Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Microbiology

Intracellular detection of viral nucleic acids

Konstantin MJ Sparrer and Michaela U Gack

Successful clearance of a microbial infection depends on the concerted action of both the innate and adaptive arms of the immune system. Accurate recognition of an invading pathogen is the first and most crucial step in eliciting effective antimicrobial defense mechanisms. In recent years, remarkable progress has been made towards understanding the molecular details of how the innate immune system recognizes microbial signatures, commonly called pathogen-associated molecular patterns (PAMPs). For viral pathogens, nucleic acids — both viral genomes and viral replication products — represent a major class of PAMPs that trigger antiviral host responses via activation of germline-encoded innate immune receptors. Here we summarize recent advances in intracellular innate sensing mechanisms of viral RNA and DNA.

Address
Department of Microbiology and Immunobiology, Harvard Medical School, Boston, MA 02115, USA

Corresponding author: Gack, Michaela U (michaela_gack@hms.harvard.edu)

Current Opinion in Microbiology 2015, **26**:1–9

This review comes from a themed issue on **Host-microbe interactions: viruses**

Edited by **Ivan Marazzi** and **Adolfo Garcia-Sastre**

For a complete overview see the Issue and the Editorial

Available online 18th March 2015

http://dx.doi.org/10.1016/j.mib.2015.03.001

1369-5274/© 2015 Elsevier Ltd. All rights reserved.

Introduction

Virtually all cells of a mammalian host organism have the capacity to detect the presence of an invading pathogen by recognizing 'non-self' structural components through germline-encoded innate immune sensors, called pattern recognition receptors (PRRs). Over the past ten years, significant progress has been made in identifying the precise viral pathogen signatures (or PAMPs) recognized by PRRs, such as specific modifications (e.g. a 5′-triphosphate moiety) of viral RNA (vRNA), or mislocalized cytoplasmic viral DNA (vDNA) [1,2]. Mammalian cells have evolved a large repertoire of PRRs, which can be grouped with respect to their subcellular localization. While Toll-like receptors (TLRs) and C-type lectin receptors (CLRs) recognize virion components in endosomes and on cell membranes (reviewed in [3]), the detection of incoming and actively replicating viruses is mediated by PRRs that are localized inside the cell. Most intracellular PRRs recognize viral nucleic acids and have the remarkable ability to distinguish 'non-self' RNA or DNA from the large pool of cellular RNAs and DNAs. At least three major classes of intracellular sensors of viral infection have been identified: (1) RIG-I-like receptors (RLRs) which sense vRNA species in the cytoplasm and play important roles in the detection of RNA viruses; (2) a structurally unrelated group of vDNA receptors (e.g. cGAS and IFI16) localized in the host cytoplasm and/or nucleus; and (3) members of the NOD-like receptor (NLR) family which, besides their established roles in sensing bacterial infections, have also been implicated in detecting viral pathogens. In addition, several other proteins have been implicated in vRNA or vDNA sensing, although their physiological roles have yet to be fully established (as discussed below).

Following ligand recognition, PRRs activate antiviral signaling cascades that converge on a group of well-characterized kinases, namely TANK-binding kinase 1 (TBK1), mitogen-activated protein kinases (MAPKs), and IκB kinase α (IKKα) and IKKβ. Through phosphorylation events, these kinases subsequently activate the interferon (IFN)-regulatory factors 3 and 7 (IRF3/7), AP-1, and NF-κB, respectively. These proteins transcriptionally induce the gene expression of type-I IFNs (mainly IFN-α subtypes and IFN-β), type-III IFN (IFN-λ), and other pro-inflammatory cytokines such as members of the interleukin (IL) protein family [1,2]. Furthermore, some PRRs activate inflammasomes, which are caspase-1-activating multi-protein complexes that cleave pro-IL-1β and pro-IL-18 to generate their mature forms [4]. Secreted IFNs bind to their respective surface receptors on both infected and uninfected neighboring cells, inducing signal transduction that leads to the expression of numerous IFN-stimulated genes (ISGs) [5,6]. ISGs encode for proteins that exert distinct antiviral effector functions such as cleavage of vRNA or induction of apoptosis. In addition, some ISGs encode for PRRs or for proteins involved in PRR signal transduction, leading to positive feedback amplification of the antiviral response in infected cells, and also sensitizing uninfected cells to fight off the viral attack. Induction of IFNs and other pro-inflammatory cytokines not only limits the spread of the viral pathogen to surrounding cells, but also facilitates viral clearance by recruiting and stimulating cells of the adaptive immune system.

