Cytoplasmic RNA sensors and their interplay with RNA-binding partners in innate antiviral response: theme and variations

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ABSTRACT

Sensing of pathogen-associated molecular patterns including viral RNA by innate immunity represents the first line of defense against viral infection. In addition to RIG-I-like receptors and NOD-like receptors, several other RNA sensors are known to mediate innate antiviral response in the cytoplasm. Double-stranded RNA-binding protein PACT interacts with prototypic RNA sensor RIG-I to facilitate its recognition of viral RNA and induction of host interferon response, but variations of this theme are seen when the functions of RNA sensors are modulated by other RNA-binding proteins to impinge on antiviral defense, proinflammatory cytokine production and cell death programs. Their discrete and coordinated actions are crucial to protect the host from infection. In this review, we will focus on cytoplasmic RNA sensors with an emphasis on their interplay with RNA-binding partners. Classical sensors such as RIG-I will be briefly reviewed. More attention will be brought to new insights on how RNA-binding partners of RNA sensors modulate innate RNA sensing and how viruses perturb the functions of RNA-binding partners.

Keywords: RIG-I; MDA5; PACT; RIG-I-like receptors; NOD-like receptors

INTRODUCTION

Innate antiviral response constitutes the first line of host defense against viral invasion. Upon viral infection, foreign molecular features, called pathogen-associated molecular patterns (PAMPs), are produced and sensed by pattern-recognition receptors (PRRs) of the host cells. Particularly, the sensing of non-self viral RNAs, as one major PAMP, by host PRRs such as RIG-I in the cytoplasm (Yoneyama et al. 2004), represents a pivotal step to elicit complex proinflammatory and immunoregulatory reactions that protect the host. RIG-I is a DExD/H-box helicase evolutionarily related to Dicer, an RNase III that cleaves double-stranded RNA (dsRNA) and pre-microRNA (pre-miRNA) (Luo et al. 2013). Whereas the optimal function of Dicer requires dsRNA-binding proteins TRBP and PACT (Chendrimada et al. 2005; Lee et al. 2006; Kok et al. 2007), RIG-I also co-opts PACT to activate interferon (IFN) production upon recognition of viral RNA (Kok et al. 2011). The interaction between RIG-I and PACT is highly representative of the trend in which RNA sensors engage RNA-binding proteins to facilitate ligand recognition and selection. In addition, the RNA-binding proteins might also adapt RIG-I signaling to other RNA-activated pathways such as miRNA biogenesis and PKR activation (Heyam et al. 2015; Hur 2019). Variations of the theme are also seen when different types of RNA-binding proteins are recruited to modulate the functions of RNA sensors. Notably, some of these interactions between RNA sensors and their RNA-binding partners are evolutionarily conserved among different species.

In this review, we will provide an overview of cytoplasmic RNA sensors including RIG-I-like receptors (RLRs), NOD-like receptors (NLRs) and other newly identified sensors (Fig. 1). For a more detailed discussion of RIG-I and other RNA sensors, we refer the readers to other recent reviews (Brisse and Ly 2019; Hur 2019; Liu and Gack 2020; Thoresen et al. 2021). Our emphasis will be on the increasingly important roles of RNA-binding partners in modulating the functions of RNA sensors. Examples will be used to demonstrate the functional interplay between the RNA sensors and their RNA-binding partners. Comparisons will be made with the roles of dsRNA-binding partners in Dicer function, where more mechanistic insights are

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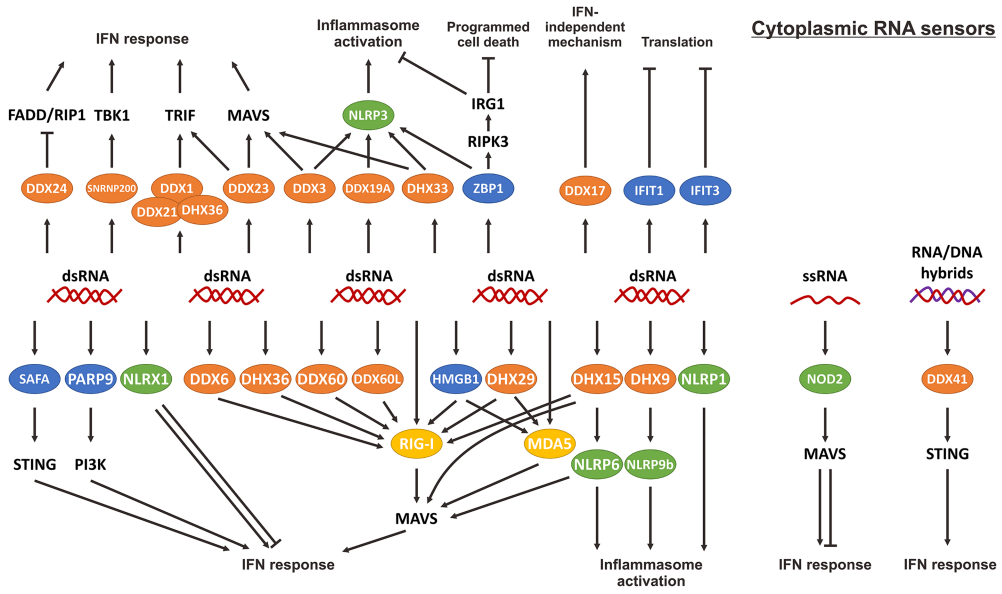

FIGURE 1. Cytoplasmic RNA sensors. Sensors and their downstream effectors are shown. RLRs are in yellow. Non-RLR DExD/H-box helicases are in orange. NLRs are in green. Other sensors are in blue. Stimulatory and inhibitory actions are highlighted by arrows and stop signs, respectively.

available. Finally, we will also summarize viral strategies to overturn innate RNA sensing by targeting the RNA-binding partners of sensors.

RLRs

RLRs, being expressed in most cell types, are key players in sensing immunostimulatory RNA of either viral or host origins and triggering subsequent innate immune signaling. RLRs are a group of PRRs encompassing three cytoplasmic RNA sensors known to have distinct roles and substrate specificity. In addition to its prototypic member RIG-I, the group also includes MDA5 and LGP2. Despite a recent report demonstrating the existence of nuclear-localized RIG-I (Liu et al. 2018), RLRs predominantly localize to the cytoplasm. Structurally, RIG-I and MDA5 are more similar in their domain architectures. They both harbor tandem caspase activation and recruitment domains (CARDs) at the amino terminus for signal transduction, a central RNA helicase core consisting of two RecA-like helicase domains for RNA sensing, and a carboxy-terminal repressor domain (CTD) for activity regulation (Chow et al. 2018). In contrast, LGP2 contains only the helicase domain and CTD but not the CARDs. Due to the lack of CARDs, LGP2 is thought to be signaling-incompetent and mainly functions to regulate RIG-I and MDA5 signaling (Bruns and Horvath 2015).

Upon viral infection, RLRs recognize and bind to virus-derived RNA ligands, leading to a conformational change to expose the active CARDs for their oligomerization and subsequent association with the mitochondrial adaptor protein MAVS (Fan and Jin 2019). Upon stimulation by RIG-I or MDA5, MAVS forms the large prion-like polymers along the outer mitochondrial membrane. The MAVS polymers then recruit TRAF2, TRAF5, and TRAF6 for activation of TBK1 and the IKK family of serine kinases (Liu et al. 2013). These kinases in turn activate IRF3 and NF-κB to drive the transcription of various antiviral genes such as IFN-β. Secreted IFN-β acts in both autocrine and paracrine fashions on the infected and neighboring cells, respectively, via the IFNAR-JAK-STAT signaling pathway to initiate the antiviral programs (Schoggins 2019).

RIG-I

RIG-I, also known as DDX58, has a low basal expression level in most cells and is highly induced by IFNs (Matsumiya and Stafforini 2010). In the resting state, RIG-I remains in a closed inactive conformation with both the CTD and CARDs folded over the helicase domain. Upon recognition of RNA ligands, RIG-I hydrolyzes ATP and undergoes a conformational change, which allows for RIG-I oligomerization and its subsequent interaction with MAVS through the CARDs, thereby initiating downstream signaling for IFN production. Oligomeric RIG-I might assemble into a filamentous form only in the presence of RNA (Cadena et al. 2019). While RIG-I responds rapidly to trigger innate immune responses for effective antiviral defense, immune homeostasis also needs to be maintained during normal physiological conditions. Dysregulation of RIG-I activation could cause severe autoimmune diseases such as Aicardi–Goutières syndrome, systemic lupus erythematosus and other rare interferonopathies (Buers et al. 2016), thus the activity of RIG-I is tightly regulated through multiple mechanisms (for review, see Rehwinkel and Gack 2020). In brief,

RIG-I activity could be regulated by post-translational modifications (PTMs), interacting proteins, noncoding RNAs, and autophagy. Some of these important regulatory mechanisms will be briefly mentioned here and more details will be provided later. Firstly, multiple PTMs by various regulatory enzymes have been shown to regulate RIG-I activity. These include ubiquitination, ubiquitin-like protein conjugation, phosphorylation, acetylation, and deamidation. For example, TRIM-like ubiquitin ligase RIPLET recognizes the RNA-bound oligomeric filament of RIG-I and catalyzes K63-linked ubiquitination of RIG-I to trigger its full activation (Cadena et al. 2019; Kato et al. 2021). The role of an unanchored K63-linked polyubiquitin chain in the activation of RIG-I has also been suggested (Zeng et al. 2010). In another case, cooperative deamidation of RIG-I by herpesviral and cellular deamidases is a viral countermeasure to evade innate antiviral response (He et al. 2015; Huang et al. 2021). Secondly, various proteins interact with RIG-I to fulfill different functions in RIG-I activation, with a number of them serving as cosensors for RNA. Particularly, PACT is one of the first dsRNA-binding proteins identified as a cellular interacting partner of RIG-I. Its direct binding to the CTD of RIG-I activates RIG-I and potentiates RIG-I-dependent type I interferon production (Kok et al. 2011). Thirdly, noncoding RNAs including long noncoding RNAs (lncRNA) and miRNAs are induced during viral infection to promote or dampen RIG-I signaling through a post-transcriptional mechanism. Whereas one lncRNA is thought to act as a scaffold for RIG-I activation (Lin et al. 2019), another lncRNA might serve as a decoy to preoccupy all ligand-binding sites in RIG-I (Jiang et al. 2018). However, it remains to be seen whether these mechanisms might indeed operate in vivo. Lastly, autophagy has emerged as a negative regulatory process for RIG-I signaling through diverse mechanisms that include autophagy-dependent degradation of RIG-I or downstream signaling molecules. A recent report has identified a novel autophagic cargo receptor CCDC50, which is induced by viral infection and specifically recognizes K63-linked polyubiquitination in activated RIG-I and MDA5, thereby subjecting them to autophagic degradation (Hou et al. 2020). In addition, two LRRC family members, LRRC25 and LRRC59, have been shown to antagonize each other in targeting RIG-I to p62-dependent autophagic degradation (Xian et al. 2020).

