Review

Zohreh-alsadat Ghoreshi, Mohsen Nakhaee, Mohammad Samie, Mohsen Sharif Zak and Nasir Arefinia*

Innate immune sensors for detecting nucleic acids during infection

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Abstract: Innate immune receptors detect nucleic acids, such as viruses, and initiate an immune response by secreting interferon (IFN) and regulating IFN-stimulated genes (ISG). In autoimmune conditions, expression of ISGs funded, show the activation of nucleic acid sensory pathways. However, the nucleus-localized innate sensors are recently found to detect pathogenic nucleic acids for initiating innate response, demonstrating a complicated crosstalk with cytoplasmic sensors and signaling molecules to form an elaborate tiered innate signaling network between nucleus and cytoplasm. to sustain immune hemostasis, these innate immune sensors develop different strategies for discriminating between self or non-self-nucleic acid. We reviewed all the sensors involved in the innate immune system in the present study. A better understanding of these sensors can lead to new treatments for infections, cancer, and autoimmune and inflammatory disorders.

Keywords: cytoplasm innate immune system; endoplasmic innate immune system; innate immune response; innate immune sensors; nuclear innate immune system.

Introduction

As a result of evolution, the immune system evolved to protect against infection, essential for the survival of the host. Pattern Recognition Receptors (PRRs) are responsible for the rapid detection of pathogens [1]. The receptors are encoded at the germline level and are stimulated by a variety of bacterial and fungal pathogen associated molecular patterns (PAMPs). Since many of these PAMPs cannot be expressed in mammals, they are considered foreign molecules [2]. A few PRRs of the innate immune system detect viral genome structures to recognize viruses that are used by host cells to construct their components [3]. As a result, the use of nucleic acid sensing to initiate the immune response to various viruses can trigger a misdirected response by autologous DNA or RNA. Hence, three critical safeguards are to impede the detection of self-nucleic acid: (a) permanent expression of nucleases in cells destroying potentially stimulating nucleic acids [3] (b) elaborate modifications in the cell such as the rich methylation pattern in mammalian RNA and DNA that are not present in the virus genome [4] and (c) nucleic acid receptors in the cytosol and cellular endosomes where these viruses replicate and there is a small concentration of host nucleic acid [5] In situations where physiological cell turnover is disturbed, such as in cancer, these levels of protection can be helpful in balancing the immune system [6, 7]. The present review aims to summarize various nucleic acid sensors in different cell areas. Understanding the immune system sensors helps develop agonist or antagonist nucleic acid-sensing pathways in clinical settings.

Nucleic acid sensors

Endosomal nucleic acid sensors

The Toll-like receptor (TLR) family detects nucleic acids in the endosome and is located in a few types of cells, especially in innate immune cells [6] TLRs have 12 members in mice (Except TLR 10), 10 members in humans and chicken, 9 members in Drosophila, and 12 members in murine [8, 9].
Among the human TLRs, TLR3 identifies double-stranded RNAs (dsRNAs), TLR7 identifies short single-stranded RNAs (ssRNAs) and short double-strand RNAs (dsRNAs), and TLR8 identifies single-stranded RNAs (ssRNA) and broken-down products. On the other hand, TLR9 is able to detect non-methylated CpG double-stranded DNAs [10]. Some nucleotides can play a critical role in stimulating these sensors [11]. As an example, the synthesis of GU-rich oligonucleotides further stimulates TLR7 and TLR8 [12]. A TLR is a transmembrane protein containing two domains. One domain is on the luminal side of the membrane with amino-terminal Leucine-Rich Repeats (LRRs), and the other one is on the cytosolic side [11] toll-interleukin-1 receptor (TIR) domain signaling in TLR7, TLR8, and TLR9 is triggered by aggregating the adaptor protein, myeloid differentiation primary response protein 88 (MYD88), which leads to Nuclear Factor κB (NF-κB) transcription of pro-inflammatory cytokine genes. In plasmacytoid dendritic cells (pDCs), the MYD88 signaling complex is able to promote transcription of genes encoding IFNα subtypes by directly activating IFN-regulatory factor 7 (IRF7). In contrast, The TLR3 adaptor is the TIR domain-containing adaptor protein inducing IFN-β (TRIF), which activates Mitogen Activated Protein Kinase (MAPK), IRF3, and NF-κB to generate inflammatory cytokines and IFN-β [3, 13] (Figure 1).