In this opinion article, we summarize recent findings on the molecular mechanisms of how intracellular innate

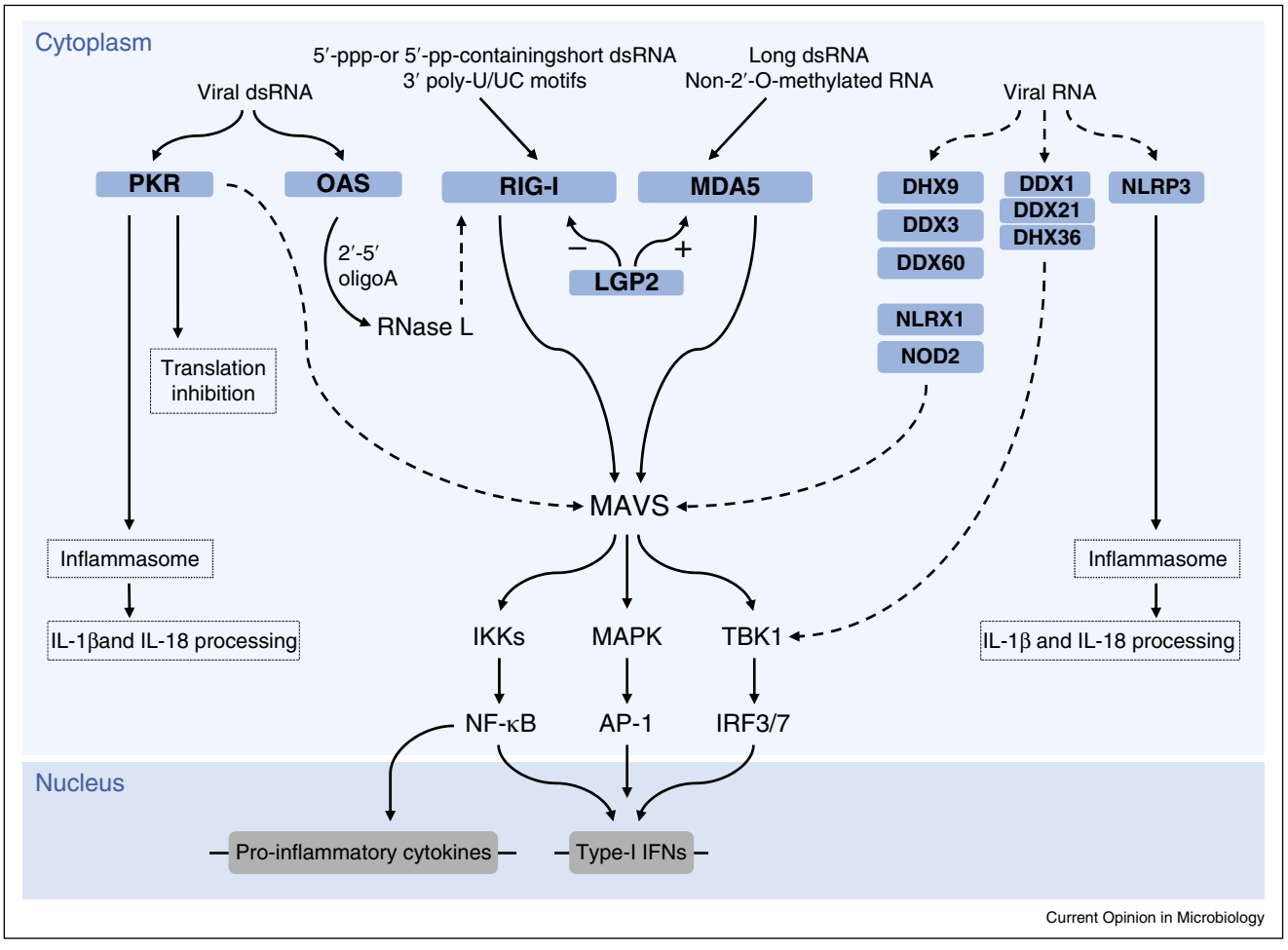
immune receptors detect vRNA and vDNA, and further outline unresolved questions in this rapidly progressing field.

