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Protect this house: cytosolic sensing of viruses

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The ability to recognize invading viral pathogens and to distinguish their components from those of the host cell is critical to initiate the innate immune response. The efficiency of this detection is an important factor in determining the susceptibility of the cell to viral infection. Innate sensing of viruses is, therefore, an indispensable step in the line of defense for cells and organisms. Recent discoveries have uncovered novel sensors of viral components and hallmarks of infection, as well as mechanisms by which cells discriminate between self and non-self. This review highlights the mechanisms used by cells to detect viral pathogens in the cytosol, and recent advances in the field of cytosolic sensing of viruses.

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Introduction

Human pathogenic viruses are a major global health concern, often leading to serious illness or death. Viral infection represents a significant challenge to host cells, as the ability to detect infection and inhibit viral replication is one of the key factors determining host susceptibility to infection. Many human pathogenic viruses have evolved strategies to avoid detection by the host cell, or to inhibit other antiviral factors, demonstrating the importance of antiviral innate immunity to protect against viral infection [1,2].

Pattern recognition receptors (PRRs) act as sensors for the products of viral infection, which are known as pathogen-associated molecular patterns (PAMPs). Viral PAMPs can include viral proteins or nucleic acids that are sensed by PRRs as non-self to elicit antiviral innate immune responses, primarily driven by type I and III interferons (IFN). This review will focus on the PRRs that sense viral nucleic acid PAMPs within the cytosol of the cell generated during RNA and DNA virus infection. We will describe how the cytosolic nucleic acid sensing PRRs, the RIG-I-like receptors (RLRs) and DNA sensors, discriminate between self and non-self to activate antiviral immune responses (Figure 1).

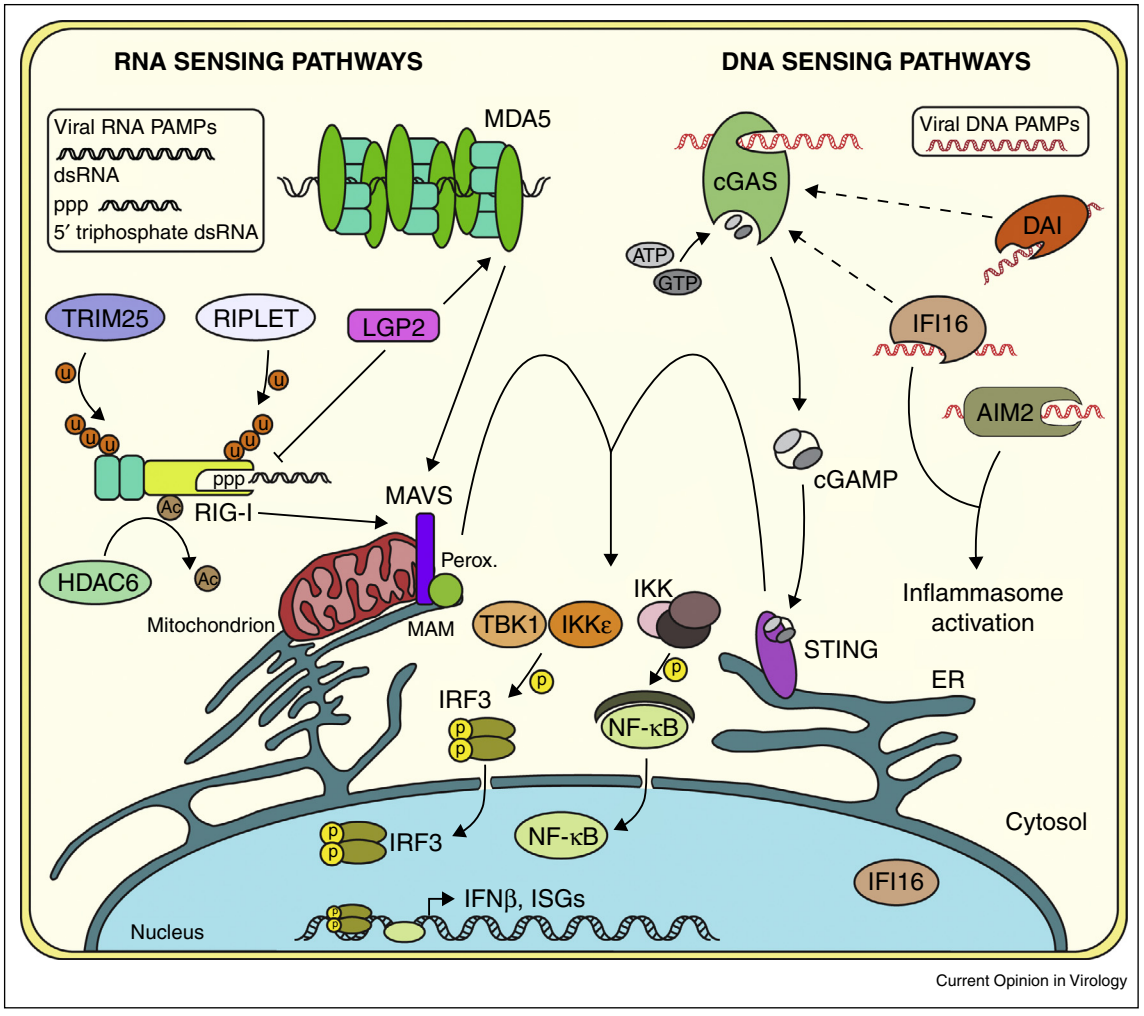
RLRs sense cytosolic viral RNA and activate antiviral responses

