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EDITORIAL

ENIGMATIC INFLAMMASOMES: LESSER-STUDIED NLRs SERIES
Series Editor: Kathy Triantafilou

Enigmatic inflammasomes

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Summary

Inflammasomes are generally thought of as large protein complexes that assemble in the cytosol in response to danger such as tissue damage or infection; once activated, they trigger production of inflammatory cytokines and drive cells towards a pro-inflammatory death – termed pyroptosis. Inflammasome activation is a two-step process; priming or Signal 1 (typically via Toll or other receptors that activate NF-kB) induces transcription of pro-forms of IL-1β and IL-18, while activation or Signal 2 (by many effectors, including a number of bacterial toxins that form pores in cell membranes) comprises activation of caspase-1 in the inflammasome that in turn cleaves pro-IL-1β and pro-IL-18 and induces release of the active pro-inflammatory cytokines. The most studied inflammasome is the NLRP3 inflammasome, but in addition to NLRP3, there are several lesser-known or enigmatic inflammasomes whose functions seem to range from non-canonical inflammasome activation, pathogen/damage, suppression or modulation of inflammation and even embryonic development. In this review series, which will be presented in two parts, we will focus on lesser-known inflammasomes, such as NLRP6 (non-canonical inflammasome activation), NLRP9 (restricting rotavirus infection in intestinal epithelial cells), NLRX1 (negative regulators of inflammation), NLRC5 (regulating antigen presentation) and NLRP7 (sensing of bacterial lipoproteins). Although the function of NLRP3 is understood, the functions of these lesser-studied inflammasomes are largely unstudied. Given that after a decade of research, new inflammasome and new inflammasome activators are still being discovered indicates that there is a lot more that we need to find out in the NLR field. Only by understanding all of the members of the NLR family, will we be able to target them therapeutically in the future.

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The innate immune system relies on germ-line-encoded pattern-recognition receptors (PRRs) in order to respond to signatures from pathogens or changes in the homeostasis of the host cells. One of the biggest families of PRRs, with more than 20 members, is the nucleotide oligomerization and binding domain (NOD)-like receptors (NLRs), which triggers a distinct defence mechanism. These NLRs assemble into cytosolic oligomeric structures called inflammasomes that activate caspase-1 and lead to the cleavage of IL-1β, IL-18 and gasdermin D leading to pyroptotic cell death.[1]

NLRs typically consist of a tripartite structure consisting of a C-terminal sensor part consisting of leucine-rich repeats (LRRs), a central adapter NACHT domain, which serves as a bridge connecting the sensor to the downstream N-terminal effector domain; consisting of either a caspase activation and recruitment domain (CARD) or pyrin domain.[2] NLRs tend to be named after their sensor part, and they tend to either recognize pathogens either directly by binding pathogen-associated molecular patterns (PAMPs) or indirectly by sensing changes in the homeostatic environment of the host cell. Their functions

are vital for the host immune defence, but aberrant activation also leads to autoimmune diseases.

The most studied NLRs are the NLR-family, PYD-containing 3 (NLRP3) and the NLR-family, caspase activation and recruitment domain (CARD)-containing 4 (NLRC4). In the case of NLRP3, it responds to an incredibly broad range of pathogens; thus, it is unlikely that it binds to PAMPs directly. It is believed that it responds to damage-associated molecular patterns (DAMPs) consisting of by-products of pathogen invasion or sterile inflammation.[3] NLRC4 is activated by specific PAMPs, such as the bacterial type III secretion systems (T3SS) and bacterial flagellin.[4,5] However, in addition to NLRP3 and NLRC4, only about half of the remaining NLRs has been characterized in any detail. These lesser-known, enigmatic inflammasomes whose functions seem to range from non-canonical inflammasome activation, pathogen/damage, suppression or modulation of inflammation and even embryonic development will be the focus of this review series.