RNA ligand specificity of RIG-I has been well characterized. RIG-I preferentially and optimally binds to short dsRNA of <300 bp (Kell and Gale 2015). The 5′-triphosphate was initially identified as the molecular signature in RNA, which is sufficient for recognition by RIG-I for activation of IFN response (Hornung et al. 2006; Pichlmair et al. 2006). Later, short double-stranded base-paired RNA carrying 5′-triphosphate was further demonstrated as the essential molecular pattern for recognition by and activation of RIG-I (Schlee et al. 2009; Schmidt et al. 2009). Moreover, base-paired viral RNA bearing 5′-diphosphate has also been shown to activate RIG-I-mediated IFN response (Goubau et al. 2014). Additionally, the lack of 2′-*O*-methylation at the 5′-terminal nucleotide of capped RNA was also shown to be the crucial determinant for RIG-I activation (Schuberth-Wagner et al. 2015). These molecular features, which are commonly found in RNA of viral origin but rarely present in host RNA, serve as crucial determinants for self and non-self discrimination by RIG-I. Furthermore, RIG-I functions largely in a sequence-independent manner, but sequence-specific recognition of some viral genomes by RIG-I has also been noted (Saito et al. 2008; Schnell et al. 2012; Kell and Gale 2015). Natural agonists of RIG-I in virus-infected cells have been well described. Particularly, copy-back type defective-interfering RNAs derived from genomes of paramyxoviruses such as the Sendai virus and the measles virus are potent activators of RIG-I (Martinez-Gil et al. 2013; Ho et al. 2016). These viral RNAs contain a 5′-triphosphate and a long base-paired region (Xu et al. 2015; Ho et al. 2016; Mura et al. 2017). Other viral RNA ligands of RIG-I include influenza A virus (IAV) panhandle structure (Liu et al. 2015), short dsRNA with overhanging 5′-triphosphate derived from the arenavirus genome (Marq et al. 2011) and the poly-U/UC tract in the 3′ untranslated region of the hepatitis C virus genome (Schnell et al. 2012). All these RNA agonists of RIG-I are potential innate immunostimulatory agents that might be further developed as antivirals or vaccine adjuvants. For example, they can serve as built-in adjuvants in mRNA vaccines.

RIG-I is involved in antiviral immune responses against almost all major virus families including both RNA and DNA viruses (Kell and Gale 2015; Zhao and Karijolich 2019). Indeed, many of these viruses are sensed by both RIG-I and MDA5 with differential potency. Viral infections that are thought to be detected by RIG-I include *Adenoviridae* (Minamitani et al. 2011), *Arenaviridae* (Habjan et al. 2008; Fan et al. 2010; Xing et al. 2015; Brisse et al. 2021), *Coronaviridae* (Li et al. 2010), *Filoviridae* (Edwards et al. 2016), *Flaviviridae* (Fredericksen et al. 2008; Saito et al. 2008; Nasirudeen et al. 2011; Schilling et al. 2020), *Hepadnaviridae* (Sato et al. 2015), *Herpesviridae* (Samanta et al. 2006; Xing et al. 2012; Chiang et al. 2018; Zhao et al. 2018), *Orthomyxoviridae* (Kato et al. 2006), *Paramyxoviridae* (Kato et al. 2006; Ikegame et al. 2010), *Picornaviridae* (Slater et al. 2010), *Poxviridae* (Myskiw et al. 2011), *Reoviridae* (Broquet et al. 2011; Sen et al. 2011), and *Retroviridae* (Solis et al. 2011; Berg et al. 2012).

MDA5

MDA5, also known as IFIH1, shows high structural similarity and some functional redundancy in pathogen recognition with RIG-I, but MDA5 indeed has distinct nonredundant functions (Brisse and Ly 2019). The molecular nature of MDA5 ligands is not well characterized, but it has been shown that MDA5 preferentially binds to and is activated by long dsRNA of over 2 kb pairs (Kato et al.

2008; Rodriguez et al. 2014). Besides, higher-order structures like RNA branches in high-molecular-weight RNAs from infected cells have also been suggested to serve as MDA5 agonists (Pichlmair et al. 2009; Rodriguez et al. 2014). Additionally, the lack of 2′-*O*-methylation in mRNA and the presence of specific AU-rich sequences in viral mRNA are recognized by MDA5 (Züst et al. 2011; Runge et al. 2014). Upon binding with RNA, MDA5 oligomerizes and forms filaments (Berke and Modis 2012).

With a distinct agonist preference compared to RIG-I, MDA5 plays differential roles in the recognition of viral infections. Although MDA5 is a major sensor of viral RNA in the cases of certain positive-sense single-stranded RNA viruses, this cannot be generalized to all RNA viruses of the same group. Indeed, MDA5 possesses broad antiviral roles against many viruses. Viral infections that are detected by MDA5 include *Coronaviridae* (Li et al. 2010), *Filoviridae* (Edwards et al. 2016), *Flaviviridae* (Fredericksen et al. 2008; Nasirudeen et al. 2011), *Hepadnaviridae* (Lu and Liao 2013), *Herpesviridae* (Xing et al. 2012; Zhao et al. 2018), *Paramyxoviridae* (Yount et al. 2008; Ikegame et al. 2010), *Picornaviridae* (Kato et al. 2006; Wang et al. 2009; Slater et al. 2010; Feng et al. 2012), *Poxviridae* (Myskiw et al. 2011), and *Reoviridae* (Broquet et al. 2011; Sen et al. 2011).

Similar to mutations in RIG-I, MDA5 mutations in humans are associated with rare interferonopathies such as Aicardi–Goutières syndrome (Buers et al. 2016). On the other hand, autoantibodies against MDA5 have been found in dermatomyositis, an idiopathic inflammatory myopathy (Kurtzman and Vleugels 2018). Hence, MDA5 activity has to be tightly regulated via multiple mechanisms. MDA5 is regulated by several types of PTMs including phosphorylation, ubiquitination and sumoylation (Rehwinkel and Gack 2020). Particularly, ubiquitin ligase TRIM65 specifically recognizes RNA-bound MDA5 filaments to catalyze K63-linked ubiquitination and activation of MDA5 (Kato et al. 2021). Similar to RIG-I, an unanchored but longer K63-linked polyubiquitin chain is thought to trigger oligomerisation and activation of MDA5 (Song et al. 2021). Besides, different MDA5 interacting partners are also involved in MDA5 regulation. One recently identified MDA5 binding partner named ZFYVE1, a zinc-finger protein containing a FYVE domain and capable of binding to dsRNA, is a negative regulator of MDA5, but not RIG-I (Zhong et al. 2020b). Notably, increasing evidence suggests the third RLR member, LGP2, as an important positive regulator of MDA5 in RNA recognition (Rodriguez et al. 2014; Duic et al. 2020). Some RNA-binding proteins reviewed below have also been suggested to regulate MDA5 activity, for example, by serving as cosensors for MDA5. As such, PACT functions as a coactivator of MDA5 by promoting MDA5 oligomerization upon dsRNA-induced activation (Lui et al. 2017). Furthermore, lncRNA ITPRIP-1 has been shown to interact with MDA5 to stabilize its binding to viral RNAs and facilitate its oligomerization for IFN signaling (Xie et al. 2018b). Again, autophagy may as well play a role in MDA5 regulation through degradation of MDA5 or downstream signaling molecules (Hou et al. 2020). Whereas most of the aforementioned regulatory mechanisms operate on both RIG-I and MDA5, some of them, such as those involving TRIM65 and ZFYVE1, are specific to MDA5. It is also noteworthy that RIG-I and MDA5 share other features required for activation with other innate signal transducers such as MAVS, including K63-linked ubiquitination, oligomerization and assembly into high-molecular-mass fibers or aggregates. These assemblies are tailor-made to facilitate ligand recognition and propagate downstream signaling.

In addition to the induction of IFN production, activated RIG-I and MDA5 can also trigger other effector functions of innate antiviral response, including NF-κB activation, inflammasome assembly, pyroptosis, apoptosis and necroptosis (Poeck and Ruland 2012; Maelfait et al. 2020). RIG-I signaling is known to be adapted to NF-κB activation via CARD9 and to inflammasome activation either directly or via MAVS (Poeck et al. 2010; Franchi et al. 2014). Pyroptosis is a result of RIG-I-mediated inflammasome activation (Lupfer et al. 2015). Induction of apoptosis by RIG-I and MDA5 is mediated through a unique mechanism known as RLR-induced IRF3-mediated pathway of apoptosis (RIPA), during which TRAF2, TRAF6, and a linear ubiquitin chain assembly complex (LUBAC) are recruited to modify IRF3, leading to its subsequent translocation with Bax to mitochondria (Chattopadhyay et al. 2010, 2016). Furthermore, RIG-I-dependent IFN response also promotes RIPK3-mediated necroptosis (Brault et al. 2018; Dunker et al. 2021). In many cases, the activation of inflammasome and cell death programs might either exert a protective role by eliminating the virus-infected cells or facilitate virus dissemination and spread by releasing a large number of virion particles.

LGP2

LGP2, also known as DHX58, lacks the CARDs, thus it is widely accepted that LGP2 is signaling-incompetent and functions in innate immune responses mainly through regulating RIG-I and MDA5 activity (Onomoto et al. 2021). Various reports have implicated LGP2 in antiviral innate responses with apparently opposing roles, by serving as an inhibitor of RIG-I signaling and an activator of MDA5 signaling. For the RIG-I signaling pathway, LGP2 has been suggested to function as a feedback inhibitor to repress RIG-I activation and antiviral response through multiple mechanisms. With a stronger RNA binding affinity than RIG-I and MDA5, LGP2 inhibits RIG-I activation by sequestration of RNA (Rothenfusser et al. 2005; Rodriguez et al. 2014). Besides, LGP2 also interacts through its CTD with RIG-I and MAVS to hinder RIG-I oligomerization and kinase

recruitment by MAVS, respectively, to negatively regulate antiviral IFN signaling (Komuro and Horvath 2006; Saito et al. 2007; Rodriguez et al. 2014). However, a later study has shown that CTD of LGP2 is dispensable for inhibiting RIG-I signaling and suggested that the inhibition is mediated through the interaction of LGP2 with TRIM25 to suppress ubiquitination of RIG-I which is required for RIG-I activation (Quicke et al. 2019). Contrary to this, characterization of *Lgp2*$^{-/-}$ mice has revealed a positive regulatory role of LGP2 on both RIG-I and MDA5 signaling (Satoh et al. 2010). The controversy remains as to whether LGP2 stimulates or suppresses RIG-I-dependent activation of type I IFN production. Plausibly, it might vary on different RNA ligands, at different subcellular compartments, during different phases of viral infection and in the presence of different cosensors such as PACT (Sanchez David et al. 2019). Indeed, in the absence of RNA, LGP2 has been found to interact with MAVS in microsomes to prevent the latter from engaging RIG-I in resting cells. However, upon dsRNA treatment or viral infection, LGP2 rapidly releases MAVS and relocalizes to mitochondria, augmenting RIG-I and MDA5 signaling (Esser-Nobis et al. 2020). Further investigations are required to determine under what physiological conditions LGP2 might positively and negatively modulate RIG-I signaling.

A consensus on the stimulatory effect of LGP2 on MDA5 signaling has emerged in the literature (Bruns et al. 2014). Particularly, loss of LGP2 increases susceptibility and reduces IFN response to several RNA viruses including encephalomyocarditis virus (EMCV) and poliovirus, which are primarily sensed by MDA5 (Satoh et al. 2010). LGP2, with no signaling capability, is believed to work by binding to and forming a complex with RNA for subsequent relaying to MDA5 to trigger IFN signaling. This resembles the role of PACT, and the idea is supported by the finding that MDA5-stimulatory RNA in EMCV-infected cells is identified in an LGP2 complex rather than in an MDA5 complex (Deddouche et al. 2014). Indeed, biochemical analysis indicates the requirement of ATP hydrolysis for RNA recognition and innate immune signaling by LGP2. Through this mechanism, LGP2 synergizes with MDA5 to engage different RNA species leading to subsequent activation of MDA5 (Bruns et al. 2013). This also explains the essentiality of ATPase activity of LGP2 in its synergistic effect with MDA5, which contrasts with the enzymatic activity-independent regulation of RIG-I by LGP2. Again, the roles of LGP2 in this scenario are similar to those of PACT. Indeed, the interaction between LGP2 and PACT is critical for LGP2-mediated regulation of both RIG-I and MDA5 signaling. It is thought that PACT functions as a key determining factor in differential regulation of RIG-I and MDA5 by LGP2 (Sanchez David et al. 2019). Upon binding with RNA, LGP2 also forms filaments and serves as the nucleator and essential partner for formation of MDA5 filaments (Uchikawa et al. 2016; Duic et al. 2020). LGP2 has been found to form hetero-oligomers with MDA5 and induces significant conformational change of MDA5 to facilitate its activation (Duic et al. 2020). Comparative analysis of RLR-bound RNA ligands in measles virus-infected cells indicates preferential recognition of nucleoprotein-coding region by LGP2 and MDA5, distinct with defective-interfering RNA recognized by RIG-I (Sanchez David et al. 2016).