**Cytosolic nucleic acid sensors**

In the cytoplasm of immune and non-immune cells, nucleic acid sensors are extensively expressed at diverse levels [14]. The melanoma differentiation-associated protein 5 (MDA5) and the DExD/H-box helicases retinoic acid-inducible gene I (DDX58 or RIG1) can detect dsRNAs. RIG-I is also triggered by the 5' end of triphosphorylation or 5' diphosphorylated short dsRNAs [15, 16]. 2'-O-methylation at their first pair base is one of the protective mechanisms for suppressing endogenous mRNAs [17]. The MDA5 ligand has been reported in both branching high-molecular RNA forms and long dsRNAs [18, 19]. MDA5 has recently been

![Figure 1: Cytosolic and endosomal nucleic acid-sensing pathways. The Figure shows some major nucleic acid-sensing pathways. Stimulation of these pathways may result in effector mechanisms beyond the production of various proinflammatory cytokines and interferon. AIM2, absent in melanoma 2; cGAMP, cyclic GMP–AMP; cGAS, cGAMP synthase; dsRNA, double-stranded RNA; ER, endoplasmic reticulum; MAVS, mitochondrial antiviral signalling protein; MDA5, melanoma differentiation-associated protein 5; MYD88, myeloid differentiation primary response protein 88; NF-κB, nuclear factor-κB; RIG-I, retinoic acid-inducible gene I; ssRNA, single-stranded RNA; STING, stimulator of IFN genes; TBK1, TANK-binding kinase 1; TRIF, TIR domain-containing adaptor protein inducing IFN-β.](image-url)
shown to be activated by endogenously synthesized RNAs although they are removed by adenosine deaminase-1 (ADAR1)-mediated editing [20, 21]. MDA5 and RIG1 have three domains: (a) the caspase activation and recruitment domain (CARD) in the N terminal, (b) the DEAxD/H box helicase domain in the central region, and (c) the ligand-binding domain at the carboxy terminus. MDA5 and RIG1 can engage comparable CARDs of the signaling adaptor mitochondrial antiviral signaling protein (MAVS) on the outer mitochondrial membrane, eventually leading to the activation of the MAVS signaling complex by multimerization of MAVS [22]. cyclic GMP–AMP (cGAMP) synthase (cGAS) is another innate immune system sensor that identifies dsDNAs [23]. The cGAS then produces the second messenger; the Cyclic Dinucleotide (CDN) or 2′3′-cGAMP, which is essential for stimulator of interferon genes (STING) activity on the endoplasmic reticulum (ER) [24, 25]. bacterial CDNs can also stimulate mouse STING directly with cyclic di adenosine monophosphate (c-di-AMP) and cyclic di guanosine monophosphate (c-di-GMP) [26, 27]. Activating the immune system and the IFN signaling leads to an increase in IFN expression, which in turn leads to more IFN responses [28]. Acute infections trigger severe immune responses in many tissues as a result of this positive feedback process [29]. Activation of TANK1 and IRF3 (upon phosphorylation) by innate immune adaptor proteins such MAVS, STING, and TRIF results in the activation of IRF7, IRF3, MAPK, and NF-kB transcription factors, resulting in the production of inflammatory cytokines and IFN [30]. Another cytosolic sensor is AIM2, which is a dsDNA receptor. It forms a multiprotein complex termed the inflammasome with apoptosis-associated speck-like protein (ASC) and caspase-1. This complex aid viral clearance by secreting pro-inflammatory cytokines like IL-1 and IL-18, as well as inducing pyroptosis, a form of inflammatory cell death [31]. AIM2 induces the development and oligomerization of ASC in response to ligand binding, which activates procaspase 1 and allows caspase 1 to be activated by proximity, resulting in the production of IL1 and IL18 [32]. Because it do not distinguish between microbial and cellular dsDNAs, scientists believe that the activation of the AIM2 inflammasome promotes the development of many autoimmune disorders [33]. AIM2 and other inflammasome components have also been shown to play a pathogenic role in various models of sterile inflammation in the skin, such as neuroinflammation [32] (Figure 1).

