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Detection of viruses by inflammasomes

Lotte Spel and Fabio Martinon

The innate immune system has evolved mechanisms to keep the viral infection under control and repair damaged tissues. Several pathways can identify the presence of pathogenic components, such as viral nucleic acids and viral proteins. Also, the innate immune system can detect cellular and tissue perturbations caused by infections. Inflammasomes are cellular pieces of machinery that can detect a pathogen's presence and its possible impact on cellular integrity. Thereby several inflammasomes, including the NLRP3 inflammasome and the AIM2 inflammasome, contribute to antiviral innate immunity. Inflammation driven by inflammasomes promotes immune defenses and initiate repair mechanisms. However, its overactivation may trigger acute inflammatory responses that may harm the host. This pathologic activation could contribute to the hyperinflammatory response observed in patients infected with viruses, including influenza, SARS, and possibly SARS-CoV2.

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Introduction

Viruses attach to cells through binding between viral surface proteins and host membrane receptors. Often undetected, the virus may initiate uptake into the endosomal pathway where the acidic environment facilitates the entry of the viral genome into the cell. Viruses can promote the fusion of viral membrane with the endosomal membrane, leading to the viral genome delivery in the cytosol. Alternatively, viral nucleic acids can translocate to the cytosol via pores or endosomal breakage. Often, sensing of viral invasion happens no earlier than upon releasing its genomic content, either by TLRs in the endosomal pathway or by nucleic acid sensors in the host cytosol.

The immune system harbors nucleic acid-sensing receptors that aim to detect and eliminate foreign nucleic acids [1]. Simpler life forms such as bacteria and archaea have evolved defense mechanisms such as the CRISPR-Cas system or RNA interference to target viral nucleic acids [2]. In vertebrates, activation of nucleic acid-sensing immune receptors participates in regulating protein antigen-directed adaptive immunity, aiming to eliminate foreign proteins.

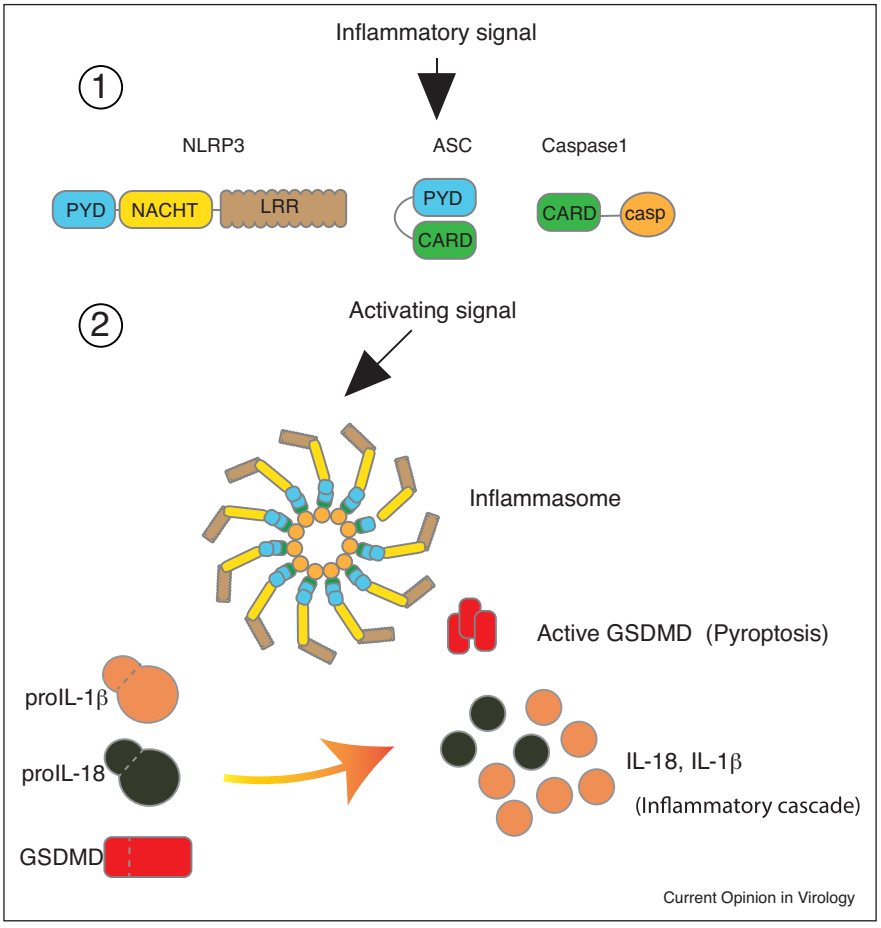
A limited number of germline-encoded innate immune receptors have been identified in the last two decades. Among them are several groups of immune receptors specializing in detecting foreign or damage-associated nucleic acids in specific cellular compartments. Toll-like receptors (TLRs), including TLR3, TLR7, TLR8, and TLR9 detect nucleic acids in the endolysosomal compartment of distinct immune cell subsets and specific-somatic cells. Nucleic acid-detecting immune receptors located in the cytosol include, among others, the RIG-1-like-receptors (RLRs), NOD-like-receptors (NLRs), and the Absent in Melanoma-2-like receptors (ALRs). Furthermore, several nucleic acid-detecting effector proteins directly detect and restrict nucleic acid function and replication [1].