NLRs

NLRs represent a specialized group of intracellular PRRs responsible for recognizing PAMPs and danger-associated molecular patterns (DAMPs) during infection, environmental insults, or cellular stresses (Carneiro et al. 2008; Corridoni et al. 2014). NLRs typically have a three-domain protein structure, which includes an amino-terminal effector domain, a central NOD (also called NACHT) domain and a carboxy-terminal leucine-rich repeat (LRR) domain (Corridoni et al. 2014). While all NLR members harbor the common characteristic NOD domain essential for dNTPase activity and NLR protein oligomerization, the 22 known human NLRs can be further classified into five subfamilies according to the amino-terminal effector domains. The five subfamilies include NLRA (A for acidic transactivating domain), NLRB (B for BIRs or baculovirus inhibitor of apoptosis protein repeats domain), NLRC (C for CARD or caspase activation and recruitment domain), NLRP (P for PYD or pyrin domain) and NLRPX, which has no homology with any other NLR proteins (Corridoni et al. 2014; Zheng 2021). With different effector domains, NLR proteins bind to distinct downstream signaling proteins leading to different outcomes. The LRR domain in NLR proteins is responsible for ligand binding and is also essential for intramolecular interaction with the NOD domain to prevent signaling under the resting state. Upon ligand recognition by the LRR domain, conformational changes will occur in NLRs that induce NLR oligomerization and the exposure of effector domains for protein recruitment and activation of downstream signaling cascades (Liu and Gack 2020).

NLRs play key roles in innate immunity by regulating inflammatory and apoptotic responses. A considerable number of NLR members are known to serve as scaffold proteins for inflammasome complex formation to promote maturation and secretion of interleukin 1β (IL-1β) and IL-18, which are both potent proinflammatory cytokines with a wide range of effects on the innate and adaptive immune systems. Recently, some NLRs have been implicated in sensing viral RNA and triggering type I interferon and inflammasome-dependent antiviral responses (Sabbah et al. 2009; Wang et al. 2015; Zhu et al. 2017).

NOD2

NOD2, also known as NLRC2, has been implicated in interferon (IFN) response against single-stranded RNA (ssRNA)

and human respiratory syncytial virus (RSV) infection (Sabbah et al. 2009). This provides the first evidence for NLR involvement in innate antiviral response as a direct viral RNA sensor. NOD2 recognizes and interacts with viral ssRNA to facilitate virus-induced IFN production. Virus-induced NOD2-mediated IFN response is MAVS-dependent. The enhanced RSV pathogenesis and greater viral susceptibility in NOD2-deficient mice provide further support to the physiological importance of NOD2 in antiviral defense. Besides, the significance of NOD2 has also been noted during infection with other viruses including IAVs and parainfluenza viruses (Lupfer et al. 2014). However, NOD2 expression has also been shown to promote Zika virus replication possibly through inhibition of IFN response. In addition, inhibition of NOD2 with a small-molecule compound exhibits broad-spectrum antiviral activity against multiple RNA viruses including dengue virus, alphaviruses, enteroviruses and SARS-CoV-2, which is mediated at least in part through augmented IFN response (Limonta et al. 2021). It remains to be clarified whether NOD2 has proviral and antiviral activity against different RNA viruses.

NLRP1

NLRP1, also called NALP1, was the first characterized sensor for triggering inflammasome activation (Martinon et al. 2002), but its physiological role as an RNA sensor against viral infection has only been identified very recently (Bauernfried et al. 2021). NLRP1 is a widely expressed protein with the highest abundance in epithelial tissues. Gain-of-function NLRP1 mutations in patients cause inflammatory phenotypes in the skin and respiratory tract (Zhong et al. 2016; Drutman et al. 2019), which is consistent with its crucial role in non-self-recognition. Human NLRP1 is stimulated by long dsRNA during Semliki Forest virus infection in keratinocytes to trigger inflammasome activation (Bauernfried et al. 2021). Human NLRP1 binds dsRNA with high affinity primarily through its leucine-rich repeat domain. Upon binding to dsRNA, ATPase activity of NLRP1 is activated, likely through a conformational change that is important for its oligomerization and formation of an inflammasome complex. This subsequently leads to IL-1β maturation and the induction of pyroptosis. Thus, human NLRP1 plays an important role in host defense by serving as a sensor of dsRNA for initiating inflammasome activation.

NLRP3

NLRP3, also called cryopyrin or NALP3, is one of the most studied NLRs and has long been known to mediate immune responses against diverse PAMPs and DAMPs through the formation of an inflammasome complex with ASC and procaspase-1 to promote the secretion of proinflammatory cytokines (Kanneganti et al. 2006). Extremely diversified signals such as crystals, extracellular ATP, nucleic acids, bacteria, fungi, and viruses are all capable of activating the NLRP3 inflammasome (Da Costa et al. 2019). The mechanistic details for activation of NLRP3 inflammasome remain to be dissected. Particularly, multiple mechanisms for the sensing of RNA virus infection by NLRP3 have been proposed. DHX33, a DExD/H-box helicase, functions as an upstream RNA sensor for NLRP3 activation (Mitoma et al. 2013). Upon stimulation with RNA, DHX33 interacts with NLRP3 to initiate NLRP3 oligomerization and trigger the inflammasome activation cascade. Other mechanisms for NLRP3 activation include sensing of ion flux by viroporins such as IAV M2 channel (Ichinohe et al. 2010; Guo et al. 2015), activation of a RIPK1–RIPK3–Drp1 signaling pathway (Wang et al. 2014), TRAF3-dependent ubiquitination and activation of ASC (Siu et al. 2019), RNA cleavage by RNase L (Chakrabarti et al. 2015), and reactive oxygen species (ROS) production (Allen et al. 2009).

NLRP6

Intestinally expressed NLRP6 has previously been shown to be required for innate antiviral response against enteric virus infection (Wang et al. 2015). Loss of NLRP6 in mice or cells leads to higher EMCV viral loads and diminished antiviral gene expression. NLRP6 restricts enteric virus infection by inducing the expression of type I/III IFNs and IFN-stimulated genes (ISGs). Although NLRP6 alone is capable of binding with long dsRNA, it forms a viral RNA-sensing complex with DEAH-box helicase DHX15 to sense viral dsRNA and induce MAVS-dependent IFN response. NLRP6-mediated signaling is independent of RIG-I and MDA5. Activation of the NLRP6–DHX15 sensing complex by rotavirus and reovirus also results in inflammasome activation (Xing et al. 2021b). Thus, NLRP6 functions with DHX15 as a viral RNA sensor which not only constitutes the first line of antiviral defense in the intestinal epithelia, but also provokes intestinal inflammation.

NLRP9b

Another intestine-specific NLR, NLRP9b, has also been shown to restrict rotavirus infection via RNA helicase DHX9 (Zhu et al. 2017). Although NLRP9b itself does not bind RNA, it recognizes short dsRNA via DHX9 and triggers the formation of an inflammasome complex, leading to IL-18 release and activation of pyroptosis through gasdermin D (GSDMD). Mice with conditional depletion of NLRP9b or other inflammasome components, caspase-1 and ASC, in the intestine are more susceptible to rotavirus infection and have higher viral loads, independent of the effects ascribed to microbiota. GSDMD-mediated pyroptosis is of particular importance to restrict rotavirus replication through induction of premature death of infected intestinal epithelial cells and maintenance of intestinal homeostasis. Hence, NLRP9b, together with DHX9, functions

as an enteric viral RNA sensor in the host innate immune defense against rotavirus infection.

NLRX1

NLRX1, the only member in the NLRX subfamily of NLRs, is unique for its mitochondrial localization through its amino-terminal mitochondrial targeting sequence (Moore et al. 2008; Tattoli et al. 2008; Hong et al. 2012). The carboxy-terminal fragment of NLRX1 has been shown to specifically bind RNA with a stronger preference toward dsRNA, and thus it is thought to be involved in the recognition of intracellular viral RNA in infected cells (Hong et al. 2012). NLRX1 indeed is an innate immune modulator with both positive and negative regulatory roles (Hong et al. 2012; Feng et al. 2017). Specifically, NLRX1 suppresses mitochondrial antiviral immunity by sequestering its interacting partner MAVS to interfere with RIG-I-MAVS-dependent signaling during viral infection (Moore et al. 2008; Allen et al. 2011). Sequestration of STING by NLRX1 has also been reported (Guo et al. 2016). In addition, NLRX1 forms a complex with mitochondrial protein TUFM to suppress IFN production but augment autophagy (Lei et al. 2012, 2013). Potentiation of innate antiviral response has also been noted in NLRX1-deficient mice (Allen et al. 2011). These findings are in favor of a role for NLRX1 as a negative innate immune regulator. On the other hand, it has also been reported that MAVS signaling, IRF3 activation as well as IFN and cytokine production are not affected in the absence of NLRX1 in cells upon Sendai virus infection or poly(I:C) stimulation (Rebsamen et al. 2011). Additionally, NLRX1 is essential for IFN production and apoptosis in macrophages by interacting with IAV protein PB1-F2 during infection (Jaworska et al. 2014). The mitochondrial viral protein PB1-F2 has been shown to suppress MAVS signaling and NLRP3 inflammasome activation, which might provide further support to the role of NLRX1 in interacting with and sequestering PB1-F2 to regulate innate immune responses in a positive manner (Cheung et al. 2020a,b,c). Finally, NLRX1 also enhances NF-κB signaling by inducing the production of ROS in response to diverse stimuli (Tattoli et al. 2008). These studies suggest a positive regulatory role for NLRX1 in innate immune responses. An explanation for the observed opposing regulatory effects of NLRX1 on innate immunity from a recent report suggests that NLRX1 could suppress MAVS-mediated IRF3 activation, but at the same time facilitate virus-induced IRF1 expression (Feng et al. 2017), leading to differential regulation of different innate immune pathways. More work is required to clarify whether and how NLRX1 differentially modulates innate immune signaling in different contexts.

OTHER RNA SENSORS

In addition to RLRs and NLRs, several other proteins have emerged as RNA sensors. Below we will review several sensors that are thought to sense viral RNA directly. However, in some circumstances, some of them might also affect RNA sensing indirectly in a manner similar to the RNA-binding protein partners of RNA sensors that will be discussed in the next section. This is not uncommon. For example, LGP2 discussed above can be seen as either an RNA sensor or an RNA-binding partner of RIG-I and MDA5 sensors.

DExD/H-box RNA helicases

DExD/H helicases are characterized by a series of amino acid motifs that form the RNA and ATP binding sites of the helicase core (Taschuk and Cherry 2020). To date, 42 DEAD-box helicases and 16 DEAH-box helicases have been identified in humans. Helicases are enzymes that catalyze the unwinding of duplex nucleic acids in an energy-dependent manner. They participate in nearly every cellular process involving RNA (Fullam and Schroder 2013). Emerging evidence suggests that cellular RNA helicases could function in the recognition of foreign nucleic acids and impact viral replication. The ability of DExD/H-box helicases to recognize RNA in a sequence-independent manner, together with its involvement in diverse cellular functions, lead them to influence innate recognition and viral infection in multiple ways. Indeed, in addition to the well-studied RLRs, various non-RLR DExD/H-box helicases have also been implicated in RNA sensing in infected cells, with antiviral or proviral roles. Non-RLR members of the family of DExD/H-box helicases with reported functions in RNA sensing are listed and introduced briefly in Table 1 below.