**Nuclear DNA sensors**

One of the DNA sensors in the nucleus is heterogeneous nuclear ribonucleoprotein A2/B1 (hnRNPA2B1), which is detects the nuclear proteins which are precipitated by biotinylated genomic DNA of herpes simplex virus 1 (HSV-1) (F strain) [34]. In addition, it is also transported to the cytoplasm during HSV-1 infection, where it detects nuclear proteins with the ability to detect pathogenic DNA and initiate cytoplasmic innate immune response [35]. The knockdown of hnRNPA2B1 in various human and mouse cells has been shown to impair the detection of DNA viruses such as adenovirus and herpes simplex virus in order to defect the production of interferon [36]. According to studies, hnRNPA2B1 belongs to the hnRN family of proteins and contains 30 RNA-binding proteins (RBPs) [37, 38]. Upon detection of the virus genome, hnRNPA2B1 dimerizes and translocates to the cytoplasm, where it induces the expression of IFNα/β through STING and cGAS signaling pathways [39] HnRNPA2B1, in addition to its functions in RNA biology, has been identified as a new innate nuclear sensor for the detection of viral DNA and the initiation of antiviral IFN-1 expression [40] (Figure 2). hnRNPA2B1 has two canonical RNA recognition motifs (RRMs) in its N-terminal, and studies have indicated its crucial roles in transcription, translation, mRNA transport, and alternative splicing [34, 38]. We still do not fully understand the mechanism by which hnRNPA2B1 suppresses viral innate immunity and senses viral DNA.

The other DNA sensor in a nucleus is gamma-interferon-inducible protein (IFI16). Like AIM, IFI16 belongs to the PYRIN domain which is inducible by IFN [41]. This sensor contains a PYD domain and two conserved hematopoietic expression domains, which are responsible for inducing IFN. At the C-terminus, there are two tandem β-barrels nucleolar localization domains (HIN A and HIN B), which contain nuclear localization (HIN) domains (A and B). These tandem β-barrels are called oligonucleotide/oligosaccharide binding (OBs), as they allow for binding of double-stranded DNA (dsDNA) or single-stranded DNA (ssDNA) [42]. Depending on the type of host cell, it can detect single-stranded or double-stranded DNA from both viral and bacterial pathogens [43, 44]. Upon detection of the pathogen’s DNA, IFI16 activates the innate immune system by activating the cytoplasmic inflammatory adaptor sensors [40]. IFI16 is translocated to the cytoplasm after detecting pathogen DNA in the nucleus, stimulating TBK1-IRF3 and NF-B signaling as well as IFN expression through interacting with STING [45–47] (Figure 2).

Through procaspase-1 and ASC, IFI16 aids in the activation of the inflammasome complex. Procaspase-1 is then proteolytically cleaved by the IFI16 inflammasome and converted to caspase-1, followed by cleavage of IL-1 and IL-18 [48, 49]. It is worth noting that there is still controversy about the detection of DNA pathogens in the nucleus
by the IFI16 and the activation of inflammasome and the STING pathway. For instance, there was no change in the production of IFNs in response to human cytomegalovirus (HCMV) infection by IFI16 knockout on human fibroblast cells [50]. This controversy may be associated with specific virus and cell types. Therefore, different cell lines and viruses may be necessary for activating the immune response. IFI16 can also restrict the replication of DNA viruses through epigenetic modifications. For example, studies [51, 52] showed that following infection with HSV1, IFI16 inhibited histone modification to repress HSV-1 proliferation. In another research [53] on latent infection with KSHV, IFI16 interacted with GLP and H3K9 methyltransferase SUV39H1 and inactivated the lytic phase genes. Other studies also proved that IFI16 could block the replication of the HCMV virus by binding to the transcription factor Sp1 and preventing it from binding to the promoter region of viral DNA polymerase gene (UL54) [54].

