

Review Article

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Inflamosomes as Activated Molecular Platform for Engagement of Innate Immune Defences

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Traditionally, innate immunity is first line of defence. These cells use multiprotein complexes called inflammasomes to produce proteins known as cytokines. The innate immune system plays a crucial role in the rapid recognition and elimination of invading microbes. The inflammasomes are large multiprotein complexes scaffolded by cytosolic pattern recognition receptors (PRRs) that form an important part of the innate immune system. In this review focus on relevant aspects concerning critical role of inflammasomes in mediating host defence, emerging links between the inflammasome and pyroptosis and autophagy, inflammasomes as design effective, safe adjuvants in the future has been discussed.

Introduction

The term “inflammasome” was coined by Jurg Tschopp and colleagues at the University of Lausanne in Switzerland to describe a caspase activating complex that processes pro-IL1b (35kd) to mature IL1b (17kd form). Inflammasomes are multimeric complexes formed in response to a variety of physiological and pathogenic stimuli. Inflammasome activation is an essential component of the innate immune response and is critical for the clearance of pathogens or damaged cells (Sharma, and Kanneganti, 2016).

The innate immune system plays a primary role in the rapid recognition and elimination of invading microorganisms, through

different processes such as phagocytosis and the induction of inflammation. Inflammation is characterized by activation of innate immune cells and production of pro-inflammatory cytokines IL-1 α , IL-1 β , and TNF α , large multiprotein complexes that sense intracellular danger signals via NOD-like receptors (NLR) (Szabo and Csak, 2012). Inflammasomes are multimolecular complexes that assemble into a platform for the activation of proinflammatory caspase1. These includes the Nod like receptor (NLR) proteins NLRP1, NLRP3, NLRC4, NLRP6 and Naip5, as well as the DNA sensing complex of AIM2 (Nature Immunology, 2012).

Pattern-recognition receptors (PRRs)

PRRs recognize pathogen associated molecular patterns (PAMPs), and damage associated molecular patterns (DAMPs). There are multiple families of PRRs including the toll like receptors (TLRs), the C type lectins, the retinoid acid inducible gene (RIG) I receptors and the NLRs.

The cytoplasmic NLRs share structural homology with plant R proteins that serve to recognize plant pathogens (Jones and Dangl, 2006).

Toll like receptors (TLRs) are membrane bound pattern recognition receptors that recognize certain extracellular phagocytized pathogen associated molecular patterns (PAMPs) and danger associated molecular patterns (DAMPs). Nod like receptors represent a second line of defense against pathogens (Fernandez *et al.*, 2014).

NLR family

A subset of PRRs, belonging to the nucleotide binding oligomerization domain (NOD) like receptor (NLR) families, detects viral and bacterial pathogens in the cytosol of host cells and induces the assembly of a multiprotein signaling platform called the inflammasome (Liu and Sun, 2012). To date, 22 NLRs have been identified in humans, and 34 have been identified in mice (Shaw *et al.*, 2010).

The NLR family is further subdivided into four groups based on the amino terminus motif, which include NLRA with an acidic transactivation domain, NLRP with a pyrin domain (PYD), and NLRC containing a caspase recruitment domain (CARD), NLRB members with a baculoviral inhibitory repeat (BIR) like domain and NLRX with a non-homologous amino terminal (Ting *et al.*, 2008).

Schematic representation of inflammasome complexes (Dunne, 2011)

Inflammasome activation leads to the generation of active caspase 1, which in turn cleaves the pro-form of IL-1 β into a mature and active form. Unrestrained ligand-independent inflammasome activation or recognition of host-derived ligands leads to autoinflammatory and inflammatory disease respectively, whereas recognition of pathogen-derived molecules is required for infection clearance.

Prototypes of inflammasomes

NLRP1 inflammasome

NLRP1 (NACHT, LRR, and PYD domains-containing protein 1), the first inflammasome described, can directly interact with caspase-1 through its C-terminal CARD domain, and in humans, the presence of ASC enhances the activity of the complex (Schroder and Tschopp, 2010). Murine NLRP1 is unable to bind to ASC because it lacks a functional PYD domain. NLRP1 is activated by the muramyl dipeptide (MDP) and the *Bacillus anthracis* lethal toxin (Szabo and Csak, 2012). Humans possess one NLRP1 gene, while duplication events that occurred after the bifurcation of rodents and primates gave rise to 3 murine variants; *Nlrp1a*, *Nlrp1b*, and *Nlrp1c*, human NLRP1 has an N-terminal PYD motif, while its murine orthologs lack this motif.

NLR3

NLRP3, are involved in the response to pathogens. IL1b is the original 'endogenous pyrogen. NLRP3 seems to be unique in its promiscuous ability to be activated by a wide array of unrelated stimuli, including microbe or host derived molecules and even totally inorganic entities such as silica, asbestos and

most famously, alum (Nature Immunology, 2012).