ZBP1

Z-DNA binding protein 1 (ZBP1), also known as DAI or DLM-1, is IFN-inducible and has initially been suggested as a cytosolic B-DNA sensor to trigger IFN response (Takaoka et al. 2007), but this finding has not been substantiated by later studies. In addition to the role of ZBP1 in the activation of IFN response, several studies have implicated ZBP1 as an inducer of cell death upon viral infection (Kuriakose et al. 2016; Nogusa et al. 2016; Thapa et al. 2016; Maelfait et al. 2017). Programmed cell death, such as pyroptosis, apoptosis and necroptosis, serves as an important immune defense mechanism to clear infected cells and restrict viral replication (Maelfait et al. 2017). Upon sensing of Z-RNA by ZBP1, RIPK3 and caspase 8 are recruited, resulting in the activation of ZBP1-NLRP3 inflammasome, the assembly of which is facilitated by caspase 6 (Zheng et al. 2020). Parallel to this, another complex containing AIM2 and pyrin is also formed to mediate inflammasome activation, pyroptosis and other forms of cell death (Lee et al. 2021). Whether these two complexes are mutually exclusive and how they cooperate in the

TABLE 1. DExD/H-box helicases involved in RNA sensing

DExD/H-box helicases	Functions in RNA sensing	Key references
DDX1, DDX21 and DHX36	Form a complex as a dsRNA sensor to trigger IFN response via TRIF pathway	(Zhang et al. 2011a)
DDX3	Binds to viral RNA and interacts with MAVS to mediate IFN induction during early viral infection	(Oshiumi et al. 2010b)
	As a sensor of abortive HIV-1 RNA to induce MAVS-mediated IFN response	(Gringhuis et al. 2017)
	Interacts with NLRP3 to induce inflammasome activation	(Samir et al. 2019)
DDX6	As a potent ISG suppressor working via the mRNA degradation machinery	(Lumb et al. 2017)
	As an RNA cosensor for RIG-I to enhance antiviral signaling	(Nunez et al. 2018; Zhang et al. 2021)
DHX9	As a viral dsRNA sensor and interacts with MAVS to mediate IFN response in myeloid dendritic cells	(Zhang et al. 2011b)
	Binds dsRNA to mediate inflammasome activation by Nlrp9b	(Zhu et al. 2017)
DHX15	As a viral dsRNA sensor and interacted with MAVS to mediate IFN response in myeloid dendritic cells	(Lu et al. 2014)
	As a viral RNA coreceptor for RIG-I to induce MAVS-mediated IFN response	(Pattabhi et al. 2019)
	Interacts with NLRP6 to mediate IFN response and inflammasome activation	(Xing et al. 2021b)
DDX17	Binds to an essential stem–loop in bunyaviral RNA to restrict infection in an interferon-independent fashion	(Moy et al. 2014)
DDX19A	As a cytosolic viral RNA sensor for porcine reproductive and respiration syndrome virus to mediate NLRP3-dependent inflammasome activation	(Li et al. 2015)
DDX23	As a viral dsRNA sensor to induce TRIF- or MAVS-dependent innate antiviral responses	(Ruan et al. 2019)
DDX24	Sequesters RNA agonists of RLR and hijacks adaptor proteins FADD and RIP1 to suppress viral RNA-dependent IFN production	(Ma et al. 2013)
DHX29	As an RNA cosensor for MDA5 to mediate antiviral immunity against EMCV	(Zhu et al. 2018)
	As a cytosolic cosensor for RIG-I to mediate nucleic acid-induced MAVS-dependent IFN response	(Sugimoto et al. 2014)
DHX33	As a cytosolic sensor of RNA such as cleavage product of RNase L to activate the NLRP3 inflammasome	(Mitoma et al. 2013; Chakrabarti et al. 2015)
	As a dsRNA and viral RNA sensor independent of RIG-I/MDA5 to induce IFN response in myeloid dendritic cells	(Liu et al. 2014)
DHX36	As a regulator of PKR-dependent antiviral stress granule to facilitate viral RNA recognition by RIG-I	(Yoo et al. 2014)
	Forms an RNA-sensing complex with DDX1 and DDX21 to activate IFN response	(Zhang et al. 2011a)
DDX41	As a sensor for RNA/DNA hybrid generated from retroviral reverse transcription to trigger an immune response	(Stavrou et al. 2018)
DDX60	Binds viral nucleic acids and promotes the binding of RIG-I to dsRNA to facilitate RLR-mediated IFN signaling	(Miyashita et al. 2011)
DDX60L	As a direct effector to inhibit HCV replication and impacts viral RNA sensing through RIG-I-dependent IFN response	(Grunvogel et al. 2015)
SNRNP200	As an RNA sensor and TBK1 adaptor for the activation of IRF3-mediated antiviral IFN response	(Tremblay et al. 2016)

induction of inflammasome activation and cell death require further investigations.

IAV is known to induce necroptosis and other forms of cell death driven by RIPK3 (Nogusa et al. 2016). ZBP1 emerges as the link between viral infection and RIPK3-mediated cell death (Kuriakose et al. 2016; Thapa et al. 2016; Maelfait et al. 2017). Particularly, ZBP1 has been implicated as an innate immune sensor of IAV PAMPs. In one study, ZBP1 has been shown to sense IAV nucleoprotein NP and polymerase subunit PB1, leading to NLRP3 inflammasome activation and induction of cell death (Kuriakose et al. 2016). However, in another study, ZBP1 has been shown to bind IAV genomic RNA and then recruit RIPK3 to initiate the downstream death signaling (Thapa et al. 2016). The results on the lethality of ZBP1-deficient mice upon IAV infection from the two studies are also contradictory (Kuriakose et al. 2016; Thapa et al. 2016). In addition to IAV, ZBP1 has also been implicated in necroptosis induced upon infection of mouse cytomegalovirus (Maelfait et al. 2017). The binding of RNA by Z-binding domains of

ZBP1 is required for the induction of necroptosis. However, one nuance of ZBP1–RIPK3 signaling has recently been demonstrated in Zika virus-infected neurons. The activated ZBP1–RIPK3 signaling in these cells does not induce necroptosis, but induces the IRG1 enzyme to synthesize itaconate (Daniels et al. 2019), which in turn inhibits viral replication, suppresses inflammasome activation and prevents cell death (Hooftman et al. 2020). Recent findings have revealed exciting new details of how ZBP1 functions in RNA sensing to impinge on IFN response, inflammasome activation and programmed cell death. However, further studies are warranted to resolve some discrepancies in the literature and to clarify several key issues concerning the ability of ZBP1 to activate both NLRP3 and AIM2 inflammasomes, the identity of IAV PAMP(s) sensed by ZBP1, the phenotypes of IAV-infected *Zbp1*$^{-/-}$ mice, and the mechanism by which inflammasome activation and cell death are induced or inhibited.

HMGBs

The family of high-mobility group box proteins (HMGBs) is comprised of four members, namely HMGB1, HMGB2, HMGB3, and HMGB4 (Taniguchi et al. 2018). HMGB1, HMGB2, and HMGB3 proteins are highly conserved with over 80% identity in their amino acid sequences. These three proteins contain two DNA-binding HMG domains and an acidic tail, while HMGB4 contains only two HMG domains but lacks the acidic tail. Except that HMGB1 has a ubiquitous expression, other HMGB proteins have a restricted expression in specific target tissues. It is thus postulated that HMGB1 may have broad roles in various tissues, while other HMGBs function redundantly in specific tissues. HMGBs are highly expressed in the nucleus but also exist in the cytosol as well as the extracellular fluids. They perform differential roles intracellularly and extracellularly. Inside the nucleus, HMGBs bind to DNA in a structure-dependent and sequence-independent manner for chromatin remodelling. HMGBs in the extracellular compartment however function as alarmins, which are endogenous molecules released to activate the immune system upon tissue damage. Although HMGBs are highly conserved, they still exhibit differential binding specificity toward different nucleic acids. HMGB1 and HMGB3 bind both dsRNA and dsDNA, while HMGB2 binds only dsDNA (Yanai et al. 2009). HMGBs have also been shown to bind all TLR agonistic nucleic acids. Loss of single or three HMGBs has been found to significantly dampen nucleic acid-stimulated as well as virus-induced innate immune responses via IRF3 and NF-κB pathways. In all, HMGBs may function as universal sentinels for nucleic acids and are required to activate nucleic-acid-induced innate immune responses in full (Yanai et al. 2009). Particularly, HMGB1 interacts with TLR9 and RLRs, suggesting that nucleic acid-bound HMGBs may function as cosensor for various PRRs to facilitate their recognition of nucleic acid agonists, leading to the potentiation of innate IFN response (Yanai et al. 2009).

IFITs

Interferon-induced proteins with tetratricopeptide repeats (IFITs) are a family of proteins induced by interferon, viral infection or PAMP recognition (for reviews, see Diamond and Farzan 2013; Fensterl and Sen 2015). As their names suggest, IFITs harbor multiple tetratricopeptide repeats, which are critical for protein–protein interactions. To date, four members including IFIT1, IFIT2, IFIT3, and IFIT5 have been characterized in humans. They have a cytoplasmic localization with no known enzymatic activity. IFITs have no basal expression under unstimulated conditions in most cell types but are rapidly and strongly induced upon viral infection. Subsets of IFIT genes are also induced selectively in different cell types, suggesting a nonredundant antiviral function for different IFITs. IFITs are also induced in an IFN-independent manner by transcription factors such as IRF1, IRF3, IRF5, and IRF7. IFITs are known to exhibit antiviral activity against various families of viruses through diverse mechanisms of action. Firstly, IFIT1 and IFIT2 inhibit translation initiation by binding to the eukaryotic initiation factor 3 (Guo et al. 2000). Secondly, IFIT1 recognizes non-2′-*O*-methylated viral RNA and inhibits viral translation possibly by competing with the preinitiation complex for viral RNA, or by serving as a scaffold for other proteins that regulate translation (Daffis et al. 2010; Habjan et al. 2013). Thirdly, IFIT1 serves as a viral RNA sensor to detect uncapped 5′-triphosphate RNA and sequester viral RNA (Pichlmair et al. 2011). Finally, IFIT1 binds to viral proteins such as helicase E1 of human papillomavirus to inhibit viral replication (Terenzi et al. 2008). IFIT3 binds to IFIT1 to stabilize the latter and enhance its binding to non-self RNA. In this regard, IFIT3 serves as a cosensor of IFIT1 to achieve optimal antiviral activity (Fleith et al. 2018).

PARP9

Poly(ADP-ribose) polymerase 9 (PARP9) belongs to the PARP family, which is known to be critical in DNA repair, cell death and survival, and chromatin remodelling. As an inactive mono-ADP-ribosyltransferase in the PARP family, PARP9 is not well characterized and its functions are largely unknown. A functional screen for activators of IFN response in the PARP family reveals that PARP9 functions as a MAVS-independent RNA sensor. PARP9 binds to viral dsRNA and recruits PI3K and AKT3 to phosphorylate and activate IRF3 and IRF7 (Xing et al. 2021a). It will be of great interest to see under what other conditions this PI3K–AKT3-dependent noncanonical pathway for IFN production might also be activated.

