Enigmatic inflammasomes –Sequel (Part 2)

Kathy Triantafilou[1,2]

[1] *Immunology Catalyst, Immunology Network, Adaptive Immunity Research Unit, GlaxoSmithKline, Stevenage, UK*
[2] *Institute of Infection and Immunity, School of Medicine, Cardiff University, University Hospital of Wales, Cardiff, UK*

Correspondence:
Professor Kathy Triantafilou, Institute of Infection and Immunity,
Cardiff University, School of Medicine,
University Hospital of Wales, Heath Park, Cardiff, CF144XN, UK.
Email: TriantafilouK@cardiff.ac.uk

Abstract
In this issue, we introduce the second part of our review series focusing on lesser-known enigmatic inflammasomes. This part of the collection introduces one more under-studied NLR, NLRP7, and not only its role as a regulator of inflammation in response to bacterial infections but also its non-inflammasome role in early pregnancy. In addition, the enigmatic function of extracellular ASC specks is also introduced, where extracellular ASC specks are presented as 'danger signals' to propagate inflammation. The series is concluded with an article that reviews the immunometabolic regulation of all of these lesser-known NLRs, demonstrating that metabolic regulation of inflammasome activation is central for the whole NLR family. These three reviews, together with the four articles that were published in the first part of the series in December 2020, offer new insights into the complex functions of NLRs, well beyond the well-known NLRP3. The review series as a whole provides a thought-provoking platform with some of the latest findings in the NLR field and sparks our imagination into what might be discovered in this space in the future.

The term 'inflammasome' was first coined almost 20 years ago by Martinon & Tschopp[1] in order to describe a stimulus-induced cytoplasmic multimeric protein complex that promotes the maturation of pro-inflammatory interleukin-1β (IL-1β) and interleukin-18 (IL-18) and the induction of an inflammatory cell death termed pyroptosis. Over the past 20 years, intense research in this area has unravelled key aspects of inflammasome activation and its role in disease processes.
As inflammasomes represent important sensors of the innate immune response, it is logical that their dysregulation is associated with augmented inflammation, at different clinical contexts, which can be detrimental to the host.

Two types of inflammasome activation have been described: canonical and non-canonical inflammasome activation. In the case of canonical inflammasome activation, two sequential stimuli are required for activation. There is a priming signal (for the transcription of pro-IL- 1β and pro-IL-18), and upon the second signal, which triggers the formation of the inflammasome complex, the inflammasome sensors (nucleotide oligomerization and binding domain (NOD)-like receptors (NLRs)) initiate inflammasome assembly by oligomerizing and recruiting pro-caspase- 1, with or without the ASC adapter. This leads to the autocatalytic cleavage of caspase-1 and processing of pro-IL- 1β and pro-IL- 18 to their mature and bioactive forms and cleavage of gasdermin D (GSDMD),[2] which is the executioner of pyroptosis. In inflammasomes where oligomerization of the NLR occurs with ASC, they form what are called 'ASC specks' and these are believed to be also released in the extracellular space during pyroptosis propagating inflammation.

In the case of the newly discovered 'non-canonical inflammasome', it signals in a caspase-1-Independent manner through direct recognition of cytosolic LPS by the CARDs of caspase-4 and caspase-5 (in humans) and caspase-11 (in mice). This elicits caspase dimerization and activation, resulting in cleavage of GSDMD.[3]

The final review of the series by Jimenez-Duran and Triantafilou[10] nicely concludes the review series by considering the metabolic regulation of lesser-known inflammasomes. There is growing evidence of metabolic regulation of NLRP3 inflammasome activation, but little is known regarding other NLRs. The authors introduce us to NLRP1, which has been reported to have both protective and worsening effects in different immunometabolic diseases. It seems to be able to act as a sensor of cellular stress, glucose and lipid metabolism and has been linked to microbiome dysbiosis and inflammatory bowel disease.