**Nuclear RNA sensors**

A large number of viral RNAs accumulate in the nucleus. Many RNA viruses, for instance, RNA viruses replication in the nucleus. Furthermore, certain DNA viruses, such as HSV-1 transcribe viral RNA in nucleus [55]. Scaffold Attachment Factor A (SAFA), a nuclear matrix protein also known as heterogeneous nuclear ribonuclear protein U (hnRNPU), is one of the virus’s RNA sensors [55, 56]. SAFA appears to bind selectively to some RNA viruses in the

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**Figure 2:** IFI16 and hnRNPA2B1 act as nuclear DNA sensors in inflammation and innate immunity. During HSV-1 infection, genomic viral DNA of HSV-1 is translocated into the nucleus. The JMJ6, arginine demethylase, is activated via homo-oligomerization. Subsequently, dimer induces the demethylation of hnRNPA2B1 dimer at Arg226, leading to the translocation of hnRNPA2B from the nucleus to the cytoplasm. hnRNPA2B1 is triggered to STING and Src and induces IFN-Is expression through TBK1-IRF3 signaling. Furthermore, in resting cells, methylated hnRNPA2B1 recruits FTO to IFI16, STING, and CGAS mRNA. FTO facilitates the demethylation of these mRNAs and restricts them in the nucleus. Upon HSV-1, demethylated hnRNPA2B1 disassociates with FTO and releases CGAS, IFI16, and STING mRNAs. The methylated mRNAs are translocated to the cytoplasm and increase the protein levels of STING, cGAS, and IFI16 to amplify the cytoplasmic innate immune signaling. After identifying the HSV-1 dsDNA, nuclear IFI16 initiates the innate immune response against pathogenic invasion through two main mechanisms: (a) IFI16-dsDNA complex is translocated from the nucleus to the cytoplasm to trigger cytoplasmic STING signaling axis to product IFN-Is expression through TBK1-IRF3 and NF-κB signaling pathways and (b) activated nuclear IFI16 after the cleavage of IL-1β and IL-18 recruits ASC and procaspase-1 to form an activated inflammasome and is translocated to the cytoplasm.
nucleus, triggering innate immune responses [57]. Studies have indicated that SAFA can interact with the RNAs of some viruses such as HIV viruses that interacts with the 3′ Long Terminal Repeat (3′ LTR) and inhibits mRNA transfer to cytoplasm and its translation [58]. SAFA can also interact with the leader RNA in VSV [56] and has four DNA/RNA binding domains. Its c-terminal responsible for identifying RNA viruses and contains arginine-glycine-glycine-rich (RGG) [59].

In VSV and HSV-1 infections, induction of IFN-β decreases in SAFA-deficient human primary cells [57, 58]. SAFA can bind directly to the double-stranded RNA genome of viruses and homodimerizes. SAFA dimerization leads to changes in the chromatin structure of IFN-1s and cytokines. This changes the structure of chromatin through binding SAFA dimers to SAFA-binding sequences and interacting with DNA Topoisomerase I (TOP1) via the middle SPRY domain and SWI/SNF-related matrix-associated actin-dependent regulator of the chromatin subfamily A member 5 (SMARCA5) [40] (Figure 3).

Another RNA detector sensor in the nucleus is the RIG-1, which is highly conserved in the cytoplasm. It has been recently found in the nucleus in addition to the cytoplasm [60, 61].

Following infection with influenza A (IAV), the ssRNA genome of the influenza virus is detected by nuclear RIGs followed by dimerization and interaction with cytoplasmic RIG-1. Activation of the cytoplasmic RIG-1 initiates the MAVS-RIG1 signaling cascade. Nuclear RIG can directly activate the MAVS signaling pathway in the late phase of infection [62] (Figure 3).

