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Advances in inflammasome research: Recent breakthroughs and future hurdles

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Abstract

Inflammasomes are a group of cytosolic multiprotein complexes that are assembled in response to pathogen- and damage-associated molecular patterns and cellular stress. Inflammasome assembly drives the maturation and secretion of proinflammatory cytokines and induces pyroptosis. Here, we will highlight some key advancements in inflammasome research with therapeutic potential.

Keywords

inflammasome; PANoptosis; pyroptosis; apoptosis; necroptosis; inflammatory cell death; PANoptosome; NLRP3; gasdermin; NLRP1; NLRC4; AIM2; Pyrin

The inflammasome field is still relatively young, with the term “inflammasome” having been coined in 2002 (1) (Figure 1). Since then, the inflammasome field has seen rapid progress with many new and groundbreaking discoveries. A wide range of functions for inflammasomes have been found. Inflammasome activation is beneficial in several infectious diseases to help clear pathogens, but it can also be associated with excessive inflammation and cytokine storm that cause significant morbidity and mortality. Inflammasome activation also contributes to pathological sterile inflammation associated with a number of autoinflammatory, neurodegenerative, and metabolic diseases, including rheumatoid arthritis, Alzheimer's disease, Parkinson's disease, and diabetes. Additionally, in the context of cancer, inflammasomes have been shown to have dual functions; they can be protective, as in colorectal cancer, or they can contribute to tumorigenesis, angiogenesis, metastasis, and immunosuppression (2).

The inflammasome complex is canonically composed of a sensor molecule, the adaptor ASC, and the effector caspase-1. Several sensors have been identified, with NLRP3, NLRP1, NLRC4, Pyrin, and AIM2 being the most well-characterized. NLRP3 specifically is involved in inflammasome activation under a wide variety of conditions, including in many pathological contexts. For this reason, several groups have worked to identify and develop inhibitors against NLRP3. Glyburide, which was first developed as a treatment for diabetes, was found to inhibit the NLRP3 inflammasome in 2009 (3). Since then, other specific

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inhibitors such as MCC950 (4) and OLT1177 (5) have been developed. Now NLRP3 inhibitors are being pursued by the pharmaceutical industry to treat inflammatory diseases.

Inflammasome pathways lead to the release of key proinflammatory cytokines, interleukin (IL)-1 β and IL-18, and a lytic form of cell death known as pyroptosis. IL-1 β and IL-18 are produced and stored in the cytosol as functionally inactive proteins. Caspase-1 cleaves both IL-1 β and IL-18 after specific aspartate residues in their linker regions, allowing release of the mature cytokines. Recently it was discovered that pyroptosis is executed through caspase-1/11-directed cleavage of gasdermin D (GSDMD) at Asp275 (corresponding to Asp276 in human GSDMD), releasing a cytotoxic GSDMD amino-terminal fragment (GSDMD-N) (6, 7). Further structural studies on gasdermin protein family members identified that gasdermin amino-terminal fragments can insert into membranes, forming pores that, in the case of GSDMD-N, allow the release of the proinflammatory cytokines and execution of pyroptosis (8).

Major strides have been made in our understanding of the interplay between inflammasome activation and inflammatory cell death. Historically, inflammasome activation was known to activate only pyroptosis, but increasing evidence has shown dynamic connections with other forms of cell death. For example, studies have connected pyroptotic components (inflammasome sensors and caspase-1 and -11) with apoptotic components (caspase-8, caspase-7, and PARP) and necroptotic components (RIPK1 and RIPK3), leading to the establishment of the concept of PANoptosis. PANoptosis is defined as the integration of the pyroptosis, apoptosis, and necroptosis pathways into a unified mechanism of inflammatory cell death. Importantly, PANoptosis is driven through a single multiprotein complex called the PANoptosome, which incorporates not only inflammasome components (NLRP3 and ASC) but also apoptotic and necroptotic molecules (9–11). PANoptosis has been shown to be activated in response to infection with pathogens including influenza A virus, *Salmonella* Typhimurium, *Listeria monocytogenes*, and vesicular stomatitis virus, and it also plays important roles in autoinflammatory diseases (10) and cancer (12). While the involvement of NLRP3 and ASC in the PANoptosome and PANoptosis have been shown, additional inflammasome components may also play a role in the PANoptosome; this requires further study.

While significant progress has been made in our understanding of the inflammasome and its implications in health and disease, several outstanding questions remain. The quest for novel inflammasomes, regulators, and upstream signaling components will provide key insights. For example, researchers have searched for a defined activation mechanism for the NLRP3 inflammasome for years. For other inflammasome sensors, a specific molecular pathway or event has been identified that causes activation, but NLRP3 has been shown to respond to a diverse array of triggers. Several models for how NLRP3 is activated have been proposed, but no consensus set of activation steps shared by all triggers has been found to date. This remains a critical challenge for developing therapies to target this inflammasome pathway.

Additionally, downstream of inflammasome activation, caspase-mediated GSDMD cleavage and subsequent pyroptosis have been established, but the full suite of caspase substrates that are cleaved during pyroptosis remains unclear. Analysis of these additional substrates may

improve our knowledge of how pyroptotic cells regulate immune activation and host defense.

Furthermore, in-depth understanding of the NLRP3 inflammasome pathway has revealed an unexpected amount of crosstalk between pyroptosis, apoptosis, and necroptosis that requires further studies. Initial studies indicate that, consistent with the compositions of inflammasomes, PANoptosomes with unique compositions can be formed in response to different stimuli (9–11). Characterizing these interactions will extend the impact of the inflammasome field and provide crucial information for the development of therapies to target a diverse array of inflammatory diseases. Additionally, the activation of these pathways is likely to be beneficial in cancer, where inflammasomes and PANoptosis can induce tumor cell death (12) and may also augment the activation of therapeutic immune responses through the secretion of inflammatory cytokines and the release of tumor cell antigens to prime the adaptive response.

It is also likely that there are diverse consequences for inflammasome activation on a single-cell and cell type-specific level. For example, how inflammasome activation signals from one cell to its neighbors to control pathogen spread or potentiate sterile tissue damage in inflammatory disease remains to be determined. Improved understanding of the connections between inflammasome-mediated pathways and how these connections play out at the cellular level will pave the way for significant therapeutic advances.

Overall, the past decade has been a truly exciting time in the inflammasome field, but there is more work to be done to fully understand how to translate these laboratory findings into patient-saving treatment options. Inflammation and aberrant cell death are hallmarks of countless diseases; therefore, it is critical that we continue pushing the boundaries in this field to find new and innovative ways to target these processes and save lives.

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Figure 1.
Timeline of the major basic science and clinical advances in the inflammasome field.