In addition, the authors introduce us to a truly enigmatic inflammasome, NLRC3, whose functions are mostly undiscovered. However, NLRC3 has been shown to play a major role in T-cell metabolism, where it seems to act as a brake for aerobic glycolysis, which is the hallmark of activated T cells and Th1 cell differentiation. Although in the first part of the series, Pickering and Booty[5] introduced us to NLRX1, in the second part of the review series, Jimenez-Duran and Triantafilou[10] introduce us to the metabolic regulation ofNLRX1. With its location in the outer mitochondrial membrane,NLRX1 is key in modulating cellular metabolism and has been linked to a variety of immunometabolic diseases, such as cancer, colitis, inflammatory bowel disease and CNS inflammation. They also introduce NLRP6 and metabolism and its effect on host–microbiota communications, as well as NLRP12 and its protective role in inflammatory bowel disease and its function as a regulator of the colonic microbiota and suppressor of inflammation to microbial ligands.

Finally, the crosstalk of lesser-known inflammasomes with other signalling pathways, such as the complement system, is discussed with a focus on the complement–inflammasome – immunometabolism axis. Jimenez-Duran and Triantafilou conclude the review series with a thought-provoking discussion regarding the metabolic control of these lesser-known inflammasomes, how these implicate a variety of perturbations in the glycolytic pathway, and mitochondrial and lipid metabolism and how it is linked to several autoimmune and metabolic diseases.

The three articles in this final instalment of the review series not only provide us with recent advances to our knowledge of enigmatic inflammasomes, such as NLRP7, but also introduce us to novel concepts of inflammasome biology such as the existence of extracellular NLR-ASC specks propagating inflammasome activation in the nearby environment, as well as how immunometabolism regulates these lesser-known inflammasomes. Together with the first part of the series, we provide an exciting review series that presents advances in the field of inflammasome activation beyond the well-known NLRP3 and provide us with some thought-provoking discussions on which are the areas that need to be addressed in the field of inflammasome research. As demonstrated by this review series, almost twenty years since the discovery of NLRs, we still have several under-studied NLRs. Due to their diversity of function, it would be exciting to watch this space in the future. We hope you enjoy the review series as much as we have and inspire you to look a little closer at these enigmatic NLRs!

REFERENCES

1. Martinon F, Burns K, Tschopp J. The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-β. Mol Cell. 2002;10:417–26.
2. Shi J, Zhao Y, Wang K, Shi X, Wang Y, Huang H, et al. Cleavage of GSDMD by inflammatory caspases determines pyroptotic cell death. Nature. 2015;526:660–5.
3. Kayagaki N, Stowe IB, Lee BL, O'Rourke K, Anderson K, Warming S, et al. Caspase-11 cleaves gasdermin D for non-canonical inflammasome signalling. Nature. 2015;526:666–71.
4. Cho SX, Vijayan S, Yoo JS, Watanabe T, Ouda R, An N, et al. MHC class I transactivator NLRC5 in host immunity, cancer and beyond. Immunology. 2021;162:252–61.
5. Pickering RJ, Booty LM. NLR in eXile: Emerging roles of NLRX1 in immunity and human disease. Immunology. 2021;162:268–80.
6. Zheng D, Kern L, Elinav E. The NLRP6 inflammasome. Immunology. 2021;162:281–9.
7. Mullins B, Chen J. NLRP9 in innate immunity and inflammation. Immunology. 2021;162:262–7.
8. Carriere J, Dorfleutner A, Stehlik C. NLRP7: From inflammasome regulation to human disease. Immunology. 2021;163:363–76.
9. de Souza JG, Starobinas N, Ibanez OC. Unknown/Enigmatic functions of extracellular ASC. Immunology. 2021;163:377–88.
10. Jimenez-Duran G, Triantafilou M. Metabolic regulators of enigmatic inflammasomes in autoimmune diseases and crosstalk with innate immune receptors. Immunology. 2021;163:348–62.