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Recognition of viruses by cytoplasmic sensors

Courtney Wilkins and Michael Gale Jr

The immune response to virus infection is initiated when pathogen recognition receptors (PRRs) of the host cell recognize specific nonself-motifs within viral products (known as a pathogen-associated molecular pattern or PAMP) to trigger intracellular signaling events that induce innate immunity, the front line of defense against microbial infection. The replication program of all viruses includes a cytosolic phase of genome amplification and/or mRNA metabolism and viral protein expression. Cytosolic recognition of viral infection by specific PRRs takes advantage of the dependence of viruses on the cytosolic component of their replication programs. Such PRR–PAMP interactions lead to PRR-dependent nonself-recognition and the downstream induction of type I interferons and proinflammatory cytokines. These factors serve to induce innate immune programs and drive the maturation of adaptive immunity and inflammation for the control of infection. Recent studies have focused on identifying the particular viral ligands recognized as nonself by cytosolic PRRs, and on defining the nature of the PRRs and their signaling pathways involved in immunity. The RIG-I-like receptors, RIG-I and MDA5, have been defined as essential PRRs for host detection of a variety of RNA viruses. Novel PRRs and their signaling pathways involved in detecting DNA viruses through nonself-recognition of viral DNA are also being elucidated. Moreover, studies to identify the PRRs and signaling factors of the host cell that mediate inflammatory signaling through inflammasome activation following virus infection are currently underway and have already revealed specific NOD-like receptors (NLRs) as inflammatory triggers. This review summarizes recent progress and current areas of focus in pathogen recognition and immune triggering by cytosolic PRRs.

Address
Department of Immunology, University of Washington School of Medicine, Seattle, WA 98195, USA

Corresponding author: Gale, Michael (mgale@u.washington.edu)

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Introduction

The immune response to virus infection begins with the recognition of viral pathogen-associated molecular patterns (PAMPs) as 'nonself' signatures. This recognition occurs through host pattern recognition receptors (PRRs). Toll-like receptors (TLRs) are a class of PRRs that recognize viral motifs presented at the cell surface or within the endosomal compartment but are not known for mediating cytosolic pathogen recognition. On the other hand, cytosolic PRRs have been identified that play major roles in the recognition of viral nucleic acid. These include the RIG-I-like receptors (RLRs), novel DNA-binding factors, and the nucleotide-binding domain-leucine-rich repeat-containing molecules (NLRs).

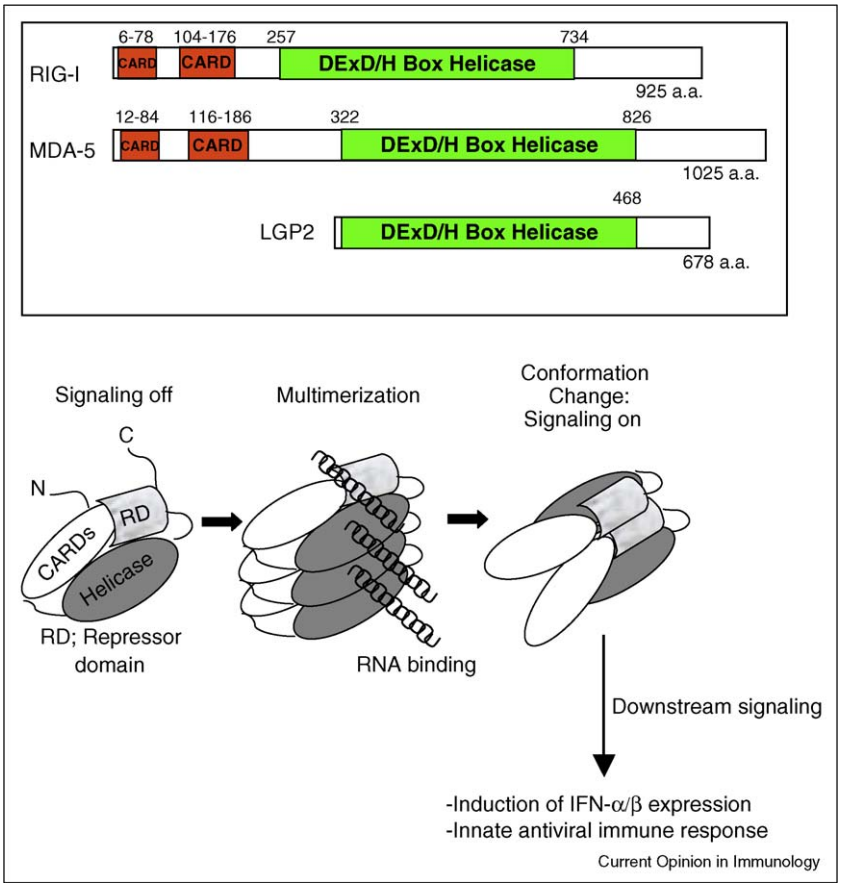
Following recognition of viral RNA or DNA, the PRRs undergo conformation changes or specific modifications that drive their signaling-active state and their downstream induction of type I interferon (IFN) and proinflammatory cytokine expression by the infected cell. Type I IFN is subsequently secreted and binds the type I IFN receptor on the cell surface in an autocrine and paracrine manner to activate Jak/STAT signaling and lead to the production of hundreds of interferon stimulated genes (ISGs). ISGs function to directly inhibit viral infection, trigger apoptosis of infected cells, and they play an important role to modulate adaptive immunity [1,2]. Overall, PRR signaling and the initiation of innate antiviral defenses represent our first line immune response to virus infection.

