CellPress

Cell Host & Microbe
Review

The cGAS-STING Defense Pathway and Its Counteraction by Viruses

Zhe Ma[1,2] and Blossom Damania[1,2,*]
[1]Lineberger Comprehensive Cancer Center
[2]Department of Microbiology & Immunology
University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA
*Correspondence: damania@med.unc.edu
http://dx.doi.org/10.1016/j.chom.2016.01.010

Upon virus infection, host cells mount a concerted innate immune response involving type I interferon and pro-inflammatory cytokines to enable elimination of the pathogen. Recently, cGAS and STING have been identified as intracellular sensors that activate the interferon pathway in response to virus infection and thus mediate host defense against a range of DNA and RNA viruses. Here we review how viruses are sensed by the cGAS-STING signaling pathway as well as how viruses modulate this pathway. Mechanisms utilized by viral proteins to inhibit cGAS and/or STING are also discussed. On the flip side, host cells have also evolved strategies to thwart viral immune escape. The balance between host immune control and viral immune evasion is pivotal to viral pathogenesis, and we discuss this virus-host stand-off in the context of the cGAS-STING innate immune pathway.

Introduction

Innate immunity is the first and most rapid line of host defense against invading microbial pathogens. Host cells initiate innate immune responses upon recognition of conserved pathogen structures, called pathogen-associated molecular patterns (PAMPs), as well as host damage-associated molecular patterns (DAMPs) by diverse pattern recognition receptors (PRRs). Upon sensing viral PAMPs and DAMPs released during virus infection, signal cascades are activated to produce type I interferon and/or multiple cytokines and chemokines, which culminate in the synthesis of many antiviral proteins. Antiviral proteins can promote growth arrest or apoptosis or inhibit cellular protein translation. Cytokines and chemokines help recruit immune cells to the site of viral infection in order to control the spread of the virus and to initiate the adaptive immune response to virus infection. PRRs can also induce antiviral proteins without the requirement of cytokine-dependent autocrine/paracrine stimulation.

Pattern recognition receptors (PRRs) are germ-line encoded receptors present either on the cell surface or within specific cellular compartments of the cytosol and have been extensively studied over the last two decades. PRRs recognize microbial signatures named PAMPs. PAMPs are usually conserved molecular components essential for pathogen survival such as nucleic acids, lipopolysaccharide (LPS), lipoproteins, bacterial flagellin, and yeast zymosan. PRRs play a significant role in recognizing invading pathogens and mediating the first steps of host defense. Hence, PRRs are extremely important for a rapid and efficient innate immune response. PRRs include sensors such as Toll-like receptors (TLRs), the nucleotide binding and oligomerization, leucine-rich proteins (NLRs), retinoic acid-like receptors (RLRs), absent in melanoma 2 (AIM2)-like receptors (ALRs), and cytosolic DNA receptors (reviewed in Brubaker et al., 2015; Medzhitov, 2007; Takeuchi et al., 2010) (Figure 1). In the context of virus infection, the best characterized PAMP is the viral genome itself and/or viral nucleic acids generated during the replication cycle in the host cell, such as single- or double-stranded RNA transcripts or DNA.

DNA Sensing Pathways and Sensors

Cytosolic DNA sensors are the least characterized among PRRs, although there is consensus that intracellular detection of pathogen DNA is critical for initiating innate immune responses. While downstream molecules such as TANK binding kinase 1 (TBK1) and the transcriptional regulators of interferon, IRF3 and IRF7, have been shown as important for cytosolic sensing pathways, it was not until 2008 that STING (also known as TMEM173, MITA, ERIS, MPYS) was identified as acting upstream of TBK1. Subsequent work characterized this STING-TBK1-IRF3 signaling cascade as critical for DNA sensing pathways that were initiated by multiple DNA sensors. STING was identified as an important molecule for cytoplasmic DNA activated innate immune responses (Ishikawa and Barber, 2008; Jin et al., 2008; Sun et al., 2009; Zhong et al., 2008). Loss of STING completely abolished cytosolic DNA-induced IFNβ production. Correspondingly, STING-deficient mice showed great susceptibility to herpes simplex virus 1 (HSV-1) infection, suggesting a STING-dependent cytosolic DNA sensing pathway (Ishikawa et al., 2009).