NLRC4

NLRC4 is an exemplar of the protective role of inflammasomes. The messy nature of pyroptosis is also an effective means of disseminating the inflammatory response and alerting the host to the presence of pathogens (Nature Immunology, 2012). NLRC4/IPAF (NLR-family CARD domain containing protein 4) inflammasome is activated by the flagellin of Gram-negative and Gram-positive bacteria or the type III secretion system (T3SS) of Gram-negative bacteria.

NLRP6

NLRP6 is uncharacteristic by virtue of the unusual ligand it recognizes and its observed downstream effects. NLRP6 identified as a negative regulator of the mitogen-activated protein kinase and NF- κ B pathway in macrophages infected with *Listeria monocytogenes*, *Escherichia coli*, and *Salmonella* (Anand *et al.*, 2012).

NLRP12

NLRP12 was initially characterized as an inhibitor of noncanonical NF- κ B signaling (Lich *et al.*, 2007). It was also involved in caspase-1 activation in response to *Yersinia pestis* and *Plasmodium* infection (Vladimer *et al.*, 2012; Ataide *et al.*, 2014). The role of NLRP12 in NF- κ B-mediated signaling makes it an important regulator of immune response after *Salmonella* infection and during colorectal cancer (Zaki *et al.*, 2014).

AIM 2 inflammasome

AIM 2 (absent in melanoma 2) is a cytosolic dsDNA sensing inflammasome activated by bacterial, viral, and mammalian host DNA to trigger caspase-1 activation (Nakahira *et al.*,

2011). AIM2 can directly bind to its ligand and may contribute to the pathogenesis of autoimmune diseases by recognizing the mammalian DNA (Rathinam *et al.*, 2010).

Inflammasome Activation

NLRP3 inflammasome assembly occurs following activation of the NLRP3 protein. Several NLRP3 inflammasome activators have been identified, and these comprise viruses (including influenza virus, adenovirus), bacteria (including *Staphylococcus aureus*, *Listeria monocytogenes*, *Shigella flexneri*), fungi, bacterial pore forming toxins, ATP, crystalline particulates (including alum, asbestos, silica, uric acid), chemical irritants and UVB (Wilson and Cassel, 2010).

Inhibitors of Inflammasomes

Pyroptosis and Apoptosis

Inflammasome assembly leads to the activation of the proinflammatory caspase. Consequently, an inflammatory immune response is mounted along with a programmed cell death, called pyroptosis (Jamilloux *et al.*, 2014). NLRC4 is an exemplar of the protective role of inflammasomes. IL1 β is the original 'endogenous pyrogen', Inflammasomes and autophagy

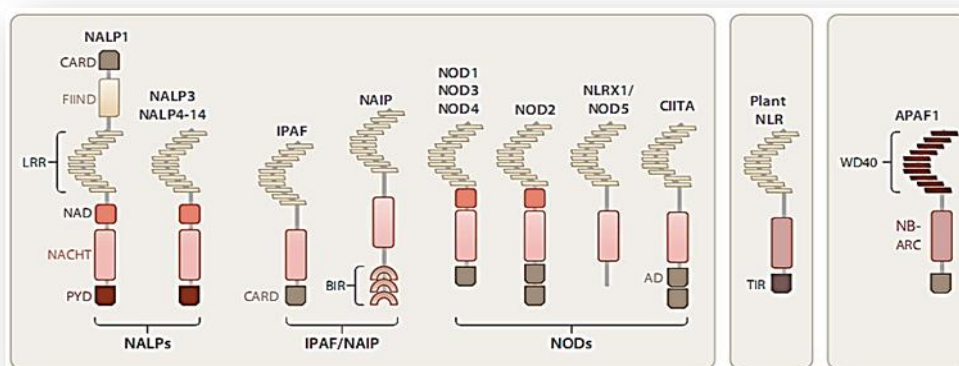
The autophagy and inflammasome pathways are ancient innate immune mechanisms for controlling invading pathogens that are linked by mutual regulation. As a cytosolic pathogen recognition receptor (PRR) complex, the inflammasome both induces and is induced by autophagy through direct interactions with autophagy proteins or through the effects of secondary molecules, such as mitochondrial reactive oxygen species and mitochondrial DNA (Rodgers *et al.*, 2014).