In this review, we summarize recent understanding of cytosolic recognition of viral nucleic acids leading to immunity and inflammation to limit virus infection.

Recognition of RNA viruses by RLRs

The RLR family consists of three members: retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated gene 5 (MDA5) and laboratory of genetics and physiology 2 (LGP2) [1]. RIG-I and MDA5 contain two N-terminal caspase activation and recruitment domains (CARDs), which are essential for their signaling activity. All three molecules have an internal DExD/H-box RNA helicase domain with ATPase activity. This ATPase activity, which is activated by ligand binding, does not appear to be required for RNA binding though it is necessary for signaling [3,4]. Finally, the C-terminus of RIG-I and LGP2 have been shown to act as a repressor domain (RD) that holds the molecule in an inactive conformation until RNA binding triggers an ATP-dependent conformational change that releases the CARD domains for signaling. In terms of RIG-I, this signaling initiation program has been defined through biochemical,

Figure 1



Upper: RLR structure diagram showing positions of functional domains. Lower: 3-step model of RIG-I activation from a monomeric resting form (left) to RNA-ligand bound, dimeric form (center) and the final active form (right). The positions of the CARDs, helicase domain, and repressor domain (RD) are indicated. Ligand binding by RIG-I facilitates a conformation change that releases it from autorepression by the RD, thus driving downstream signaling of innate antiviral immunity. Model adapted from Ref. [5].

genetic, and virologic studies (Figure 1) [5]. After binding nonself-ligand, RIG-I and MDA5 interact via their CARD domains with the signaling-adaptor molecule, IPS-1 (also known as MAVS, VISA, and Cardif), which recruits a signaling complex to activate transcription factors, including IRF3 and NF-κB. These events lead to the induced expression of IFN-β, IRF3-target genes, and NF-κB target genes to drive antiviral and inflammatory responses against infection (Figure 2) [6–9].

A large research effort has focused on understanding the ligands that are recognized by each of the RLRs. Despite the structural similarity between RIG-I and MDA5, they were found to be responsible for IFN induction by distinct sets of viruses. While RIG-I recognizes a number of both positive and negative stranded viruses (including Hepatitis C virus, respiratory syncytial virus and related paramyxoviruses, vesicular stomatitis virus and influenza A virus), MDA5 is responsible for the recognition of picornaviruses and is the primary sensor of the dsRNA mimetic poly(I:C) [10,11]. Interestingly, both sensors appear to respond to reoviruses (a segmented dsRNA virus), and West Nile virus and Dengue virus (positive-stranded RNA viruses) (Table 1) [11,12]. Much of the virus specificity between the two PRRs has been found to reside in the particular RNA structures or nucleotide composition recognized by each.

RNA recognition by RIG-I requires the presence of a free 5′-triphosphate structure [13]. This requirement allows for differential recognition of nonself/viral RNA versus self-RNAs, as host RNA is either capped or post-translationally modified to remove the 5′-triphosphate. The exact nature of the RNA recognized by RIG-I is still rather controversial. RIG-I was first reported as binding dsRNA [14]. Although it has been reported that ssRNA bearing a 5′-triphosphate is recognized by RIG-I [15], a recent report suggests that the RNA requires some double-strandedness and that previous results were because of unintended hairpins produced by T7 *in vitro* transcription [16]. However, this assertion requires validation from other groups in addition to strict biochemical