Engagement of these viral nucleic sensors activates several pathways, initiating the transcription of interferon (IFN) and proinflammatory cytokines. These inflammatory mediators contribute to the recruitment of innate immune cells and the development of an immune response.

In addition to these transcriptional programs, viral infections can engage inflammasomes, a group of signaling pathways that relies on the activation of proteolytic enzymes. Inflammasomes activate the proteolytic activity of inflammatory caspases such as caspase-1. These enzymes are involved in the maturation of cytokines, including IL-1β. They can also trigger a proinflammatory form of death of the infected cells by a process termed pyroptosis [3] (Figure 1).

The inflammasomes currently known to be involved in innate antiviral immunity include those activated through NLRP3, RIG-I and AIM2. However, the exact contribution of inflammasomes to viral pathogenesis and immunity is still poorly understood. Here, we will review some concepts that emerged, indicating that several stimuli can engage inflammasome in the course of viral infection. This activation can contribute to limit viral replication, but in some instances, it may lead to harmful inflammation.

Figure 1



Generic NLRP3 inflammasome activation.
Upon infection, a priming signal is generated **(a)**. Pathways such as TLRs are engaged and induce NFκB and Type I Interferon. These transcriptional programs can upregulate gene transcription of inflammasome components, including NLRP3, Caspase-1, and ASC, as well as inflammasome substrates proIL-1β, proIL-18, and GSDMD. Then, viral products, as well as perturbation of cellular integrity, may initiate an activation program **(b)**, leading to the oligomerization and assembly of the active inflammasome complex. Inflammasome proteolytic activity mediated by the caspase-1 will cleave its substrates. Cleaved GSDMD forms membrane pores. These pores permeabilize the plasma membrane facilitating the passive release of cleaved cytokines IL-1β and IL-18. GSDMD pores can also destabilize the membrane to cause cell death, triggering the leakage of cellular content by a process termed pyroptosis. IL-1β, IL-18, and other inflammatory mediators released upon pyroptosis will contribute to immune responses and initiate an inflammatory cascade.

Inflammasomes induced by the detection of viral genome

The family of NOD-like receptors (NLRs) includes many cytosolic proteins involved in detecting pathogen-associated or damage-associated molecular patterns (PAMPs or DAMPs). NLRP3 is the only member of this family described to play a role in viral infections through sensing viral RNA and subsequent activating inflammasome complex. Influenza infection in mice lacking inflammasome components NLRP3, ASC, or caspase-1, resulted in reduced IL-1β and IL-18 secretion, reduced lung cellular influx, decreased inflammatory cytokines, and increased lethality [4–6]. Although these studies highlight the pivotal role of the NLRP3 inflammasome in influenza antiviral immunity, its beneficial effect during the course of infection is complex and will be discussed in more detail below. Recent studies identified a role for Z-DNA binding protein-1 (ZBP1) in regulating NLRP3 gene expression after influenza infection [7]. ZBP1-deficient mice presented reduced inflammation compared to wild type animals. Furthermore, ZBP1-deficient mice showed less tissue damage after influenza infection. In this context, the IFN regulatory factor 1 (IRF1) transcription factor upregulates ZBP1 expression to promote NLRP3 inflammasome activation and ZBP1-induced cell death [8].

