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**REVIEW ARTICLE**

# ROLE OF INFLAMMASOMES IN ACTIVATION OF INTERLEUKIN 1

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**ABSTRACT**

Inflammasomes play a major role in the activation of interleukin 1. Interleukin-1 is a pleiotropic pro-inflammatory cytokine, which induces systemic and local responses to infection. In this Monograph we have focused on the cascade which leads to the activation of Interleukin 1.



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## INTRODUCTION

Inflammation is a protective immune attempt by the otherwise conserved innate immune system in response to harmful stimuli, such as pathogens, dead cells or irritants, and is tightly regulated by the host. Insufficient inflammation can lead to persistent infection of pathogens, while excessive inflammation can cause chronic or systemic inflammatory diseases. (Chen and Nunez, 2010) Tissue damage is a common outcome in local and acute inflammation, thereby allowing an efficient tissue repair response. Interleukin-1 plays an important role in these fundamental and beneficial processes.Secretion of IL-1 requires caspase-1activity, and activation of the protease takes place in innate immune complexes, called inflammasomes. (Medzhitov, 2008) Innate immune function depends upon the recognition of pathogen-associated molecular patterns (PAMPs) which are derived from invading pathogens and danger-associated molecular patterns (DAMPs), induced as a result of endogenous stress, by germ line-encoded pattern-recognition receptors (PRRs). (Chen and Nunez, 2010) Innate immune signalling receptors monitor the extracellular space as well as many sub cellular compartments for signs of infection, damage or other cellular stressors. (Martinon *et al*., 2002) These special receptors are expressed by many cell types encompassing macrophages, neutrophils, monocytes, and epithelial cells. (Schroder and Tschopp, 2010) The activation of pattern recognition receptors by pathogen-associated molecular patterns and their post-receptor signalling via stimulation by danger-associated molecular patterns can ultimately drive the recruitment of inflammasome complexes and play a crucial role in the activation of specific inflammatory cascades. (Abdul-Sater *et al*., 2009)

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### Interleukin 1

Interleukin-1 is a pleiotropic pro-inflammatory cytokine, which induces systemic and local responses to infection. It induces expression of adhesion molecules on endothelial cells. Along with the induction of chemokines, this stimulates the infiltration of inflammatory and immunocompetent cells. (Dinarello, 2009a) It also causes fever, vasodilatation, and hypotension and enhances pain sensitivity. Based on these activities it acts as a central mediator in various acute and chronic inflammatory diseases, thus indicating a potential target for therapeutic intervention (Dinarello, 1998; Dinarello, 2004). Expression of IL-1 is regulated at the transcriptional level by nuclear factor κB (NF-κB) that is also responsible for expression of TNFα. (Dinarello, 2009a) Biological responses of IL-1 are mediated by the IL-1 receptor type I (IL-1RI), which is ubiquitously expressed., IL-1RI and TLRs have the same cytoplasmic signalling domain, the Toll/interleukin-1 receptor (TIR) domain demonstrating the prominent role of IL-1 signalling for inflammation (Dinarello, 2009a). Pro Interleukin - 1 is activated by the protease caspase-1. (Dinarello, 2009a; Kuida *et al*., 2003; Li *et al*., 1995). Caspase-1 activity is required for the activation of proIL-1, but also for the unconventional secretion of proIL-1 and of many other proteins involved in inflammation, repair and cytoprotection (Keller *et*

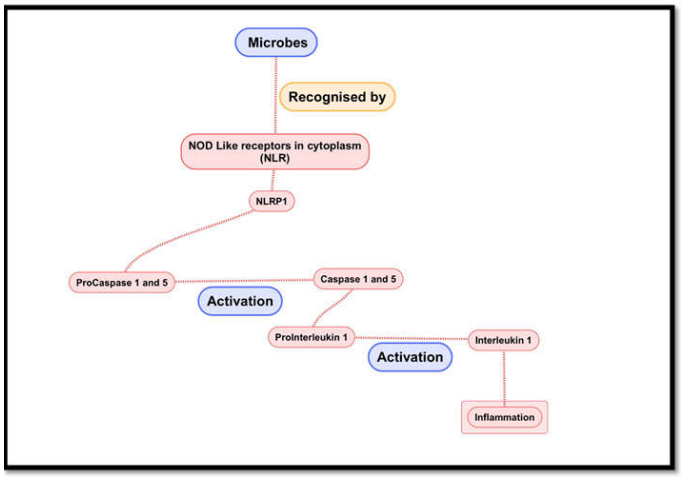
*al*., 2008; Nickel and Rabouille, 2009). Caspase-1 is initially expressed as an inactive precursor, which is activated in large complexes called inflammasomes (Martinon *et al*., 2009)

