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Inflammasomes - Role In Periodontal Disease: A Review

[1]Dr. Nivetha.R, [2]Dr. Sangeetha.S, [3]Dr. Savithri.N.K , [4]Dr. Gauthamkumar.N, [5]Dr. Gowrishankar.N, [6]Dr. Kalaiyazhagi.M

[1,6]Postgraduate Student, [2]Senior Lecturer, [4]Head of the Department, [5]Reader
Department of Periodontics, Madha Dental College and Hospital, Chennai.

***Corresponding Author:**
Dr. Sangeetha. S
Senior Lecturer, Department of Periodontics, Madha Dental College and Hospital,Chennai.

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Abstract

Inflammasomes play a major role in the inflammatory process and innate immunity. It acts as a receptor and sensor of the innate immune system that controls caspase-1 activation and triggers inflammation in response to pathogenic microorganisms and molecules of host protein. Inflammasomes participate in the onset or progression of diseases with major public health effects, such as metabolic disorders and neurodegenerative diseases. Finally, there have been reports of recent advances that indicate the need for prospective therapies that focus on inflammasome activity in inflammatory illnesses. The areas of inflammasome research will be the main topics of this review.

Keywords: Nucleotide-Binding Domain**(NBD),** Absent in melanoma**(AIM)** Caspase activation and recruitment domain **(CARD)**, Leucine-rich repector domain **(LRR)** , Fusobacterium nucleatum **(*Fn*)**.

Introduction

Inflammasomes are cytosolic molecular factors that typically include a sensor protein, adaptor protein, apoptosis-associated speck-like protein (ASC), and pro-inflammatory caspase-

1 [1]. Pathogen recognition receptors (PRRs) are the important components of the inflammasome complex, which includes the nucleotide-binding domain (NBD), leucine-rich receptor proteins (LCR),NOD-like receptors (NLRs), and is absent in melanoma (AIM) [2]. When exposed to certain stimuli, the relevant NLR or AIM2 (absent in melanoma) can oligomerize to form a caspase-1-activating scaffold. Activated caspases cleave the proinflammatory cytokines into their bioactive forms and cause pyroptosis, a type of inflammatory cell death [3, 4]

Canonical Inflammasomes

Nod like receptor (NLR) family

All the members of the NLR family share a central nucleotide-binding domain (NBD). It also has a leucine-rich repeat (LRR) domain at the C-terminus and a variable N-terminal domain, depending on whether the N-terminus contains a pyrin or a caspase activation and recruitment domain (CARD). The NLR family is divided into two subtypes: NLRP and NLRC. NLRP1, NLRP3, NLRC4, NLRP6, and NLRP12 are known as putative inflammasome sensors We still don't know if other NLR family members can produce or control inflammasome assembly in response to unidentified stimuli Figure:1[5]

Nod like receptor protein-1(NLRP-1)

The first cytosolic receptor known for its capacity to serve as a platform for caspase-1 activation was NLRP1 [6]. The conventional NBD and LRR domains, the pyrin domain (PYD), the function-to-find, and the C-terminal CARD domains are all present in the human NLRP1 domain. A genetic

model that shows mice with the NLRP1a gene mutation (Q593P) develop a systemic inflammatory illness that is driven by caspase-1 and IL-1 provides proof that NLRP1a can cause inflammasome activation [7].

NLRC4 Inflammasome.

It is a recognised cytosolic receptor for activating caspase-1 [8]. The classical NBD and LRR domains, pyrin domain (PYD), function-to-find, and C-terminal CARD domains, as well as pyrin domains, are all present in human NLRP1. a genetic model that exhibits a change in myelopoiesis, resulting in a noticeable change in the quantity and functionality of hematopoietic progenitor cells that is dependent on caspase-1 but independent of IL-1R signalling As a result of abnormal inflammasome activation and cell-intrinsic pyroptosis, a considerable loss of hematopoietic progenitors is seen [9].