Recent studies have indicated that the distribution of innate immune sensors does not follow the trend observed in the past, similar to IFI16 and RIG-1 that were discussed above. Another cytoplasmic innate immune sensor; i.e., cGAS, has also been found to be involved in the

Figure 3: Nucleus RNA sensors such as SAFA, nucleus-localized RIG-1, and ZBP1 act in innate immunity and inflammation. Some nucleus RNA sensors such as SAFA act as a viral dsRNA sensor and trans-activator to initiate the innate immune response and restrict viral infections. After recognition of viral dsRNAs by SAFA, it homodimerizes. Then, dimers bind to the multiple SAFA-binding sequences in the enhancers of IFNB1 and interact with TOP1 and SMARCA5, which can cause the transformation of chromosome conformation and activation of the super-enhancers and distal enhancers of IFN-Is and cytokine genes. In IAV infection, nucleus-localized RIG-1 recognizes IAV replication in the nucleus and activates the canonical cytoplasmic RIG-1-MAVS signaling cascade. Furthermore, ZBP1 recognizes viral Z-RNAs in the nucleus during the genome replication of orthomyxoviruses (IAV and IBV). By activating ZBP1, RIPK3 can activate MLKL in the nucleus via phosphorylation. Subsequently, the phosphorylated MLKL initiates the disruption of the nuclear envelope and facilitates the leakage of nuclear DNA into the cytoplasm. Translocation of the activated MLKL to the plasma membrane can cause cell death by necroptosis.
identification of cytoplasmic DNA, to be capable of translocation from the cytoplasm to the nucleus, and to be involved in mitosis and DNA repair [63, 64]. Another innate immune sensor is the Z-DNA binding protein (ZBP1), which was originally introduced as a DNA sensor for detecting multiple ds-DNA in the cytoplasm [65]. Recent findings revealed the ability of ZBP1 to detect the RNAs of such viruses as Influenza A virus (IAV) in the nucleus [66–70] (Figure 3). Defective RNAs are generated during influenza B and A genome replication, which do not have full-length genomes and have a Z conformation (Z-formation) [40].

ZBP1 has two Zα domains at the N-terminus. during IAV infection, One of the domains (second Zα domain) recognizes Z-RNAs. Activation of ZBP1 activates RIPK3. It phosphorylates Mixed Lineage Kinase Domain Like Pseudokinase (MLKL) upon activation. As a result, MLKL causes nuclear envelope disruption, enabling Damage-Associated Molecular Patterns (DAMP) leakage into cytoplasm. Then, MLKL is translocates to the plasma membrane and allows DAMPs leak into the extracellular space and induces necrosis and calling neutrophil [66, 71].

ZBP1 is the only innate immune system RNA sensor that detects Z-RNAs, whereas other RNA sensors detect A-RNAs (A-form). Additionally, ZBP1 is able to detect pathogenic Z-DNAs that have a similar structure to Z-RNAs [40].

**Crosstalk between the cytoplasmic and nuclear innate sensors**

The activation of the nuclear innate sensor is not just restricted to nuclei for initiating innate immune responses. RNPA2B1 and IFI16 (except for SAFA and ZBP1) transfer to the cytoplasm and interact with cytoplasmic innate sensors of the immune system, which play an important role in activating and developing the innate immune system [40]. A crucial cytoplasmic adaptor protein that triggers the innate immune system is STING. It is triggered by immunostimulatory DNAs. Nuclear sensors such as RNPA2B1 and IFI16 detect pathogenic DNAs in the nucleus and translocate to the cytoplasm, where they interact with adapter proteins, eventually producing IFN type 1 [40, 41, 70]. It has been demonstrated that hnRNPA2B1 interaction with the cGAS-STING pathway is necessary for it to respond to and control HSV-1 infection [34] hnRNPA2B1 deficiencies inhibit the cytoplasmic cGAS-STING signaling cascade by impairing its function [34]. The methyltransferase-like 3 (METTL3)-METTL14 complex is essential for m6A methylation of cGAS, STING, and IFI16 mRNAs, as well as their translocation into the cytoplasm. cGAS, STING, and IFI16 mRNAs can interact with hnRNPA2B1 and bind to the RNA demethylase fat mass and obesity-associated protein (FTO) to form an hnRNPA2B1/FTO/mRNA complex [40]. Interestingly, upon infection with bacteria (such as *Listeria monocytogenes* and Francisella novicida) and DNA viruses (such as HSV-1), the cooperation of IFI16 and cGAS in the cytoplasm induce the full activation of the innate immunity response [45, 72, 73].