SAFA

Scaffold attachment factor A (SAFA), also known as heterogeneous ribonucleoprotein U, is a nuclear matrix protein that has initially been implicated as a nuclear viral dsRNA sensor for both DNA and RNA viruses (Cao et al. 2019). It has been demonstrated that SAFA potentiates antiviral immune response by activating both enhancers and super-enhancers of important antiviral effectors through chromatin remodelling. Very recently, SAFA has been shown to be a novel cytoplasmic RNA sensor for severe fever with thrombocytopenia syndrome virus (SFTSV) infection to trigger innate antiviral response (Liu et al. 2021a). Upon SFTSV infection, SAFA remains in the cytoplasm through an interaction with SFTSV nucleocapsid protein. Cytoplasmic SAFA then recognizes cytoplasmic SFTSV genomic RNA and promotes subsequent activation of the STING-TBK1 signaling pathway. On the other hand, it has previously been shown that SFTSV infection induces BAK/BAX-dependent mitochondrial DNA (mtDNA) release (Li et al. 2020b). Thus, it remains elusive whether activation of the STING pathway might be caused by mtDNA release and/or SAFA-mediated RNA recognition. Further investigation is required to clarify this.

RNA-BINDING PROTEIN PARTNERS OF RNA SENSORS

In this part, we will focus on RNA-binding proteins that are not RNA sensors per se but interact with RNA sensors to modulate their sensing activity (Fig. 2). Because RNA sensors also bind to RNA, it is technically challenging to rule out the possibility that the interactions between RNA sensors and their RNA-binding protein partners are mediated by RNA. The functional outcome of these interactions is more important than RNA dependence. As described above, the interaction between RIG-I and RIPLET occurs only in the presence of RNA (Cadena et al. 2019). Likewise, TRIM65 interacts with MDA5 only when RNA induces oligomerization and filament formation of MDA5 (Kato et al. 2021). When we discuss the interactions between RNA sensors and their RNA-binding protein partners, several critical issues should be taken into full consideration. Firstly, it is of interest to see mechanistically how the RNA-binding protein partners modulate the sensing activity of the RNA sensors. Presumably, the partners might select or recruit certain types of RNA to the sensors. In addition, the partners could induce conformational change or alter the catalytic activity or activation threshold of the sensors. Secondly, many RNA-binding protein partners of RNA sensors are multifunctional and are critically involved in other processes of RNA recognition and processing (Heyam et al. 2015). How these different processes are coordinated and differentially regulated requires more analysis. Thirdly, different RNA-binding protein partners of

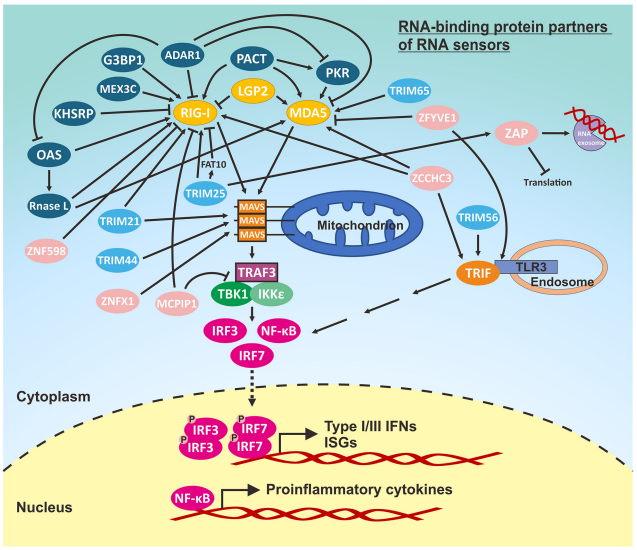

FIGURE 2. RNA-binding protein partners of cytoplasmic RNA sensors. RLRs are in yellow. TRIM proteins are in blue. PACT, TRBP and other RNA binding proteins are in dark blue. Zinc-finger proteins are in pink. TBK1/IKKε are in green. IRF3 and NF-κB are in red. Stimulatory and inhibitory actions are highlighted by arrows and stop signs, respectively.

RNA sensors might interact with each other to modulate the sensing activity jointly. They could be the components of the same multisubunit protein complex for RNA sensing. Their actions might either be synergistic or antagonistic. Thus, these partners should not be studied in isolation.

PACT

PACT, also known as PRKRA, a dsRNA-binding protein harboring three tandem repeats of dsRNA binding motifs, has initially been identified as a direct protein activator of PKR through their heterodimerization in response to diverse stress signals, leading to inhibition of protein translation (Patel and Sen 1998; Patel et al. 2000). Although PACT activation of PKR and its impact on proinflammatory response have been well documented (Chukwurah et al. 2021), more recent studies have also reported a negative regulatory role for PACT on PKR activation (Clerzius et al. 2013; Dickerman et al. 2015; Meyer et al. 2018). Phenotypic defects in PACT-deficient mice can be rescued by additional knockout of PKR or expression of a dominant-negative mutant of PKR, suggesting a primary function of PACT as a suppressor of aberrant PKR activation (Dickerman et al. 2015). Furthermore, the PKR-suppressive role of PACT has also been observed during HIV infection (Clerzius et al. 2013) and under the deficiency of the splicing factor TIA1/TIAL1 (Meyer et al. 2018). Additionally, PACT has also been implicated to mediate RNA interference and miRNA processing (Lee et al. 2006; Kok et al. 2007).

Soon after the discovery of PACT, its importance and involvement in innate antiviral response were documented in Newcastle disease virus infection (Iwamura et al. 2001). We have also shown that the interplay between PACT and IAV polymerase is critical to the outcome of viral infection and antiviral response (Chan et al. 2018). One prominent role for PACT in innate antiviral response is to serve as a cellular activator of both RIG-I and MDA5 for induction of IFN signaling and potentiation of antiviral response (Kok et al. 2011; Ho et al. 2016; Lui et al. 2017). Specifically, we have previously shown PACT to be a cellular activator of RIG-I by physically binding to the carboxy-terminal repression domain of RIG-I and potently stimulating RIG-I-induced type I interferon production (Kok et al. 2011). Additionally, PACT also functions as a coactivator of MDA5 by promoting MDA5 oligomerization subsequent to dsRNA-induced activation (Lui et al. 2017).

Exactly how PACT activates RIG-I and MDA5 remains to be elucidated. As mentioned above, the role of PACT resembles that of LGP2, which lacks a CARD domain and is therefore considered incompetent for signal transduction. In this regard, PACT also binds LGP2, and this binding controls the inhibition of RIG-I and the activation of MDA5 by LGP2 (Sanchez David et al. 2019). One probable role of PACT is to concentrate RLR agonists for subsequent transfer to RLRs. This requires selective and high-affinity binding with RNA. Indeed, PACT interacts with measles virus defective-interfering RNA of the copy-back type, an agonist of RIG-I (Ho et al. 2016). This and other RNA agonists of PACT and RIG-I hold the promise to be further developed as antivirals and vaccine adjuvants. Notably, biochemical and structural analysis of the role of PACT and its homolog TRBP in Dicer function in miRNA biogenesis has revealed mechanistic details for guide strand selection. In particular, PACT enhances the guide strand selection of some miRNAs (Noland and Doudna 2013). Reconstitution experiments indicate that PACT inhibits pre-siRNA processing by Dicer. In addition, Dicer-TRBP and Dicer-PACT complexes produce different miRNA isoforms (Lee et al. 2013b). The importance of PACT and TRBP to Dicer function has been verified by the use of a catalytically active Dicer that cannot bind PACT or TRBP (Wilson et al. 2015). Together with TRBP, PACT plays an important role in selecting specific RNA substrates and ensuring fidelity and specificity of Dicer cleavage. Although these findings obtained with Dicer might not be translated directly to RIG-I and MDA5, it could not be ruled out that the general principle might also apply in RLR-mediated RNA sensing. Further investigations similar to those performed on PACT and Dicer are required to clarify whether PACT might be a key determinant of substrate concentration and selection for RIG-I and MDA5. Nevertheless, the interaction between RIG-I and PACT represents a theme in which RNA-binding partners facilitate the function of RNA sensors.

TRBP is a homolog of PACT. Whereas PACT is an activator of PKR, TRBP exhibits an inhibitory effect on PKR (Park et al. 1994). However, both TRBP and PACT facilitate Dicer-mediated small RNA processing (Kok et al. 2007; Wilson et al. 2015). Whereas PACT and TRBP have apparently opposing functions on PKR, they cooperate to facilitate Dicer. Detailed analysis of the effects of PACT and TRBP on PKR and Dicer does indicate that the roles of PACT and TRBP are indeed distinct and complementary. Consistent with this, the inhibitory effect of TRBP on RIG-I activation has recently been documented (Vaughn et al. 2021). Interestingly, this inhibition is independent of PACT or PKR but requires TRBP's dsRNA binding ability. It will be of interest to determine whether TRBP might sequester RIG-I agonists and how TRBP could affect MDA5 activation.

PACT and TRBP can form homodimers and heterodimers (Kok et al. 2011; Heyam et al. 2017). Interestingly, structural asymmetry has been observed in PACT and TRBP homodimers, and it is ascribed to residue composition in the homodimer interface (Heyam et al. 2017). The same carboxy-terminal dsRNA-binding domain in PACT or TRBP also mediates the interaction with Dicer. In the case of Dicer, a 1:1 complex of Dicer-PACT or Dicer-TRBP can be formed with Dicer interacting with either PACT or TRBP (Heyam et al. 2017). Although the coexistence of both PACT and TRBP in a multicomponent macromolecular complex cannot be excluded, their direct interaction with Dicer is mutually exclusive (Heyam et al. 2017). Whether PACT and TRBP interact with RIG-I and MDA5 in a similar manner remains to be determined. Because the inhibitory effect of TRBP on RIG-I is PACT-independent (Vaughn et al. 2021), their interaction with RIG-I might indeed be mutually exclusive.

PKR

PKR is a dsRNA-activated serine–threonine kinase that plays a major role in a number of different cellular processes such as mRNA translation, transcriptional control, regulation of apoptosis, and proliferation (for reviews, see Gal-Ben-Ari et al. 2018; Chukwurah et al. 2021). Particularly, PKR is well-known for its role as a key innate immune sensor. PKR harbors two tandem amino-terminal dsRNA-binding motifs (dsRBMs) and a carboxy-terminal kinase domain (Hull and Bevilacqua 2016). PKR, as its name suggested, was originally described as a dsRNA activated kinase, but more recent studies have shown that ssRNA or RNA with 5′-triphosphate and limited secondary structure could also activate PKR (for review, see Hull and Bevilacqua 2016). In the presence of RNA agonists, PKR dimerizes via binding of RNA by its dsRBMs and then autophosphorylates to become activated. Phosphorylated active PKR will subsequently phosphorylate and suppress eIF2α, thereby inhibiting translation initiation and causing apoptosis. In addition to its role as a PRR to trigger translation repression

upon RNA recognition, PKR has also been shown to modulate innate IFN response at several different steps. Firstly, PKR contributes to MDA5-induced IFN response against certain RNA viruses via regulation of IFN transcript stability (Schulz et al. 2010). Secondly, PKR transduces the activation signal of MDA5 in the activation of IFN production through direct interaction with MDA5 (Pham et al. 2016). The catalytic activity of PKR is required for this function. Thirdly, in response to osmotic stress, PACT and PKR are activated to inhibit the interaction between NF-κB c-Rel and NFAT5, but promote the formation of an NF-κB p65–NFAT5 complex. As a result, NFAT5-dependent osmoprotective gene expression is suppressed and p65-dependent proinflammatory gene expression is enhanced (Farabaugh et al. 2020). Finally, PKR is the target of other innate immune regulators such as ADAR1, RNase L and Dicer (Nie et al. 2007; Manivannan et al. 2020; Montavon et al. 2021). Taken together, PKR is a dsRNA-binding protein kinase that interacts with MDA5 and exerts its regulatory effects at multiple steps of the RNA sensing pathway.