**Role of inflammasomes**

The term inflammasomewas coined by JurgTschopp and his research team in2002. Inflammasomes are nucleotide binding-domain-like receptors containing multimeric protein complexes functioning as a molecular platform activated upon cellular danger or stress signals which trigger the maturation and secretion of pro-inflammatory cytokines such as interleukin-1β and -18. The inflammasomes consist of an inflammasome sensor molecule, the adaptor protein ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain) and pro caspase 1 and 5. (Martinon *et al*., 2002) Inflammasome activation causes a rapid, proinflammatory form of cell death called pyroptosis. (Miao *et al*., 2011) Nucleotide-binding-domain-like receptors are a family of cytosolic pattern recognition receptors that are critical in surveying the cytoplasm for pathogen-associated molecular patterns or danger-associated molecular patterns (Martinon *et al*., 2009). Several members of the nucleotide binding-domain-like receptor gene family participate in the assembly of inflammasomes and the main members demonstrated to form inflammasomes in cells are NLRP1, NLRP3 and NLRC4. (Abdul-Sater *et al*., 2009; Jin and Flavell, 2010) Inflammasomes can control the mediation of pro-inflammatory responses in a diverse group of chronic diseases ranging from gout to cancer, to bacterial and viral infections (Drexler and Yazdi, 2013; Martinon *et al*., 2009). The role of the inflammasomes in mediating host metabolic responses and the dysregulation of inflammasome components are associated with various inherited chronic inflammatory and immune disorders, highlighting its relevance in human disease (Schroder and Tschopp, 2010). In particular, the imbalance of interleukin-1β activity is among the focal points of both microbial-associated and non-microbial inflammatory diseases. The progression of periodontitis is inflammatory with the main triggers of oral inflammation residing in the oral micro biome and the balance of its components (Hajishengallis and Lamont, 2014).

**Activation of interleukin 1**

In a cell-free system from a macrophage cell line, the NLRP1inflammasome was identified as a caspase-1-activating platform. The complex consists of the large backbone protein NLRP1, the small ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain) adaptor protein, procaspase-1 and -5. The NLRP1 inflammasome assembles via homotypic interactions of death domain folds. Thereby, procaspase-1 and -5 are brought into close proximity, which leads to their activation. Active caspase- 1 in turn activates proIL-1 and 18, resulting in secretion of the active cytokines and therefore in inflammation in vivo. (Schroder *et al*., 2009; Stutz *et al*., 2009) The inflammasomes contains inflammasome sensors which connect to caspase 1 via ASC, which is an adaptor protein encoded by PYCARD that is common to all inflammasomes. ASC consists of two death fold domains namely one pyrin domain and one caspase activation and recruitment domain (CARD). ASC interacts with the upstream inflammasome sensor molecules via the pyrin domain (Vajjhala *et al*., 2012). This interaction triggers the assembly of ASC into a large protein speck consisting mainly of multimers of ASC dimers. (Fernandes-Alnemri *et al*., 2007; Proell *et al*., 2013) Using its CARD, ASC brings monomers of procaspase 1 into close proximity, which initiates caspase 1 self- cleavage and the formation of the active hetero tetrameric caspase 1. Active caspase 1 proteolytically activates a number of proteins (Shao *et al*., 2007), including pro-IL-1β and pro-IL-18 (Thornberry *et al*., 1992; Gu *et al*., 1997), and induces their release via a non-classical secretion pathway (Dinarello, 2009). The transcription of pro-IL-1β is induced by the activation of the transcription factor nuclear factor-κB (NF-κB), whereas pro-IL-18 is constitutively expressed and its expression is increased after cellular activation. Therefore, these potent pro-inflammatory cytokines are controlled by two checkpoints: transcription as well as maturation and release (Dinarello, 2009). Caspase 1- mediated activation of members of the IL-1β cytokine family leads to the recruitment and the activation of other immune cells, such as neutrophils, at the site of infection and/or tissue damage.




**Role in periodontal disease pathway**

Periodontitis is an inflammatory disease that leads to the destruction of the tissues surrounding the teeth. The release of inflammatory mediators such as prostaglandins, matrix metallo proteinases, and cytokines promotes the tissue damage (Pihlstrom *et al*., 2005). The pro-inflammatory cytokine interleukin (IL)-1β is one of the main factors in the inflammatory process, since it affects nearly all cell types and is involved in bone resorption (Dinarello, 1998; Lee *et al*., 2010). The relationship between the interleukin-1 cytokine family and the NLRP3inflammasome complex has been well established in almost all studies. Higher levels of IL-1β are detected in the gingival crevicular fluid (GCF) in sites affected by periodontitis, relative to GCF from healthy sites (Zhu *et al*., 2015; Gamonal *et al*., 2000). IL-1β levels in gingival tissues and GCF correlates with the inflammatory status of periodontal disease, indicating the fundamental role of IL-1β in the pathogenesis of periodontitis (Oh *et al*., 2015).

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