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Innate immune control of alphavirus infection

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Alphaviruses are important human pathogens that cause diseases ranging from acute and chronic polyarthralgia to encephalitis. Transmitted by mosquito vectors, alphaviruses have high potential for emergence and have initiated several recent epidemics. The innate immune response is critical for controlling the acute phase of alphavirus disease, and the induction of type I interferon (IFN) is essential in this response. In this review, we discuss our current understanding of innate host sensors that initiate antiviral responses following alphavirus infection, and the IFN-induced effector proteins that limit alphavirus replication and dissemination.

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Introduction

The genus Alphavirus (family *Togaviridae*) includes ~30 currently recognized viral species [1]. These single-stranded, positive-sense RNA viruses are primarily arboviruses transmitted between mosquito vectors and vertebrate hosts. Alphaviruses include human pathogens that, in some cases, have recently caused explosive epidemics involving millions of people [2,3]. Although infections with alphaviruses such as chikungunya (CHIKV), o'nyong nyong (ONNV), Ross River (RRV), Mayaro (MAYV), and Sindbis (SINV) viruses are typically not life threatening, they can cause severe and often chronic myalgia and arthralgia. In addition, CHIKV is associated with severe neurological disease in the young and the elderly [4]. Other alphaviruses, including Venezuelan (VEEV), western (WEEV), and eastern (EEEV) equine encephalitis viruses can cause encephalitic and sometimes fatal infections in humans [5]. Thus, there is a pressing need to improve an understanding of the innate immune mechanisms that control alphavirus infection.

Type I IFN is essential for control of alphavirus infection

The innate immune response provides a first line of defense against alphavirus infection. Central to this response is type I interferon (IFN), as mice deficient in the IFN receptor (*Ifnar1*$^{-/-}$) are highly susceptible to infection with numerous alphaviruses [6–11]. Furthermore, attenuated strains of alphaviruses often display increased virulence in *Ifnar1*$^{-/-}$ mice [8,12–14]. Experiments in bone marrow chimeric mice revealed that IFN signaling in nonhematopoietic cells is essential for CHIKV control, while IFN signaling in hematopoietic cells is dispensable [15]. Nevertheless, both cell types likely contribute to IFN production, as expression of transcription factors responsible for IFN induction (IRF3/7) by either hematopoietic or nonhematopoietic cells is sufficient for CHIKV control [16•]. However, our understanding of the specific cell types that produce IFN in response to alphavirus infection and the pathogen recognition receptors (PRRs) that induce this response is limited.

Innate sensing of alphaviruses

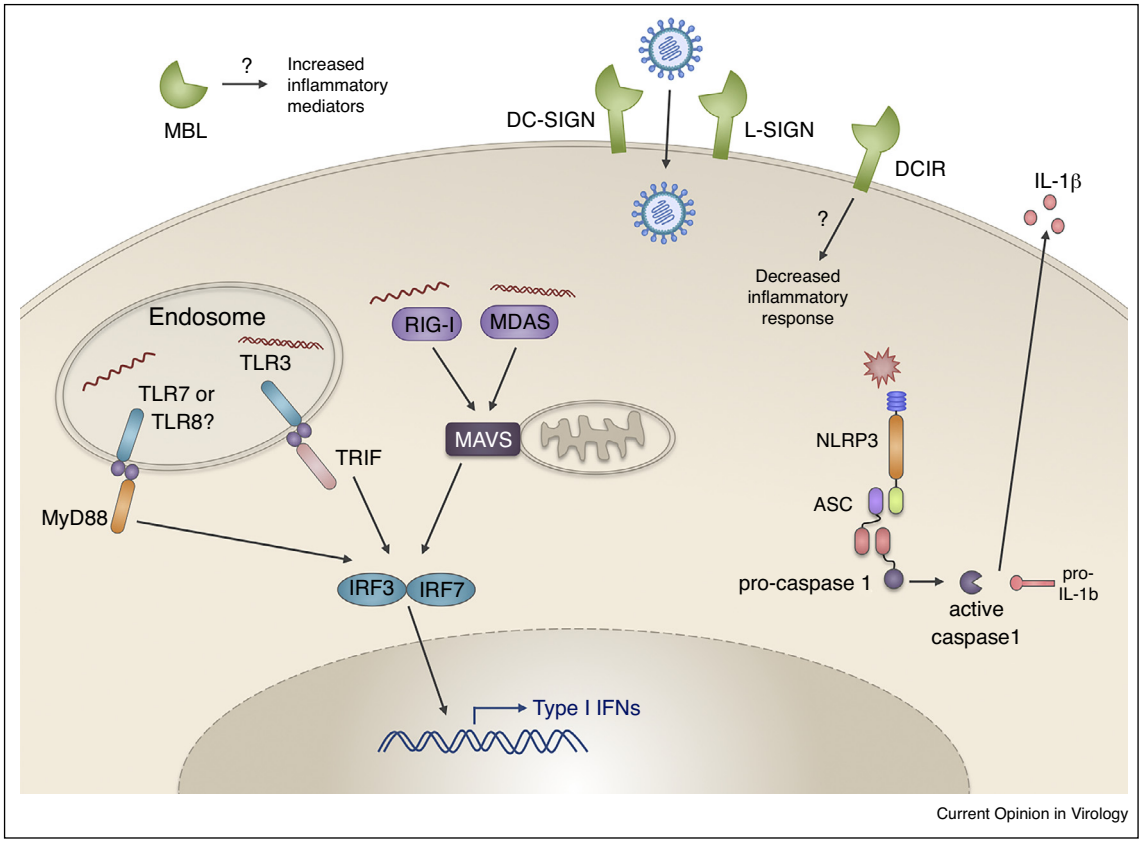
Viral RNAs serve as pathogen associated molecular patterns (PAMPs) that are recognized by host PRRs, including Toll-like receptors 3, 7, and 8 (TLR3, TLR7, and TLR8), and RIG-I-like receptors (RLRs) [17]. Engagement of PRRs activates signaling cascades, which ultimately induce IFN production. While IFN is essential for alphavirus control, the relative contributions of these PRRs during alphavirus infection have not been fully elucidated. The host also can respond to viruses through additional receptors, including Nod-like (NLRs) and C-type lectin (CLRs) receptors [18,19]. The role of NLRs and CLRs in alphavirus infection has recently begun to be appreciated (Figure 1).