ADAR1

The ADAR proteins belong to a gene family comprising three members, namely ADAR1, ADAR2, and ADAR3 (Lamers et al. 2019; Quin et al. 2021). ADAR1 is critically involved in balancing immune activation and self-tolerance. ADAR mutations as one of the causes of Aicardi–Goutières syndrome, a severe human autoimmune disease, are suggestive of the important negative regulatory roles of ADAR proteins in innate immune response (Rice et al. 2012). While ADAR1 and ADAR2 possess adenosine deaminase activity to catalyze adenosine-to-inosine (A-to-I) editing at millions of sites in humans (Lamers et al. 2019; Heraud-Farlow and Walkley 2020), ADAR3 is catalytically inactive (Chen et al. 2000). Notably, the primary role of RNA editing by IFN-inducible ADAR1 is to dampen innate immune activation by unedited endogenous RNA. Stable dsRNA structures are believed to form by unedited inverted paired sequences, such as Alu elements, which could trigger the activation of various dsRNA sensing pathways. ADAR1 has been implicated in modulating canonical RLR-MAVS, PKR as well as oligoadenylate synthetase (OAS)-RNase L pathways (for review, see Lamers et al. 2019).

Loss of ADAR1 in mice is embryonic lethal which has been associated with excessive IFN expression (Hartner et al. 2009). Later, it has been found that further deletion of MDA5 or MAVS could rescue lethality in ADAR1-deficient embryonic mice (Mannion et al. 2014; Liddicoat et al. 2015). Although deletion of RIG-I did not rescue embryonic lethality in ADAR1-deficient mice (Pestal et al. 2015), in vitro studies did show a negative role for ADAR1 on RIG-I activation. These findings suggested that RLRs are stimulated by endogenous dsRNA in the absence of ADAR1 and that ADAR1 is capable of blocking RLR signaling for IFN production, particularly through the MDA5–MAVS axis. A-to-I editing by ADAR1 is believed to be a crucial mechanism for dampening MDA5–MAVS signaling induced by endogenous RNA since the enzymatic activity of ADAR1 was shown to be essential for survival (Liddicoat et al. 2015). As such, MDA5 induces Z-RNA formation in Alu repeats, thereby providing a site for ADAR1 to anchor. Consequent editing by ADAR1 destabilizes dsRNA, leading to the termination of MDA5 action (Herbert 2021). *Adar* knockout alleles in mice can be rescued by concomitant deletion of *Mavs* or *Mda5* (Bajad et al. 2020). PKR, LGP2, and IFN response are also required for the lethality of *Adar* mutant mice (Maurano et al. 2021). Although contradictory results have been reported showing RNA binding rather than editing activity of ADAR1 being responsible for suppressing RIG-I activation (Yang et al. 2014), this might be explained by differences in cell type-dependent activity of ADAR1. All in all, current findings indicate that A-to-I editing of endogenous RNA by ADAR1 is a critical element to prevent over-stimulation of RLRs and to maintain cellular homeostasis in RLR signaling. This has important implications in innate antiviral response.

Besides, ADAR1 also functions to prevent translation arrest and stress granule formation mediated by PKR (Lamers et al. 2019). PKR is activated in response to cytoplasmic dsRNA. Upon activation, autophosphorylation of PKR takes place leading to subsequent phosphorylation of eIF2α to shut down mRNA translation as a defense mechanism against viral infection (Dar et al. 2005; Dey et al. 2005). By blocking the activation of PKR, an important antiviral PRR, through both editing-dependent and -independent mechanisms, ADAR1 served as a proviral host factor to promote replication of viruses including measles virus, vesicular stomatitis virus (VSV), and human immunodeficiency virus (HIV). In the case of an editing-independent mechanism, ADAR1 might bind directly with PKR to interfere with its dimerization and autophosphorylation, leading to the inhibition of eIF2α phosphorylation and stress granule formation. Restriction on viral mRNAs translation is then removed.

Lastly, ADAR1 also blocks the OAS-RNase L pathway. Upon dsRNA recognition, OAS proteins including OAS1, OAS2 and OAS3 produce 2′,5′-oligoadenylates (2–5A_n) (Lamers et al. 2019). This second messenger then binds to RNase L to trigger its dimerization to give the enzymatically active form. RNase L can cleave both viral and host RNA, leading to translation arrest, autophagy and apoptosis. RNase L deletion in cultured cells rescues the lethal phenotype of ADAR1-deficient cells. Additionally, IFN-induced 2–5A_n accumulation is higher in RNase L/ADAR1 double knockout cells than in wild-type and RNase L-knockout cells. These findings suggest that ADAR1 prevents the activation of OAS.

In summary, ADAR1 is an RNA editing enzyme that binds to and modifies RLR ligands. It also exerts an inhibitory effect on PKR and OAS-RNase L pathways.

G3BP1

Ras-GTPase–activating SH3 domain-binding protein 1 (G3BP1) is a crucial component of the mammalian cell stress granules (SG) which help minimize stress-related damage and promote cell survival (Mahboubi and Stochaj 2017). Viral infection has also been associated with SG assembly which attenuates viral replication (Onomoto et al. 2012; Cobos Jimenez et al. 2015). G3BP1 is a multidomain protein highly conserved among species. It carries a nuclear translocation factor-2-like domain, an acidic region, an RNA recognition motif (RRM), and a carboxy-terminal glycine-rich RGG motif (Kim et al. 2019). G3BP1 influences viral RNA-induced IFN response as predicted by an integrative computational biology study (van der Lee et al. 2015). More recently, a report by Kim et al. (2019) has demonstrated G3BP1 as a critical positive regulator of the RIG-I-mediated IFN pathway. G3BP1 colocalizes with RIG-I and VSV. G3BP1 binds to both RIG-I and viral dsRNA via its RGG domain. Their computational modelling further reveals a juxtaposed interaction between G3BP1 RGG and RIG-I RNA-binding domains. Collectively, the studies suggest that G3BP1 might act as a cosensor of RIG-I to facilitate the sensing of viral RNA.

KHSRP

K-homology splicing regulatory protein (KHSRP) is an adenine and uridine-rich element (ARE)-binding protein, serving as an important negative regulator of cytokine expression post-transcriptionally via various mechanisms including translational silencing, RNA instability, microRNA maturation, and transcriptional repression (for review, see King and Chen 2014). Indeed, most mRNAs encoding type I IFNs contain AREs in their 3′-UTRs, subjecting them to mRNA decay or translational control through an ARE-dependent mechanism (King and Chen 2014). A new function for KHSRP in innate antiviral response has been identified in two global RNAi screens (Soonthornvacharin et al. 2017). KHSRP serves as a negative regulator of the RIG-I pathway. It interacts with the carboxy-terminal repressor domain (CTD) of RIG-I to maintain RIG-I in the inactive state, thereby attenuating the sensing of viral RNA. Loss of KHSRP increases RIG-I-mediated antiviral signaling and reduces viral replication both in vitro and in vivo. Furthermore, KHSRP inhibits the binding of viral RNA to RIG-I plausibly through competition for binding to the RIG-I CTD, leading to suppression of RIG-I-mediated IFN response.

MEX3C

Mex-3 RNA binding family member C (MEX3C) belongs to a family of four RNA-binding proteins, named MEX3A, MEX3B, MEX3C, and MEX3D, which have been implicated in RNA metabolism (Buchet-Poyau et al. 2007; Pereira et al. 2013). MEX3C is an E3 ubiquitin ligase with a role in regulating RIG-I-mediated IFN response (Kuniyoshi et al. 2014). MEX3C colocalizes with RIG-I in the stress granules in virus-infected cells. MEX3C could mediate K63-linked ubiquitination of RIG-I and induce IFN production. Loss of MEX3C in mice dampens RIG-I-dependent IFN production upon viral infection. Thus, MEX3C plays a critical role in the induction of RIG-I-mediated innate antiviral response.

OAS-RNase L

The OAS family of IFN-inducible enzymes are activated in response to dsRNA to synthesize 2′–5′ phosphodiester-linked oligoadenylates (2–5A_n) from ATP (Hovanessian and Justesen 2007; Kristiansen et al. 2011; Hur 2019). The 2–5A_n serves as a second messenger and binds to the inactive monomeric RNase L to induce its homodimerization or oligomerization for activation (Han et al. 2014; Hur 2019). Activation of RNase L then leads to the cleavage of cellular and viral RNAs, resulting in cell death, inflammasome activation and inhibition of protein synthesis, cell growth, and viral replication (Hovanessian and Justesen 2007; Kristiansen et al. 2011; Chakrabarti et al. 2015; Hur 2019). OAS-RNase L pathway represents an important innate antiviral response for counteracting viral infection. The OAS family comprises four members including OAS1, OAS2, OAS3, and OASL, with OASL being the only enzymatically inactive member (Hur 2019). Structurally, OAS1, OAS2, and OAS3 contain one, two, and three tandem repeats, respectively, of the nucleotidyl transferase (NTase) domain, which serves as template-independent nucleotide polymerase. Upon dsRNA binding, OAS NTases will undergo a conformational change to activate its enzymatic activity for 2–5A_n production, and subsequently trigger a downstream RNase L pathway. On the other hand, OASL, though enzymatically inactive, also exhibits broad antiviral activity (Schoggins et al. 2011; Hur 2019). OASL harbors two tandem repeats of ubiquitin-like domains and a pseudoNTase domain for RNA binding. These domains are essential for the antiviral activity of OASL. A study has demonstrated that OASL interacts and colocalizes with RIG-I, and specifically mediates RIG-I activation by mimicking polyubiquitin through its carboxy-terminal ubiquitin-like domain (Zhu et al. 2014).

As mentioned above, RNase L not only functions as a terminal executioner in IFN signaling to mediate RNA cleavage and cell death (Boehmer et al. 2021), but also serves as a node for interaction with upstream regulators such as PKR to modulate IFN production either positively

or negatively, depending on the cell type (Banerjee et al. 2014; Manivannan et al. 2020).

TRIM proteins

Tripartite motif (TRIM) proteins constitute the largest family of RING domain-containing E3 ubiquitin ligase involved in diverse cellular processes such as differentiation, autophagy, apoptosis, DNA repair and tumor suppression (Hatakeyama 2017). There are more than 80 TRIM family members in humans which typically share a conserved RING-B-box-coiled-coil domain organization (van Gent et al. 2018). Many studies have implicated TRIM proteins in the innate immune response against viral infection via various mechanisms (for review, see van Gent et al. 2018). Below, we will focus on the roles of RNA-binding TRIM proteins in RNA sensing. RNA-binding roles of TRIM proteins have been postulated to regulate their fate or ubiquitination efficiency (Williams et al. 2019).

TRIM21

TRIM21 is a ubiquitous E3 ubiquitin ligase serving as a cytosolic antibody receptor (Mallery et al. 2010). TRIM21 detects antibody-bound virions that enter the cytosol after cellular receptor attachment, endocytosis, and endosomal escape, thereby providing early protection to cells from potential productive infectious events and preventing fatal viral infection (Vaysburd et al. 2013). Antibodies are normally excluded from the cytosol, and their presence in the cytosol is sensed by TRIM21 to activate innate immune pathways involving NF-κB, AP-1 and IRF3/5/7 (McEwan et al. 2013). RNA binding by TRIM21 has been postulated from the finding that replacing the proposed RNA-binding peptide in the TRIM25 PRY/SPRY domain with a homologous sequence from TRIM21 does not affect the RNA binding in the chimeric protein (Choudhury et al. 2017; Williams et al. 2019). Whether RNA-binding property is a universal conserved feature of PRY/SPRY domains is still under debate. In one study, TRIM21 has been implicated in the potentiation of nucleic acid sensing by cytosolic sensors cGAS or RIG-I (Watkinson et al. 2015). It has been suggested that TRIM21 mediates the rapid degradation of incoming viral capsids in the cytosol, thereby promoting early detection of viral genomes by cGAS and RIG-I. TRIM21 has also been shown to promote innate antiviral response through K27-linked polyubiquitination of MAVS (Xue et al. 2018). Without TRIM21, no significant induction of immune response in the first 8 h occurs upon infection by both DNA and RNA viruses such as adenovirus and rhinovirus, whereas transfection of viral genomes triggers a robust immune response in the same timeframe. Thus, TRIM21 facilitates an early immune response upon infection which ensures the best protection of the host against infection.