AIM2 Inflammasome

It is diametrically opposed to NLRs, the non-NLR AIM2's HIN-200 domain. During pathogenic infection, it can directly bind its stimulus to cytosolic DNA. AIM2 can also create a caspase-1-containing inflammasome. The connections between AIM2's two domains resulted in its autoinhibitory conformation, which is eased by the sugar phosphate backbone of dsDNA48. The PYD domain is displaced by DNA binding [10], which frees the PYD domain to entice ASC to the complex [11,12].AIM2 maintains itself in an inactive state until its ligand attaches .since it is unable to engage with ASC unless autoinhibition is relieved.

Non canonical Inflammasomes

Initially, it was discovered for caspase-11, caspase-1, and caspase-3 activation. [13]. Pro- IL-1 or pro-IL-18 processing has recently been shown to be indirectly enhanced by promoting NLRP3 inflammasome activation [14]. More interestingly, caspase-11 is a receptor unrelated to the conventional LPS receptor, TLR4. It detects intracellular LPS and some intracellular bacteria, directly causing cell death and IL-1 secretion. Notably, active caspase-4 has the ability to stimulate the activation of the primed NLRP3 inflammasome without the requirement of a conventional NLRP3 activating stimulus [15].

Mechanisms of Inflammasome activation

Multimeric protein complexes called inflammasomes form in the cytosolic membrane after Pathogen associated molecular pattern (PAMPs) or Disease associated molecular pattern (DAMPs) are detected [16,17]. Canonical inflammasomes generally work as a scaffold to attract the dormant zymogen pro-caspase-1, despite the fact that there are basic differences between inflammasomes that are stimulated. The auto-proteolytic cleavage of pro-caspase-1 proteins into active caspase-1 is induced by their oligomerization .The physiologically active cytokines IL-1 and IL-18 are produced by active caspase-1, a cysteine-dependent protease, from the precursor cytokines pro-IL-1 and pro-IL-18, respectively [19,20]. The inflammatory cell death process known as pyroptosis can also be induced by active caspase-1 [21,22].

Inflammasomes In Host Defense Against Infections

The principal role of inflammasomes in the innate immune system is probably defence against invading pathogens through pyroptosis and/or the secretion of IL-1 and IL-18. These are the main effects of inflammasome activation. This is further supported by the large number of microbe-sensing NLRs, ALRs, and RLRs that may directly and indirectly detectmicroorganisms (e.g., NLRC4, AIM2, NLRP1b, IFI16, RIG-I) (e.g., NLRP3). Intracellular pathogens, extracellular pathogens that exude poisons or inject virulence proteins into the host cell, and passively "invading" commensals are the three broad groups of inflammasome-activating bacteria. Throughout the body, mucosal and nonmucosal surfaces are often colonised by all three types of inflammasome-activating microorganisms. Unsurprisingly, inflammasome proteins are expressed on these microbes' surfaces, with macrophages and dendritic cells playing the largest roles.[23]

Periodontal Pathogens And Inflammasomes

Microbes that cause periodontitis are implicated in inflammasome signaling. Fusobacterium nucleatum *(Fn)* forms benefit from the suitable environment created by Porphyromonas gingivalis *(Pg)*, a significant Gram-negative bacteria linked to periodontitis. the activation of toll-like receptors (TLR) signalled by the leucine protein sensor (LPS) that stimulates NLRP3, pro-IL-1, and pro-IL-18 and produces danger signals like ATP damage and release

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of reactive oxygen species (ROS) is involved in inflammasome activation.

Many inflammatory cytokines are secreted as a result of this process. [24,25] The Gram-negative anaerobic periodontal pathogen Aggregatibacter actinomyctemcomitans (Aa) is also involved in inflammasome activation [26]. In particular, AA can kill human leukocytes by activating caspase-1 and releasing IL-1 by generating virulence factors such as LPS, leukotoxin, and cytolethal distending toxin. Another periodontal pathogen, Treponema denticola[27,28]

Conclusion And Future Directions

The activation of inflammasomes is intricately linked to essential biological processes. Inflammasomes are involved in cell repair, metabolism, and proliferation in addition to the elimination of damaged cells. It has been shown that a number of molecules thought to be important for maintaining cellular homeostasis also play a crucial role in regulating inflammasome activity. Further research is necessary to understand the inflammasome's newly found roles in cell metabolism and proliferation.

