independent activity. At present, there is no evidence for or against the use of NSAIDs as COVID-19 treatment. Nevertheless, it is recommended that NSAIDs should be prescribed cautiously to COVID-19 patients, including when used as analgesic[55].

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