On a molecular level, presence of viral RNA has also been proposed to trigger NLRP3 inflammasome activation in a manner depending on RNA-modulating proteins

including DHX33 [9] and RNase L [10] and the production of reactive oxygen species (ROS) [4]. Viral RNA is also sensed by retinoic acid-inducible gene-1 (RIG-1), a cytosolic pattern recognition receptor of the RIG-1-like receptor family. Numerous RNA viruses activate RIG-1 upon infection, triggering downstream IFN signaling events [11]. In addition, RIG-1 has been proposed to initiate inflammasome complex formation by directly engaging ASC, inducing its oligomerization, subsequent caspase-1 maturation and interleukin-1 production [12–14].

Besides NLRP3-mediated and RIG-1-mediated inflammasome activity, a critical role for AIM2 inflammasome was described for RNA virus infections, including Chikungunya virus, Zika virus, and influenza [15,16]. AIM2 belongs to the family of interferon-inducible HIN-200 proteins and senses cytoplasmic dsDNA. Hence, the role of AIM2 in DNA virus infections such as adenovirus, retrovirus, and vaccinia has been extensively studied [17]. In contrast, its contribution to the pathology of RNA viruses was only recently discovered. Additional studies are needed to elucidate the mechanism by which RNA viruses can activate the AIM2 inflammasome.

Inflammasomes induced by the expression of viral proteins

Among the viral proteins that may engage inflammasomes, viroporins are present in several types of viruses and may activate immune responses by engaging sensors of cellular integrity, mostly inflammasomes. Viroporins include virus-encoded proteins with ion channel activity [18] that target membrane stability of the ER, the trans-Golgi-network (TGN), or mitochondria. Viroporins are essential for virus pathogenicity, as the deletion of viroporin-encoding genes from the virus genome significantly reduces the formation of virus progeny [19–21]. Importantly, viroporin-induced changes in membrane stability can be recognized by NLRP3 and activate the inflammasome (Figure 2). The best-characterized viroporin is the M2 protein of the Influenza A virus. While trafficking through the secretory pathway to reach the plasma membrane for viral assembly, M2 activity enables proton export into the cytosol across the TGN [22]. Alteration of ionic concentrations of intracellular compartments, including TGN by M2 triggers NLRP3 inflammasome activation [23], possibly including a role for ROS production.

Viroporins of other respiratory viruses have been shown to deploy similar functions as Influenza M2. Rhinovirus 2B proteins create pores in ER and Golgi membranes, reducing Ca^{2+} and H+ levels from the lumen of these organelles [24]. Respiratory syncytial virus (RSV) SH proteins are localized to the Golgi network, where they form Na+/K+ channels [24]. The ionic flux induced by 2B or SH proteins triggers NLRP3 inflammasome activation, though the exact molecular mechanism remains elusive.

As for coronavirus infections (SARS and MERS), studies have reported higher IL-18 and IL-1β levels, not only in the blood of the patients but also in lungs and lymphoid tissues, indicating increased inflammasome activation [25–27]. Several lines of evidence suggest that SARS-Cov2 may also promote inflammasome activation. Based on genome sequence similarities, it is believed that the COVID19 virus, SARS-CoV2 originated in bats which host over 30 different coronaviruses while remaining asymptomatic [28]. This phenomenon may be explained by the fact that bats have a deficient NLRP3 splicing product that prevents its ability to detect stimuli and is unable to assemble a pro-inflammatory complex [29]. This hypothesis is supported by the presence of viroporins in the SARS-CoV1 and SARS-CoV2 genomes.