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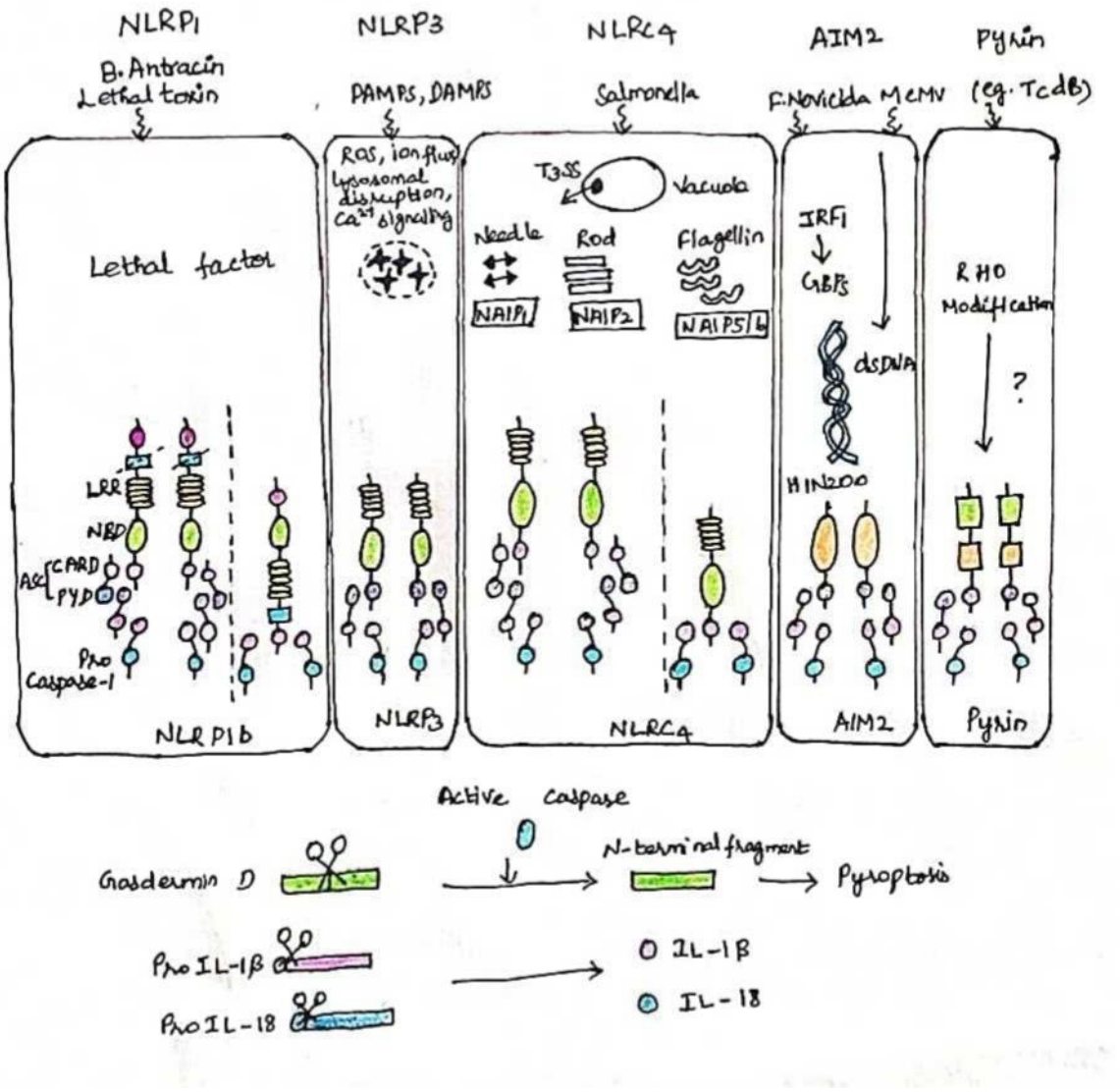
Figure 1: Canonical Inflammasomes



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