Cytosolic sensing of vRNA

Detection of vRNA by RLRs

Cytosolic vRNA is predominantly recognized by DExD/H-box RNA helicases of the RLR family (Figure 1). This family consists of retinoic acid-inducible gene-I (RIG-I), melanoma differentiation-associated gene 5 (MDA5), and laboratory of genetics and physiology 2 (LGP2), all of which are able to directly bind RNA through their helicase and C-terminal domains (CTD) [1,2]. In addition, both RIG-I and MDA5 possess a pair of caspase activation and recruitment domains (CARDs), which mediate downstream signaling and thereby cytokine induction. In contrast, LGP2 lacks the CARD signaling module. Following vRNA binding, RIG-I switches from an auto-inhibited 'closed' conformation into its active tetrameric form, in which the CARDs are exposed [7–9]. In contrast to RIG-I, MDA5 is thought to adopt an extended conformation under normal conditions; upon vRNA binding, MDA5 then forms filaments along the viral dsRNA strand [10••]. The exposed CARDs of RIG-I

Figure 1



Detection of cytosolic vRNA by RLRs and other proteins. Viral 5′-triphosphate (5′-ppp)-containing or 5′-diphosphate (5′-pp)-containing short dsRNA as well as poly-U/UC motifs are recognized by RIG-I, whereas MDA5 binds to long dsRNA or non-2′-O-methylated vRNA. The RNA binding and/or signaling activities of RIG-I and MDA5 are negatively and positively regulated by LGP2, respectively. Signaling induced by RIG-I and MDA5 converges on MAVS, which serves as a scaffolding protein to activate the key transcription factors NF-κB, AP-1 and IRF3/7 via several kinases (IKKs, MAPK, TBK1). NF-κB, AP-1 and IRF3/7 then act in concert to induce the gene expression of type-I IFNs and other pro-inflammatory cytokines. PKR and OAS both recognize viral dsRNA. Upon activation, PKR leads to inhibition of cellular translation. Furthermore, PKR activates the inflammasome, resulting in IL-1β and IL-18 processing and release. Upon dsRNA binding, OAS produces 2′–5′ oligoA, which activates RNase L. RNA fragments generated by RNase L can serve as RIG-I ligands, amplifying RIG-I-mediated antiviral signaling. Viral RNA is also sensed (directly or indirectly) by DHX9, DDX3, DDX60, NLRX1 and NOD2, leading to activation of MAVS-dependent signaling. The DDX1–DDX21–DHX36 complex signals downstream via the adaptor protein TRIF (not depicted), leading to TBK1 and IRF activation. In response to RNA virus infection, NLRP3 and inflammasomes are activated, which leads to maturation of IL-1β and IL-18. Solid arrows indicate well-established signaling events. Dashed arrows indicate signaling events that are indirect or that have not yet been fully elucidated.

Download English Version:

https://daneshyari.com/en/article/3399036

Download Persian Version:

https://daneshyari.com/article/3399036

Daneshyari.com