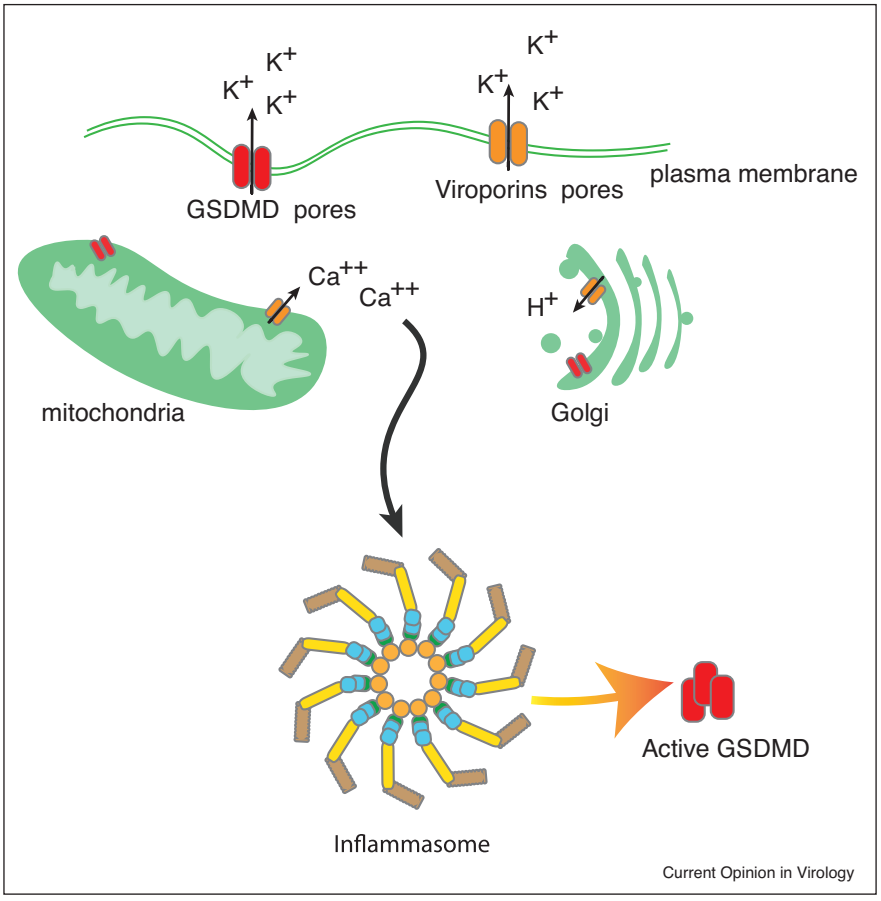
SARS-CoV1, the virus causing SARS and SARS-Cov2 encode two viroporins; the envelope (E) protein and the orf3a protein. SARS-CoV1 envelope E and orf3a proteins potential to activate inflammasome has been studied in several cellular models with different outcomes. In LPS-primed bone marrow macrophages, ectopic expression of envelope E or orf3a, induced IL-1β secretion, which was abolished upon expression of oligomerization-deficient mutants unable to form ion channels [25,30]. Both envelope E and orf3a expression, but not their oligomerization-deficient mutants, triggered a perinuclear accumulation of NLRP3 in an ASC speck, typically observed during inflammasome activation [25]. Also, in THP1 cells, expression of envelope E and orf3a resulted in IL-1β secretion, which was dependent on NLRP3 [31]. Interestingly, this study showed an additional NLRP3-independent mechanism of inflammasome activation by orf3a in HEK293T cells. In this model, the TRAF3-dependent ubiquitination of ASC underlies inflammasome formation. Direct interaction between orf3a, TRAF3, and ASC was observed independent of orf3a ion channel activity. Similarly, the interaction between orf3a and caspase-1 was reported in an experimental setup, which was independent of orf3a ion channel activity [32].

These studies suggest that the expression of viral proteins altering cellular homeostasis are possible components of the host response to the infection and may sometimes contribute to harmful inflammation. How this aspect of viral infection contributes to viral pathogenesis and immune response may depend on the virus involved, the tissue infected, and host susceptibility to inflammatory pathways.