There are many DNA sensors that have been identified to date. Among the DNA sensors, DNA-dependent activator of IFN-regulatory factors (DAI) was the first cytosolic DNA sensor to be identified. It was shown to be important for HSV-1-triggered IFNβ production (Takaoka et al., 2007). However, DAI-deficient mice displayed a normal response against cytosolic DNA stimulation, indicating the possibility of redundancy in cytosolic DNA-sensing pathways (Ishii et al., 2008). In 2011, DDX41 was identified as another DNA sensor that plays a role in DNA sensing in dendritic cells. Depletion of DDX41 resulted in a reduction of IFNβ production when cells were stimulated with poly dA:dT or poly dG:dC, and infected with HSV or influenza (Zhang et al., 2011b). However, DDX41 knockout animal studies are absent,

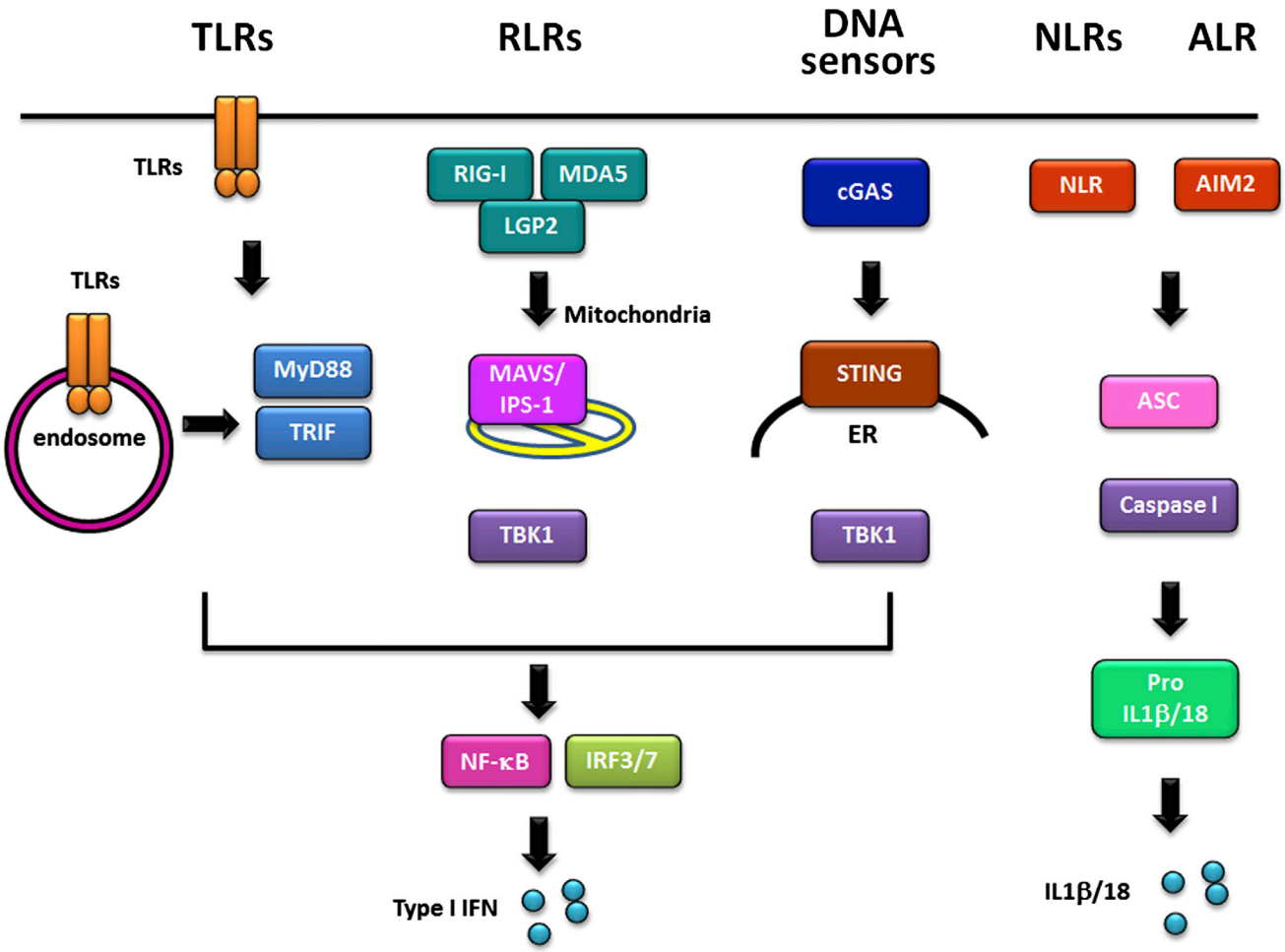

Figure 1. Pattern Recognition Receptors in Cells

Schematic of different pattern recognition receptors in the cell and the signaling pathways that are activated by each PRR. TLRs are either anchored on the cell surface or are present in endosomal compartments. TLRs utilize myeloid differentiation primary response gene 88 (MYD88) or TIR-domain-containing adaptor-inducing interferon (TRIF) as an adaptor protein to recruit downstream molecules, which eventually culminate in the production of pro-inflammatory cytokines and/or type I interferon (IFN). The RLR family is comprised of three receptors, RIG-I, melanoma differentiation-associated gene 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2), each recognizing specific RNA ligands. RLRs signal through the adaptor protein MAVS (also called IPS-1, Cardif, and VISA) located on the mitochondria to trigger the production of type I interferons together with NF-κB. NLRs are cytosolic PRRs that contain a nucleotide-binding domain (NBD), an LRR region, and an N-terminal effector that is typically a caspase activation and recruitment domain (CARD) or a pyrin domain (PYD). Several NLR proteins are members of a large complex called the inflammasome, which includes ASC and procaspase I. Inflammasome induction by a number of different PAMPs, results in the activation of IL-1β and IL-18 from pro-IL-1β and pro-IL-18, respectively. AIM2 is a non-NLR family protein that recognizes cytosolic dsDNA. Similar to NLRs, upon stimulation, AIM2 forms an inflammasome with procaspase I and ASC to induce IL-1β and IL-18.