In HSV-1 virus infection, the IFI16 is responsible for detecting its nucleic acid, and it is unclear whether the IFI16 is transmitted from the nucleus to the cytoplasm or interacts with the cytoplasmic cGAS. IFI16 also activates the STING pathway via recruiting TANK-binding kinase 1 (TBK1), which plays an important role in the innate immune response [74]. Nevertheless, studies on keratinocytes and fibroblasts during HSV-1 infection indicated that interactions between nuclear IFI16 and cGAS increase their stability in the nucleus [75]. Studies on IAV infection have also demonstrated that both nuclear RIG-1 and cytoplasmic RIG-1 are involved in the detection of IAV infection. IAV replication stimulates nuclear RIG-1, whereas vRNPs activate cytoplasmic RIG-1. Activated nuclear RIG-1 is translocated to the cytoplasm and interacts with cytoplasmic, where it forms oligomers with cytoplasmic RIG-1 and activates the RIG-1-MAVS signaling pathway, which leads to IFN-1 production [70]. These findings show that the innate immune system is completely activated by the collaboration of innate immune sensors in the cytoplasm and nucleus through cytoplasmic signaling adapter proteins.

**Regulation of innate immune sensor signaling**

Overexpression and activation of innate immune system sensors can lead to autoimmune disorders [74, 75]. Activation of the innate immune sensors must be controlled at the transcriptional and translational levels. Detection of pathogenic nucleic acids during viral infections causes the production of interferon. IFNs induce a variety of IFN-stimulated genes (ISGs) like IFI16, SAFA, and RIG-I. The downstream signaling pathway of these nuclear innate sensors amplifies the innate immune system response to exogenous pathogens [57, 76] the level of innate immune sensors is regulated after responding to the infection in the late phase to avoid their excessive activation. Studies have revealed proteasome as one of the most important negative regulators of innate immune responses, which is activated following K48-linked polyubiquitination [77]. For instance, the levels of RING finger protein 122 (RNF122), RNF125, and E3 ubiquitin ligases are increased in the late phase of viral infections, which directly mediates the K48-linked
polyubiquitination of RIG-I, leading to the proteasomal degradation of RIG-I [78, 79] PAMPs are detected by innate immune sensors, prompting them to oligomerize and trigger downstream signaling cascades. For instance, hnRNPA2B1 binds to viral DNAs and dimerizes via the RNA recognition motif (RRM) domains [34]. Moreover, the RRM domain has the Arg, which binds to cGAS, IFI16, and STING mRNAs in the nucleus and is usually monomethylated in uninfected cells [40] JMJD6 arginine demethylase is activated via homo-oligomerization upon HSV-1 infection. JMJD6 dimerization results in the demethylilation of the hhnRNPA2B1 dimer at Arg [40]. This causes the cytoplasmic translocation of hnRNPA2B1 and is disassociated with STING, CGAS, and IFI16 mRNAs [40]. During viral infections, IFI16 binds to the same location of pathogenic dsDNAs via PYRIN domain (PYD)-PYD interaction to form filaments [80] NLS acetylation in IFI16 by P300 acetyltransferase promotes IFI16 cytoplasmic export [43]. The production of IFN- and proinflammatory cytokines is triggered by the detection of viral RNAs by SAFA, followed by their dimerization and activation [57] RIG-I is also dimerized and activated via viral RNAs. During IAV infection, nuclear RIG-I interacts with activated cytoplasmic RIG-I, thereby forming an oligomer [81, 82].