Inflammasomes contribution to antiviral immunity

The primary physiological function of inflammasomes is to initiate an immune response and to contribute to the maintenance of tissue homeostasis and repair. However,

Figure 2



Viroporins mediated inflammasome activation.
Viral viroporins trigger perturbations in cellular integrity and ionic balances leading to NLRP3 inflammasome activation. By forming pores in intracellular compartments such as the TGN, and the plasma membrane, viroporins permeabilize membranes leading to the influx of Ca^{2+} and efflux of K+. These changes are detected by NLRP3 as a signal 2, leading to inflammasome assembly. The cleavage of GSDMD by the inflammasome leads to the formation of GSDMD pores that mimic the effects of viroporins, thereby amplifying the ionic imbalance and inflammasome activation.

deregulated inflammasome activation is harmful. Hyperactive inflammasomes are associated with hereditary and acquired autoinflammatory diseases [33]. Inflammasomes also contribute to the development of diseases with complex etiology characterized by inflammation and tissue damage. In the lung, aberrant inflammasome activation is a hallmark of acute infections. Inflammasomes are also involved in the progression of several chronic pulmonary diseases [34]. Targeting inflammasomes or inflammasome-dependent cytokines such as IL-1β are being investigated as a therapeutic strategy in such conditions. For example, to reduce acute inflammation in the lungs of cystic fibrosis patients [35]. High levels of inflammasome markers IL-18 and cleaved caspase-1 in COVID19 patient sera associated with severe disease and poor clinical outcome (preprint: https://www.medrxiv.org/content/10.1101/2020.08.05.20168872v1). Indeed, a small cohort study showed that anti-IL-1 therapy using Anakinra in patients with severe COVID19 reduced the need for invasive mechanical ventilation at ICU as well as mortality [36].

IL-1β activates the IL-1R that triggers a transcriptional program leading to the production of multiple inflammatory mediators, including IL-6 and TNF. During viral infection, the contribution of NLRP3 inflammasome to antiviral immunity may change depending on the circumstances, or the infection stage. In the context of Influenza infection, using the potent NLRP3 inhibitor MCC950, it was shown that NLRP3 inflammasome plays a crucial role in virus clearance early in the disease; however, it induced harmful inflammation during late-stage infection [37]. While early signaling cascades, including NLRP3 inflammasome, initiate a proper innate immune response against viral infection, they also induce the expression of co-stimulatory molecules on antigen-presenting cells

essential for activating adaptive immune responses. Inflammasome-mediated secretion of cytokines and DAMPs provide endogenous adjuvant for stimulation of adaptive immunity in this context [38]. However, the prolonged presence of inflammatory mediators may cause cytokine storms and an increased influx of immune cells leading to tissue damage [39,40]. The importance of such timing of inflammasome activation and inhibition during viral infection was also suggested in a COVID19 patient with autoinflammatory disease. Continuous colchicine treatment, a drug inhibiting inflammasome activation, before infection prevented the patient from developing severe COVID19 and rendered the patient with only mild symptoms. However, as inflammasome inhibition dampened the activation of a proper adaptive immune response, the patient failed to control the virus and required additional medication overcome the infection [41].

After initial activation, regulating the inflammasome response seems a key factor for preventing unprecedented injury and lethality during viral infections. Individuals shown to have weaker inhibition potential towards NLRP3 inflammasome include obese and elderly patients who are typically more severely affected by viral infections than healthy or young individuals [42–44]. The power to actively regulate inflammasome responses would provide a clinical strategy to prevent virus-associated organ damage or deaths [45].

Conclusions

Inflammasomes are emerging as crucial pathways of the innate immune system that contribute to viral immunity. These sensors can detect viral molecules as well as cellular perturbations caused by viruses. While initial research identified several activating mechanisms and inflammasomes engaged by viruses such as SARS or Influenza, little is known on the precise contribution of these pathways to viral immunity in humans. Several questions need to be addressed. For example, patients with hypersensitive inflammasomes may be susceptible to respond to viral infection with an acute cytokine storm response. While this has been demonstrated in the context of sterile inflammation, it could contribute to aberrant inflammation in the course of a viral infection, as observed in COVID19, for example. Identifying the mechanisms that could contribute to aberrant inflammation and the exact contribution of inflammasomes may help better manage these responses and take advantage of the development of therapeutic strategies aimed at targeting inflammasomes or inflammasome downstream mediators.

Conflicts of interest statement

Nothing declared.

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