Inflammasomes and adjuvanticity

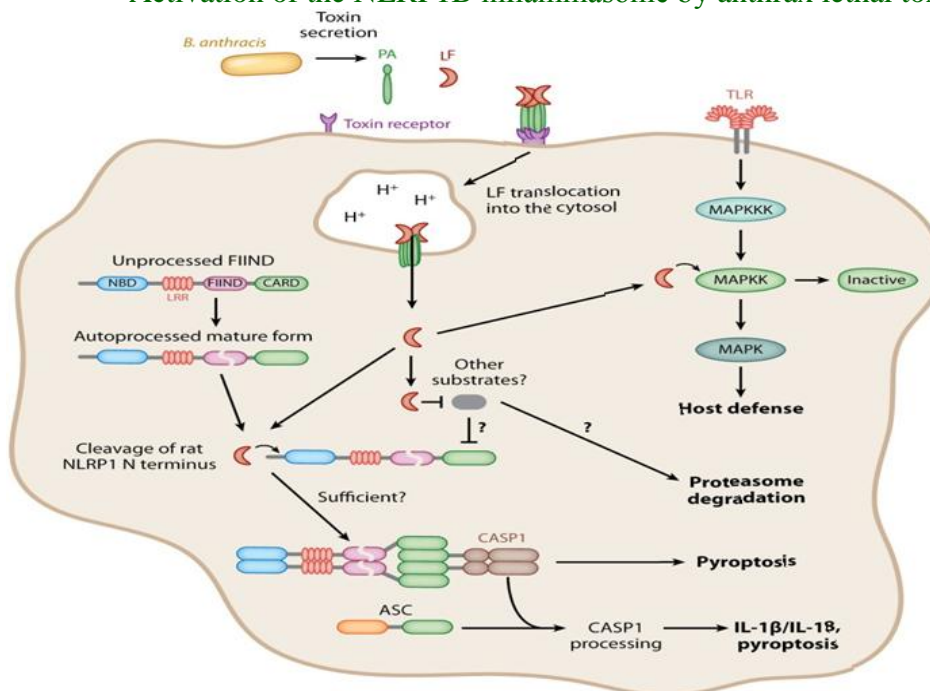
Adjuvants are materials that enhance the immune response to an antigen. The NALP3 inflammasome has been associated with several autoinflammatory conditions including gout. The NALP3 inflammasome is a crucial element in the adjuvant effect of aluminum and can direct a humoral adaptive immune response. Many of the inflammasome activators have adjuvant properties; these include MDP (muramyl

dipeptide), MSU (monosodium urate), alum, silica dust. Alum defines particle materials based on aluminium salt precipitates that are the most widely used adjuvants in human vaccines. Alum activates a Th2-biased immunity with elevated Th2-dependent antibody isotypes IgG1 and IgE, both MSU and alum depend on an intact inflammasome including NALP3, ASC, and caspase-1 to trigger a Th2-biased response (Martinon *et al.*, 2009).

Schematic representation of inflammasome complexes (Dunne, 2011)



Activation of the NLRP1B inflammasome by anthrax lethal toxin



Inflammasomes and disorders

The discovery that NLRP3 (NLR-related protein 3) can recognize host-derived particulate matter such as uric acid and cholesterol crystals has led to this inflammasome being implicated in a number of inflammatory diseases, including gout, atherosclerosis and Type 2 diabetes. In addition, aberrant NLRP3 activation has also been observed in a number of heritable disorders now referred to as cryopyrinopathies (Dunne, 2011).

Atherosclerosis has also been associated with chronic inflammation. Accumulation of immune cells and cytokine production are hallmarks of atherosclerotic plaques (Hansson, 2005). IL-1 β is one of the proinflammatory cytokines involved in the pathogenesis of metabolic disorders (Davis *et al.*, 2011). Inflammasomes have been linked to a variety of autoinflammatory and autoimmune diseases, including neurodegenerative diseases (multiple sclerosis, Alzheimer's disease and Parkinson's disease) and metabolic disorders (atherosclerosis, type 2 diabetes and obesity) (Strowig *et al.*, 2012).

Inflammasomes and carcinogens

The inhibition of inflammasomes or neutralization of their products, mainly interleukin 1 β (IL1 β) and IL18, has profound effects on carcinogenesis and tumor progression. Thus, inflammasomes are promising therapeutic targets in cancer related clinical conditions (Zitvogel *et al.*, 2012). The clinical importance of inflammasomes reaches beyond infectious disease, as dysregulated inflammasome activity is associated with numerous hereditary and acquired inflammatory disorders (Broz and Dixit, 2016).

A major challenge in NLR and inflammasome research is that current knowledge of NLR signaling pathways and disease function is highly fragmented. The long-term aim of the “NLR and inflammasome signaling” research unit is to gain insight into the role of NLRs and inflammasomes in human disease. Translation of newly gained knowledge will contribute to the development of innovative diagnostics and therapeutic approaches for autoimmune and infectious diseases. Recently, inflammasome function has been implicated in more common human conditions, such as gout, type II diabetes and cancer. This raises the possibility that anti-IL-1 therapeutics may have broader applications and may be utilized across diverse disease states that are linked insidiously through unwanted or heightened inflammasome activity. In addition to removal of damaged cells, inflammasomes are also involved in cell repair, metabolism, and proliferation. Various molecules believed to be involved in the maintenance of cellular homeostasis have been demonstrated to act as critical regulators of inflammasome function and vice versa.

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