Tripartite motif containing 25 (TRIM25) is located in the nucleus and is thought to act as an antiviral factor during IAV infection [83]. Additionally, TRIM25 has the ability to polyubiquitinate nuclear RIG-I via linking to K63 [84, 85]. Studies have shown that RIPLET, an essential E3 ligase in antiviral immunity, mediates polyubiquitination and oligomerization of K63-linked proteins, but not TRIM25. RIPLET is capable of cross talking RIG-I filaments and causing RIG-I hemo-oligomerization [86]. On the other hand, pathogens have evolved mechanisms to evade the immune system by using mechanisms that inhibit the negative regulation of innate sensors. During an early stage of infection with HSV-1 in human fibroblasts, the virus encoding ICP0 (E3 ubiquitin ligase) could directly interact with IFI16 and cause its degradation by proteasomes [87]. Furthermore, two other studies showed that ICP0 did not degrade IFI16 in cells without infection [86, 87]. Additionally, IE1 (transactivating protein) could initiate the degradation of IFI16 during HCMV infection. By interfering with PYD-PYD interaction from IFI16 through the Pyrin Association Domain (PAD), pUL83 (tegument protein) suppressed the production of IFNs in HCMV [88]. The virus can suppress IFI16 by another mechanism in the late phase of HCMV infection. The viral protein kinase, pUL97, binds to IFI16 and phosphorylates it, which then mislocalizes to the cytoplasmic virus assembly complex [89]. Expression of pUL97 alone fails to induce mis-localization and the nuclear egress of IFI16. These findings prove that other HCMV components are vital for inhibitions mediated by either pUL83 or pUL97.

Post-translational modifications are another important mechanism for controlling innate immunity and inflammation [77]. In Influenza A virus (IAV) infection, the ZBP1 is polyubiquitinated and its necrosis role is ceased [70]. In addition to acetylation, methylation, and polyubiquitination phosphoserilacin, glycosylation, lipidation, phosphorylation, and simulation are involved in post-translational modifications [70]. In this context, phosphorylation plays a crucial role in transcription factors and signal molecules [90]. After the phosphorylation of transcription factors such p65 and IFR3, these factors translocate to the nucleus to transcribe proinflammatory cytokine genes and immune sensors [40]. Additionally, SUMOylation (Small Ubiquitin-like Modifier proteins) of MDA5 and RIG-I increases antiviral immune responses [89, 90]. Therefore, further investigations into the negative and positive regulation of innate sensors and downstream signal molecules are required.

Long non-coding RNAs (lncRNAs) are also significant regulators and controllers of innate immune responses (95, 96) One of these lncRNAs is lincRNA-Cox2, which interacts with hnRNPA2B1 and inhibits TLR-induced inflammatory gene expression [37]. Previous studies have suggested that SAFA is a sensor involved in epigenetic regulation, which affects chromatin structure by interacting with chromatin-associated RNAs (caRNAs) [91]. Furthermore, Inc-Lsm3b binds to cytoplasmic RIG-I and suppresses the interaction between viral RNA and RIG-I in the late phase of infection via RNA viruses to avoiding excessive activation of the innate immune signaling system through negative regulation of RIG-I activation [92]. Hence, further studies are required to identify more lncRNAs.

Summary and outlook

As outlined in this review, the nuclear and cytoplasmic innate immune systems are involved in recognizing a wide range of nucleic acids. Therefore, having accurate knowledge about these sensors and their interactions with each other can be very useful in the design of nucleic acid agonists and antagonists. These agonists or antagonists can improve the treatment of a wide range of diseases from acute or chronic viral infections, cancer and autoimmune disorders. Nonetheless, clinical success depends on a better understanding of cell signaling and the complex molecular pathophysiology of these diseases. Therefore, accurate knowledge of the molecular characteristics of
different diseases can lead humans to their main goal of controlling various diseases and cancers through the production of effective agonists and antagonists. For instance, antagonists of endosomal TLRs may have limited direct effects on non-haematopoietic cells and can mainly target hematopoietic cells. In contrast, non-hematopoietic cells are direct target cells of agonists or antagonists of cytosolic nucleic acid receptors.

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