This exciting review series is named 'enigmatic inflammasomes', as we are focusing on inflammasomes that very little is known about and have not been widely studied; thus, they constitute an enigma for the field of immunology. The series highlights recent advances in the understanding of the role of these inflammasomes. The review series will be published in two parts, with the first part presented here, focusing on lesser-known inflammasomes with diverse functions, such as NLRC5 (regulating antigen presentation), NLRX1 (negative regulator), NLRP6 (non-canonical inflammasome activation) and NLRP9 (embryonic development and restricting rotavirus infection in intestinal epithelial cells). In the second part of the review series, we will continue to highlight not only lesser-known NLRs, such as NLRP7 but also enigmatic components and functions of the inflammasome, such as the function of extracellular ASC specks, and the involvement of these lesser-known inflammasomes in the regulation of immunometabolism.

In the first review article of this series, Cho et al[6] introduce NLRC5, which is a lesser-known inflammasome with a unique function that bridges both innate and adaptive immune responses: regulation of MHC class I expression and antigen presentation. The authors discuss the recent findings that NLRC5 is a major transcriptional regulator of MHC class I. The fact that deletion of NLRC5 leads to impaired MHC class I, as well as MHC class I pathway-related gene expression, demonstrates that NLRC5 is a transactivator of the MHC class I pathway. As expected, the physiological consequence of NLRC5 deficiency leads to an impaired immune function against bacterial and viral pathogens, since there is impaired MHC class I expression and consequently impaired CD8 T-cell activation. The authors further highlight the revelation that NLRC5 has been found to be a central target for immune evasion by several cancer types, thereby demonstrating the role of NLRC5 not only in immune regulation but also in cancer immunity.

Pickering and Booty[7] focus on a truly enigmatic inflammasome, NLRX1. NLRX1 not only has a unique structure and localization but most likely it also has a unique function unlike any of the other NLRs. The authors discuss the structure of NLRX1 and the importance of its mitochondrial localization, reviewing current evidence that suggests that NLRX1 is a central homeostatic gatekeeper between mitochondrial biology and immunological response. The authors discuss emerging links between NLRX1 in cancer biology, autoimmunity and other inflammatory diseases and propose areas that could benefit from therapeutically targeting NLRX1.

Building on inflammasomes that have 'inflammasome'-dependent and 'inflammasome'-independent functions, Zheng et al[8] introduce us to NLRP6. NLRP6 is an NLR that can form a functional inflammasome that can recruit caspase-1 and caspase-11, but on the other hand, NLRP6 can also exert its function in an 'inflammasome'-independent manner regulating gut microbiome composition, goblet cell function and related susceptibility to gastrointestinal inflammatory, infectious and neoplastic diseases. The authors highlight the emerging functions of NLRP6 in the gut, liver and other organs and suggest that NLRP6 can harness a context-specific pro-inflammatory or anti-inflammatory innate immune activation.

Finally, Mullins and Chen[9] introduce another less-characterized NLR, NLRP9. NLRP9 is unique in the fact that it is proposed to be expressed and function solely in the reproduction system. The authors discuss how NLRP9 has been implicated to function in preimplantation embryo development. They also discuss recent evidence suggesting that NLRP9 might not be solely present in the reproductive system, but also in the intestines, in the lung tissue and in the brain. Most interestingly, the authors discuss NLRP9's involvement in limiting rotavirus infection in the intestine and suggest potential functions in different tissues and organs.

Since the discovery of inflammasome, the general consensus has been that they are intracellular cytosolic signalling platforms, controlling IL-1β and IL-18 secretion, but evidence is now emerging that they are so much more. They seem to be able to control antigen presentation, mitochondrial homeostasis, microbiome composition and even embryonic development. Their dysregulation seems to lead to so many autoimmune and neoplastic diseases that targeting them therapeutically seems to be the way forward. These four groups of authors provide us with fantastic reviews of the most up-to-date literature on these enigmatic inflammasomes. They present to us the above-mentioned inflammasomes, which have inflammasome-independent, pleiotropic and multifaceted functions – far beyond the canonical

inflammasome function of just regulating IL-1β and IL-18 secretion – which make them not only enigmatic but also intriguing and spark our interest leaving us wanting to discover more in order to be able to harness them and target them therapeutically in health and disease. I hope that you enjoy reading this first instalment of the review series as much as I have and I look forward in sharing with you the next instalment.

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