TRIM25

TRIM25 is a multidomain, RING-finger E3 ubiquitin ligase with various crucial roles in RNA-dependent pathways. It has been reported to bind RNA, which modulates its ubiquitination activity, subcellular localization and antiviral activity (Sanchez et al. 2018). TRIM25 is especially well-known for its vital role in RIG-I activation. TRIM25 has been shown to bind RIG-I and subsequently mediate K63-linked ubiquitination to the amino-terminal CARDs of RIG-I to enhance RIG-I signaling activity (Gack et al. 2007). However, the relevance of TRIM25 to RIG-I activation has been challenged (Cadena et al. 2019; Hayman et al. 2019). Studies by several different groups have suggested RIPLET, instead of TRIM25, as the requisite E3 ubiquitin ligase for RIG-I activation (Oshiumi et al. 2009; Kato et al. 2021). Furthermore, TRIM25 has been reported to regulate RIG-I negatively by stabilizing the ubiquitin-like protein FAT10, which binds and sequesters RIG-I from signaling (Nguyen et al. 2016). A negative regulatory role of TRIM25 has also been shown in K48-linked polyubiquitination and proteasomal degradation of MAVS (Castanier et al 2012). These findings might suggest a dual role for TRIM25 in regulating RIG-I-mediated IFN production and antiviral response (Gack et al. 2007; Martin-Vicente et al. 2017). Whether and how TRIM25 indeed mediates its effect on innate immune signaling through RIG-I or alternative mechanisms requires further elucidation. In addition to its roles in RIG-I regulation, TRIM25 has been shown as an E3 ubiquitin ligase for ISG15 (Zou and Zhang 2006) as well as a cofactor of another cytosolic RNA sensor ZAP to inhibit viral replication (Li et al. 2017; Zheng et al. 2017). Interestingly, RIG-I activates TRIM25-dependent ISG15 conjugation by stabilizing TRIM25 mRNA (Wu et al. 2020). On the other hand, whereas ISG15 conjugation of RIG-I serves a negative regulatory role (Kim et al. 2008), ISG15 conjugation activates MDA5 (Liu et al. 2021b). These findings reflect the diverse roles of TRIM25 in innate immunity. Further investigations are required to clarify whether and how TRIM25 might mediate ISG15 conjugation but not K63-linked ubiquitination of RIG-I. In addition, it will be of interest to see whether RIG-I could induce a feedback regulatory loop through ISG15 conjugation to inhibit RIG-I but activate MDA5 concurrently.

TRIM44

TRIM44 is localized in the cytoplasmic compartment, contributing to diverse pathological conditions like tumors, growth disorders, and neurodegeneration (Xiao et al. 2020). TRIM44 is an atypical TRIM family protein that lacks the RING-finger domain but harbors a zinc-finger domain that is often found in ubiquitin-specific proteases (USPs). The zinc-finger domain of TRIM44 functions as USP and thus TRIM44 is known as "USP-like-TRIM" (Urano et al.

2009). TRIM44 has also been reported to play important regulatory roles in the innate immune response. TRIM44 is induced in response to Sendai virus infection, which stabilizes MAVS by suppressing its K48-linked ubiquitination and subsequent degradation (Yang et al. 2013). Thus, TRIM44 serves as a positive regulator of the RIG-I pathway to enhance IFN production and promote antiviral response against viral infection.

TRIM56

TRIM56 is an IFN- and virus-inducible E3 ubiquitin ligase previously shown to restrict viral replication (Wang et al. 2011; Kane et al. 2016; Liu et al. 2016). It has been shown that the E3 ubiquitin ligase activity, the carboxy-terminal structural integrity and the RNA-binding property of TRIM56 are essential for its antiviral activity against bovine viral diarrhoea virus and Zika virus, both of which are positive-sense single-stranded RNA viruses (Wang et al. 2011; Yang et al. 2019). On the contrary, another study has reported that a 63-residue carboxy-terminal tail of TRIM56 is sufficient to curtail the replication of influenza A and B viruses, negative-sense single-stranded RNA viruses (Liu et al. 2016). On the other hand, it has also been reported that TRIM56 associates with innate immune signaling adaptor STING and promotes its ubiquitination, thereby enhancing cytosolic dsDNA-induced IFN response (Tsuchida et al. 2010). TRIM56-mediated ubiquitination of STING is further accentuated by UBXN3B (Yang et al. 2018). TRIM56 also mediates monoubiquitination and consequent activation of cGAS (Seo et al. 2018). These findings indicate the involvement of TRIM56 in both RNA and DNA sensing pathways. Mechanistically, it has been shown that TRIM56 acts as a positive regulator of TLR3 signaling (Shen et al. 2012). Extracellular dsRNA-induced expression of IFNs and ISGs is significantly enhanced by TRIM56 overexpression, whereas activation of IRF3 and production of IFNs/ISGs are substantially blunted by TRIM56 depletion. Particularly, the importance of TRIM56 on the establishment of an antiviral state by TLR3 and TLR3-mediated cytokine production has been noted during hepatitis C virus infection. Independent of the E3 ubiquitin ligase activity of TRIM56, it mediates its effect on the TLR3 pathway through the interaction with TRIF, an adaptor protein for TLR3 signaling against viral infection.

TRIM65

TRIM65 has been implicated in microRNA regulation and innate immunity (Li et al. 2014; Lang et al. 2017; Williams et al. 2019). Particularly, TRIM65 is involved in MDA5-mediated RNA sensing and IFN response (Lang et al. 2017). TRIM65 interacts specifically with RNA-bound oligomeric MDA5 to promote K63-linked ubiquitination, and subsequent activation of MDA5 (Kato et al. 2021). Depletion of TRIM65 does not affect RIG-I, TLR3, or cGAS signaling, whereas TRIM65 deficiency abolishes MDA5-mediated immune response including EMCV-induced IRF3 activation and IFN production. Eminently, *Trim65*-null mice are more susceptible to EMCV infection than wild-type animals and fail to produce type I IFN in vivo. Together, these findings indicated that TRIM65 is an essential component for MDA5 signaling and that TRIM65-mediated ubiquitination is crucial for MDA5 oligomerization and filament assembly.

Zinc-finger proteins

Zinc fingers are compact protein domains harboring zinc ions for domain stabilization (Krishna et al. 2003). Zinc fingers are structurally diverse and exist in various zinc-finger proteins for different biological processes, such as replication and repair, transcription and translation, metabolism and signaling, cell proliferation and apoptosis (Krishna et al. 2003). Zinc fingers typically function as interaction modules for binding nucleic acids, proteins and small molecules (Krishna et al. 2003). Zinc-finger proteins are frequently regarded as DNA-binding proteins, but various classes of zinc-finger proteins have also been found to bind RNA and are involved in RNA metabolism (Fu and Black shear 2017). Zinc-finger proteins are classified into eight fold groups according to their structural homology (Krishna et al. 2003). Below, we will discuss a few RNA-binding zinc-finger proteins with a role in RNA sensing and innate immunity.

MCPIP1

Monocyte chemoattractant protein 1-induced protein 1 (MCPIP1), also known as ZC3H12A for zinc-finger CCCH-type containing 12A, is a CCCH-type zinc-finger protein belonging to the MCPIP family, which has originally been identified as a gene induced by MCP-1 (Zhou et al. 2006). With RNase activity, MCPIP1 has subsequently been shown to degrade mRNA of various proinflammatory cytokines and is thus implicated as a negative regulator of the cellular inflammatory responses (Matsushita et al. 2009; Lin et al. 2013; Sun et al. 2018). MCPIP1 contains a CCCH-type zinc-finger domain with RNA-binding potential at the middle region and a NYN domain with RNase activity at the amino terminus (Lin et al. 2013). An earlier study has implicated MCPIP1 as a broad-spectrum antiviral factor against diverse DNA and RNA viruses (Lin et al. 2013). The activities of RNase, RNA binding and oligomerization of MCPIP1 are essential for its antiviral function. It has been proposed that MCPIP1 binds to and degrades viral RNA directly, resulting in the inhibition of viral replication. Another study has also implicated MCPIP1 as a host antiviral factor, which binds and degrades viral RNA during HBV infection (Li et al. 2020a). However, the impact of MCPIP1 on type I IFN response has not been investigated. Later, three

independent studies about the effect of MCPIP1 on IFN response appeared but with contradictory findings (Chen et al. 2018; Qian et al. 2018; Sun et al. 2018). One work suggests MCPIP1 as a positive regulator of IFN response, independent of its RNase or deubiquitinase activity (Qian et al. 2018). MCPIP1 potently promotes type I IFN signaling by enhancing ISRE promoter activity and ISG expression. On the other hand, the other two studies suggest a negative regulatory role for MCPIP1 in IFN production, thereby serving a proviral function (Chen et al. 2018; Sun et al. 2018). MCPIP1 is thought to interact with several important effectors of IFN signaling including MAVS, TRAF3, TBK1, and IKKε, while at the same time MCPIP1 perturbs the formation of TRAF3–TBK1–IKKε complex, thereby negatively regulating the activation of IRF3. Alternatively, MCPIP1 also attenuates IFN response by degrading RIG-I mRNA upon IAV infection (Sun et al. 2018). Whether MCPIP1 indeed serves as a positive or negative regulator of IFN response with antiviral or proviral roles warrants further investigations.

ZAP

Zinc-finger antiviral protein (ZAP), also known as ZC3HAV1 or ZC3H2, is an interferon-inducible host antiviral factor that has been implicated in inhibiting replication of different viruses including HIV-1, SARS-CoV-2, Sindbis virus, Ebola virus, hepatitis B virus, and murine leukemia virus (Gao et al. 2002; Bick et al. 2003; MacDonald et al. 2007; Muller et al. 2007; Zhu et al. 2011; Mao et al. 2013; Nchioua et al. 2020). Additionally, ZAP is also known to regulate cellular gene expression post-transcriptionally through binding to specific host mRNA or a host factor for RNA processing (Zheng et al. 2017). TRIM25, an E3 ubiquitin ligase mentioned above, has been implicated in modulating the antiviral activity of ZAP (Li et al. 2017; Zheng et al. 2017). Loss of TRIM25 abolishes antiviral activity of ZAP, which relates to the importance of TRIM25-mediated ubiquitination for optimal ZAP binding to target RNA (Zheng et al. 2017). The RNA-binding property of ZAP is crucial to its functions, and it comes from the four CCCH-type zinc-finger domains at the amino terminus of ZAP (Zheng et al. 2017). The binding of RNA by ZAP is sequence-independent but structure-dependent (Chen et al. 2012; Zheng et al. 2017). The antiviral activity of ZAP depends on its binding to viral mRNAs (Lee et al. 2013a). Mechanistically, ZAP contains a CpG dinucleotide-binding pocket, and it binds to selected CpGs in viral RNAs as well as some cellular mRNAs (Meagher et al. 2019), such as those encoding IFN-repressed genes (Shaw et al. 2021), to target them to degradation by nucleases such as KHNYN (Ficarelli et al. 2019, 2020). Particularly, during murine leukemia virus (MLV) infection, ZAP serves as a cytosolic RNA sensor, independent of TLR and RLR pathways, to repress translation and promote degradation of viral transcripts (Lee et al. 2013a). ZAP also exhibits antiviral activity against HIV-1 and SARS-CoV-2, plausibly mediated at least in part through CpG nucleotides (Ficarelli et al. 2020; Nchioua et al. 2020). Recoding the viral genome by increasing the occurrence of CpG without changing the protein-coding capacity provides a new strategy to construct live attenuated strains of RNA viruses that are particularly susceptible to ZAP-dependent degradation (Odon et al. 2019).