TLRs

TLRs are a family of conserved pathogen recognition receptors, and all but TLR3 signal through the adaptor protein MyD88 [20]. Studies in *MyD88*$^{-/-}$ mice suggested that TLR signaling may contribute to control of CHIKV infection, as *MyD88*$^{-/-}$ mice had increased viremia and enhanced dissemination compared with WT mice [15,21]. Similarly, RRV-infected *MyD88*$^{-/-}$ mice exhibited more severe disease and had increased viral tissue burdens [22]. These effects were likely due to sensing of RRV by TLR7, as *MyD88*$^{-/-}$ and *Tlr7*$^{-/-}$ mice had similar viral tissue burdens and disease progression following RRV infection [22].

TLR3 appears to restrict CHIKV, although there are conflicting reports in the literature. One study found

Figure 1



Host sensing of alphavirus infection. Following infection, multiple host sensors have been shown to respond to alphavirus infection. The alphavirus genome and replicative intermediates can engage Toll-like-receptor 3 (TLR3), TLR7, and the RIG-I-like receptors RIG-I and MDA5. These sensors signal through the downstream adaptor proteins MyD88, TRIF, or MAVS to activate a signaling cascade that results in activation of transcription factors IRF3 and IRF7, which translocate to the nucleus and induce type I IFN. Several C-type lectin receptors (CLRs) have been reported to respond to alphaviruses. DC-SIGN and L-SIGN can enhance alphavirus entry. DCIR responds to alphaviruses by decreasing inflammation, although the signaling pathway by which this occurs is not understood. MBL, a soluble c-type lectin, increases inflammatory mediators in response to alphaviruses. Nod-like receptors are also engaged by alphaviruses, although the activating signal is not known. NLRP3, and likely other NLRs, can be activated during alphavirus infection, driving the formation of an inflammasome composed of NLRP3, ASC, and caspase-1. Activation of caspase-1 by the inflammasome allows for proteolytic cleavage of pro-IL-1β, resulting in secretion of IL-1β.

that *Tlr3*$^{-/-}$ mice were more susceptible to CHIKV infection, as evidenced by increased viremia and tissue burdens [23•]. Moreover, CHIKV infected *Tlr3*$^{-/-}$ mice had exacerbated inflammation in the inoculated foot that was accompanied by a massive infiltration of myeloid cells compared with CHIKV-infected WT mice. Bone marrow chimeric mice revealed that TLR3 expressed by hematopoietic cells contributes to control of CHIKV viremia, whereas expression of TLR3 by nonhematopoietic cells enhanced inflammation [23•]. In contrast, a separate study found no difference in viral tissue burdens in CHIKV-infected wild type (WT) or *Tlr3*$^{-/-}$ mice [15]. Regardless, the protective role of TLR3 during CHIKV infection is further supported by studies in mice lacking TRIF, an adaptor protein downstream of TLR3, as *Trif*$^{-/-}$ mice infected with CHIKV had increased viremia and swelling in the inoculated foot [21].

Whether TLR sensing is critical for control of other alphavirus infections has not been thoroughly investigated. However, a neuroadapted strain of SINV was equally virulent in WT, *Tlr3*$^{-/-}$, and *MyD88*$^{-/-}$ mice, with no observed difference in IFN production within the CNS [24]. A second study found that *MyD88*$^{-/-}$ and WT mice were equally susceptible to the AR86 strain of SINV, while *Trif*$^{-/-}$ mice succumbed to infection only slightly more rapidly than WT mice [25]. Thus, findings with one alphavirus species may not be broadly applicable to all alphaviruses.

RLRs

RLRs, including RIG-I and MDA5, are a family of cytoplasmic RNA helicases that signal through the adaptor molecule MAVS to activate transcription factors IRF3 and IRF7, driving transcription of IFN and other proinflammatory cytokines [17]. Studies in cell culture