The RLRs, members of the DExD/H box family of helicases, include retinoic acid-inducible gene I (RIG-I), melanoma differentiation factor 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2). This family of cytosolic viral sensors is crucial for recognition of a large number of RNA viruses [3]. These sensors distinguish virus-associated RNAs from cellular RNAs to activate downstream signaling of antiviral innate immunity driven by mitochondrial antiviral signaling protein (MAVS), which aggregates into filaments following activation by PRRs [4]. Filamentous MAVS serves as a platform for interaction with other proteins involved in the signaling cascade, such as tumor necrosis factor receptor-associated factor (TRAF) proteins, which are important for MAVS signaling through TANK-binding kinase 1 (TBK1) and IκB-kinase-ε (IKKε), and the IκB kinase complex (IKK) [5]. TBK1/IKKε and IKK phosphorylate IRF3/IRF7 and the inhibitory subunit of NF-κB (IκBα), respectively. The transcription factors IRF3, IRF7, and NF-κB then translocate to the nucleus to induce transcription of type I IFNs (IFN-α and IFN-β). Type I IFN production drives autocrine and paracrine responses through the IFN-α/β receptor, which activates the JAK/STAT signaling pathway to ultimately induce the transcription of hundreds of IFN-stimulated genes (ISGs). These include many antiviral factors, which can inhibit viral replication in various ways [6–8].

RIG-I

RIG-I senses a number of RNA viruses including flaviviruses, alphaviruses, coronaviruses, reoviruses, paramyxoviruses, orthomyxoviruses, rhabdoviruses, arenaviruses, and bunyaviruses [9,10]. RIG-I recognizes PAMPs, including short double-stranded RNA (dsRNA) containing either a 5′ triphosphate or 5′ diphosphate moiety that are generally unique to viral RNA [11,12,13•]. Interestingly, a recent report identified RIG-I as a PRR for Crimean-Congo hemorrhagic fever virus (CCHFV), whose RNA genome is 5′-monophosphorylated, implicating an additional ability

Figure 1



Major pattern recognition receptors (PRRs) that sense RNA and DNA virus pathogen associated molecular patterns (PAMPs) in the cytosol. Following RIG-I sensing of short dsRNA, this sensor is further activated through K63-linked ubiquitination by TRIM25 and RIPLET, as well as through lysine deacetylation by HDAC6. Following sensing of long dsRNA, MDA5 oligomerizes along the dsRNA. Both RIG-I and MDA5 activate signaling through the adaptor MAVS located on mitochondria, mitochondrial-associated ER membranes (MAM), and peroxisomes (perox.), leading to the activation and nuclear translocation of IRF3 and NF-κB and the production of type I IFN and ISGs. Viral DNA PAMPs are sensed by cGAS which catalyzes the production of cGAMP after binding to DNA. cGAMP then signals through the adaptor STING, located on ER membranes to activate IRF3 and NF-κB. Other viral DNA sensors in the cytosol such as DAI and IFI16 are also postulated to function through this pathway. Activation of IFI16 or AIM2 following viral DNA detection leads to inflammasome activation.

of RIG-I to sense 5′-monophosphate-containing viral RNAs [14•]. Therefore, while canonical ligands of RIG-I have been identified, future research may uncover additional features of ligands, such as post-transcriptional RNA modifications, that allow RIG-I to distinguish self from non-self. Indeed, self-RNAs are distinguished from foreign RNAs by post-transcriptional modifications of their 5′ triphosphate ends, which contain the RNA cap structures. These include cap0: 7-methylguanosine addition to the gamma phosphate on the 5′ end of mRNAs; cap1: identical to cap0, with 2′-O-methylation of the first nucleotide following the 5′ triphosphate; and cap2: identical to cap1, with an additional 2′-O-methyl group on the second nucleotide. The 2′-O-methylation present in cap1 is crucial for avoiding recognition by RIG-I [15••,16••]. In addition, 2′-O-methylation protects host mRNAs from sequestration by IFN-induced proteins with tetratricopeptide repeats (IFITs), which would otherwise inhibit the translation of these proteins [17]. In fact, certain viruses including flaviviruses, coronaviruses, and alphaviruses have co-opted cellular RNA capping strategies, likely to evade detection by RLRs [18,19].

RIG-I contains several functional domains that regulate sensing of PAMPs and its subsequent activation. It is comprised of two N-terminal caspase activation and