ZCCHC3

Zinc-finger CCHC-type containing 3 (ZCCHC3) is a CCHC-type zinc-finger protein critically involved in regulating innate immune response (Lian et al. 2018a,b; Zang et al. 2020). It not only influences cytosolic dsRNA sensing by RLRs (Lian et al. 2018b), but also plays a crucial role in cytosolic dsDNA sensing by cGAS (Lian et al. 2018a). Cytosolic RNA is primarily sensed by RLRs including RIG-I and MDA5. ZCCHC3 binds to dsRNA and enhances the binding of RIG-I and MDA5 to dsRNA, thereby potentiating the activation of RIG-I- and MDA5-mediated IFN response (Lian et al. 2018b). ZCCHC3 also recruits TRIM25 to RIG-I and MDA5 to facilitate their K63-linked ubiquitination and activation. However, as discussed above, whether TRIM25 mediates K63-linked ubiquitination of RIG-I and MDA5 remains controversial (Oshiumi et al. 2009; Kato et al. 2021). It would therefore be of interest to see whether ZCCHC3 might recruit RIPLET or TRIM65 to RIG-I and MDA5, respectively. While ZCCHC3 depletion significantly dampens the expression of IFN and cytokines in cells, ZCCHC3-deficient mice are also more susceptible to RNA virus infection. These findings support the notion that ZCCHC3 functions not only as a cosensor of RIG-I and MDA5 but also as a positive regulator of RLR signaling. Likewise, ZCCHC3 is also critical to TLR3-mediated innate immune response in endosomes (Zang et al. 2020). ZCCHC3 serves as a positive regulator for TLR3-mediated signaling. It facilitates the recruitment of adaptor protein TRIF to TLR3 upon stimulation, thereby enhancing TRIF oligomerization for TLR3-mediated signaling. Collectively, ZCCHC3 might contribute to multiple aspects of the innate immune response.

ZFYVE1

Zinc-finger FYVE-type containing 1 (ZFYVE1) is a guanylate-binding protein with distinct roles in the innate immune response. It has been demonstrated as a positive regulator of TLR3-mediated signaling (Zhong et al. 2020a) and a negative regulator of MDA5-mediated signaling (Zhong et al. 2020b). ZFYVE1 interacts with poly(I:C) and TLR3 through its FYVE domain (Zhong et al. 2020a). Thus, ZFYVE1 enhances TLR3 signaling by promoting ligand binding to TLR3 (Zhong et al. 2020a). The reduced expression of antiviral genes and susceptibility to

inflammatory death induced by poly(I:C) in ZFYVE1-deficient mice also support the positive regulatory role of ZFYVE1 in TLR3-mediated innate immune response (Zhong et al. 2020a). Subsequently, the same group reported a negative regulatory role for ZFYVE1 in MDA5-mediated signaling (Zhong et al. 2020b). As discussed above, its effect is specific to MDA5 and it does not affect RIG-I-mediated signaling. While the loss of ZFYVE1 in cells enhances the expression of MDA5-mediated antiviral genes, loss of ZFYVE1 in animals also protected them from lethality induced by EMCV that is sensed by MDA5 (Zhong et al. 2020b). Interaction of ZFYVE1 with MDA5 and viral RNA has been noted (Zhong et al. 2020b). ZFYVE1 competes with MDA5 for viral RNA binding and thus dampens the activation of MDA5 (Zhong et al. 2020b). The distinct roles of ZFYVE1 on TLR3 and MDA5 might appear at odds, but this also illustrates the complexity and the tight control of the innate immune system.

ZNF598

Zinc-finger protein 598 (ZNF598) is a ubiquitously expressed E3 ubiquitin ligase with an amino-terminal RING-finger domain as well as four amino-terminal and one carboxy-terminal C2H2-type zinc-finger domains (Garzia et al. 2017). ZNF598 is an RNA-binding protein that binds to the translating mRNA and tRNAs on ribosomes and has been implicated in ribosome-associated quality control (Garzia et al. 2017). ZNF598 is also known as a negative regulator of RIG-I to prevent an excessive innate immune response during viral infection (Wang et al. 2019a). ZNF598 interacts with RIG-I and attenuates RIG-I-mediated IFN response. Depletion of ZNF598 potentiates IFN expression in IAV-infected cells, which is mainly mediated through the RIG-I pathway. Mechanistically, ZNF598 promotes noncovalent binding of the ubiquitin-like modifier FAT10 to RIG-I, so that RIPLET-mediated K63-linked ubiquitination of RIG-I is hindered (Wang et al. 2019a). RIG-I activation is known to require RIPLET-mediated K63-linked ubiquitination (Oshiumi et al. 2009, 2010a, 2013; Cadena et al. 2019; Hayman et al. 2019). As a result, RIG-I activation and thus RIG-I-mediated innate immune response are both attenuated in the presence of ZNF598. This represents an important mechanism to prevent an excessive immune response.

ZNFX1

Zinc-finger NFX1-type containing 1 protein (ZNFX1) is an IFN-induced, mitochondrial-localized helicase belonging to the helicase superfamily 1 (Wang et al. 2019c). ZNFX1 acts as a dsRNA sensor to specifically counteract RNA viruses such as VSV, EMCV and IAV (Wang et al. 2019c). ZNFX1 binds to viral RNA directly and then specifically interacts with MAVS, but not TRIF, MyD88 or STING, to elicit a type I IFN response upon virus infection. Loss of ZNFX1 in cells and mice enhances viral replication and dampens IFN production. The ability for ZNFX1 in eliciting an IFN response has also been shown to be RIG-I- and MDA5-independent. ZNFX1 deficiency in humans predisposes to severe viral or bacterial infections, monocytosis and multisystem inflammation (Le Voyer et al. 2021; Vavassori et al. 2021). All these findings suggest that ZNFX1 plays a crucial role as a novel RNA sensor in the antiviral immune response against RNA viruses.

VIRAL PERTURBATION OF RNA-BINDING PARTNERS OF RNA SENSORS

Viral countermeasures to evade host RNA sensing have been well described (Beachboard and Horner 2016; Chatterjee et al. 2016). Since existing reviews primarily focus on the viral perturbation of RNA sensors (Chan and Gack 2016; Fung et al. 2020), we will provide a nonexhaustive discussion on how viruses subvert the function of RNA-binding partners of RNA sensors. The viral counter-defense not only provides a glimpse of the complexity of virus-host interaction, but also highlights the importance of the RNA-binding partners in RNA sensing.

With crucial roles in RLR-mediated IFN response, PACT is a key host factor frequently targeted by viruses for IFN antagonism. Diverse classes of viruses have developed measures to antagonize PACT-mediated IFN response for their successful survival and replication. In many cases, the viruses encode a viral dsRNA-binding protein to perturb the function of PACT. Herpes simplex virus 1 Us11 protein is the first example for this viral strategy (Kew et al. 2013). The study also reminds us of the importance of viral RNA sensing even during the course of DNA virus infection. MERS-CoV ORF4a protein provides another example in which a viral dsRNA-binding protein counteracts PACT activation of RIG-I and MDA5 (Siu et al. 2014). In the case of Ebola virus VP35 protein, mutual antagonism between PACT and VP35 has been shown (Luthra et al. 2013). Whereas VP35 suppresses the IFN-inducing property of PACT, PACT also suppresses the activity of VP35 in viral RNA replication. The infection outcome is therefore affected by this pair of interacting partners. Generally consistent with this trend, mutual antagonism between IAV polymerase and PACT has also been reported (Chan et al. 2018). In addition, various other viral proteins including arenavirus nucleoprotein (Shao et al. 2018), IAV NS1 (Tawaratsumida et al. 2014), as well as mouse hepatitis virus and SARS-CoV nucleocapsid (Ding et al. 2017), have also been shown to suppress PACT-induced RLR-dependent IFN production through specific interaction with PACT.

Interestingly, it is not uncommon for viruses to use one single IFN-antagonizing protein to target several different RNA sensors and their RNA-binding protein partners. For example, IAV NS1 and Ebola virus VP35 are also known to antagonize the function of PKR, RIG-I, MDA5, OAS-

RNase L, and ZAP (Krug 2015; Tang et al. 2017; Banerjee and Mitra 2020). Likewise, vaccinia virus E3L also targets PKR, RIG-I, MDA5, OAS-RNase L, ZBP1, and ADAR1 (Marq et al. 2009; Perdiguero and Esteban 2009). On the other hand, some viruses use more than one IFN antagonist to target the same RNA sensor or RNA-binding partner. In particular, both IAV and SARS-CoV-2 use multiple viral proteins to target PACT and RIG-I (Wong et al. 2016; Malik and Zhou 2020). Recombinant viruses defective of one or more of the viral antagonists of PACT and RIG-I are severely attenuated. For example, NS1-deficient IAV has been used as a live attenuated vaccine in animals (Richt and García-Sastre 2009) and is a promising platform for development of live attenuated vaccines in humans (Wang et al. 2019b).

Viral subversion of PKR and ADAR1 has been reviewed elsewhere (George et al. 2009). Additional examples in which RNA-binding partners of RNA sensors are targeted by multiple viral proteins or viral RNA have been noted. The activity of G3BP1 in RNA sensing is known to be suppressed by foot-and-mouth disease virus 3A and leader proteins (Visser et al. 2019; Yang et al. 2020). Notably, a dengue virus noncoding RNA known as subgenomic flaviviral RNA also binds to G3BP1 and inhibits its activity (Bidet et al. 2014). In the case of ZAP, porcine reproductive and respiratory syndrome virus Nsp9 (Zhao et al. 2019) and Nsp4 (Zhao et al. 2020), herpes simplex virus 1 UL41 (Su et al. 2015), as well as enterovirus A71 3C protease (Xie et al. 2018a) bind to and counteract the antiviral activity of ZAP.

CONCLUDING REMARKS

Understanding of the mechanisms for detecting foreign RNA in the cytoplasm during viral infection has advanced substantially in recent years. This lays the ground for the development of new antivirals, vaccines and vaccine adjuvants, as exemplified in the exploration of RNA agonists of RIG-I and PACT as vaccine adjuvants, and the test of NS1-deleted IAV strains as vaccines. Cytoplasmic RNA sensors ranging from the prototypic member RIG-I to the newly identified PARP9 and SAFA operate in a discrete and coordinated manner to accomplish the very sophisticated task of RNA sensing. The RNA sensors partner with various RNA-binding proteins to fine-tune their sensing activity so that PAMP recognition could be accurate and the innate antiviral response would be activated with high specificity and the right magnitude. As more and more RNA sensors and their RNA-binding protein partners have been found, cross-talk and orchestration of different RNA sensing pathways emerge as the most important topics for further exploration. Biochemical and structural analysis of the RNA–protein and protein–protein complexes should also be revealing. The study of RNA sensing is also highly relevant to SARS-CoV-2 research, which has become one of the top priorities in the middle of the ongoing pandemic of COVID-19. Key questions concerning RNA sensing and SARS-CoV-2 include how SARS-CoV-2 RNA is sensed, what PAMPs are sensed by what PRRs, how SARS-CoV-2 antagonizes host RNA sensing, and what implications the IFN antagonism of SARS-CoV-2 has in pathogenesis, antiviral and vaccine development. New insights into these questions will not only derive new knowledge in SARS-CoV-2-host interaction, but also reveal new strategies for COVID-19 prevention and intervention.

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Cytoplasmic RNA sensors and their interplay with RNA-binding partners in innate antiviral response: theme and variations

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