and these might be needed for deciphering the functional role of DDX41 in innate immune pathways. Besides direct sensing, an indirect method of DNA sensing occurs through RNA polymerase III where B-form DNA can be transcribed by RNA polymerase III and recognized by RIG-I resulting in the induction of interferon responses (Ablasser et al., 2009; Chiu et al., 2009).

IFI16 was identified as a DNA sensor that also signals through STING-TBK1. IFI16 was shown to directly bind vaccinia virus (VACV) DNA and recruit STING to induce IFNβ induction. Knockdown of IFI16 using small interfering RNA showed reduced VACV DNA-stimulated IFNβ signaling (Unterholzner et al., 2010). IFI16 was linked to innate immunity against many viral infections and has been shown to be modulated by viruses to facilitate viral replication. For example, IFI16 has been described as a nuclear viral DNA sensor that is important for HSV-1 triggered IRF3 signaling and induction of inflammasomes (Johnson et al., 2013; Morrone et al., 2014; Orzalli et al., 2012). IFI16 was shown to be degraded during HSV-1 infection in a proteasome-dependent manner, and HSV-1 ICP0 protein was identified as an IFI16 binding protein that facilitated IFI16 degradation (Diner et al., 2015b; Orzalli et al., 2013). Upon infection with an ICP0-null virus, IFI16 served as a restriction factor for HSV-1 viral replication and gene expression. Interestingly, IFI16 can be acetylated and can accumulate in the cytoplasm (Ansari et al., 2015; Li et al., 2013). Therefore, it is thought that IFI16 can serve as both a nuclear and cytosolic sensor of DNA. In addition, human cytomegalovirus (HCMV) was also shown to trigger IFI16-induced signaling pathways, and its tegument protein pUL83 inhibits this response by interacting with IFI16 (Li et al., 2013). Additionally, IFI16 was shown to play a role in inducing the inflammasome