

Host Factors Modulate Virus-Induced IFN Production via Pattern Recognition Receptors

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Abstract: Innate immunity is the first line of defense in the human body, and it plays an important role in defending against viral infection. Viruses are identified by different pattern-recognition receptors (PRRs) that activate the mitochondrial antiviral signaling protein (MAVS) or transmembrane protein 173 (STING), which trigger multiple signaling cascades that cause nuclear factor- κ B (NF- κ B) and interferon regulatory factor 3 (IRF3) to produce inflammatory factors and interferons (IFNs). PRRs play a pivotal role as the first step in pathogen induction of interferon production. Interferon elicits antiviral activity by inducing the transcription of hundreds of IFN-stimulated genes (ISGs) via the janus kinase (JAK) – signal transducer and activator of transcription (STAT) pathway. An increasing number of studies have shown that environmental, pathogen and host factors regulate the IFN signaling pathway. Here, we summarize the mechanisms of host factor modulation in IFN production via pattern recognition receptors. These regulatory mechanisms maintain interferon levels in a normal state and clear viruses without inducing autoimmune disease.

Keywords: pattern recognition receptors, interferon-signaling pathway, host factors

Introduction

Viral infection is a serious threat to human health. The innate immune system is the first line of defense against virus invasion. Pattern recognition receptors (PRRs) of host cells recognize pathogen-associated molecular patterns (PAMPs) of viruses, which activates innate immune response signaling pathways and induces interferon and cytokine expression.^{1,2} Interferon is the main factor of host cell resistance to virus invasion, and it is divided into type I interferon (IFN- α , IFN- β), type II interferon (IFN- γ), and type III interferon (IFN- λ 1, IFN- λ 2, IFN- λ 3, IFN- λ 4).^{3,4} Interferon binds to specific IFN receptors on the cell surface and activates the JAK/STAT signaling pathway to induce the expression of interferon-stimulating genes (ISGs), which enhance antiviral abilities by regulating the activity of natural killer (NK) cells, macrophages, and T cells.⁵

Pattern recognition receptors of host cells primarily include Toll-like receptors (TLRs), RIG-I receptors (RLRs), and NOD-like receptors (NLRs), which recognize RNA viruses,⁶ and receptors that recognize DNA viruses, such as cyclic GMP-AMP synthase (cGAS), DEAD-Box helicase 41 (DDX41) and interferon gamma-inducible protein 16 (IFI16).³ TLR3 induces interferon expression via the toll/interleukin-1 receptor (TIR) domain-containing adaptor inducing IFN- β (TRIF)-TANK binding kinase 1 (TBK1)/inhibitor κ B kinase ϵ (IKK ϵ)-IRF3 pathway.² Intracytoplasmic pattern recognition RLRs, such as retinoic acid-inducible gene-I (RIG-I) and melanoma differentiation-associated gene 5 (MDA5), recognize intracytoplasmic viral dsRNA, activate the RIG-I/MDA5-MAVS-TBK1/IKK- ϵ -IRF3 signaling pathway, and induce interferon expression.^{6,7} By recognizing DNA viruses, the DNA pattern recognition receptor cGAS synthesizes the second messenger cGAMP, which binds to STING and activates the cGAS-STING-TBK1/IKK-IRF3 signaling pathway to induce interferon expression.⁸

Thorough research of interferon signaling pathway has discovered an increasing number of host factors that regulate interferon signaling pathways by regulating the activity of PRRs, adaptors, kinases and transcription factors. This approach enriches the understanding of the interferon signaling pathway and provides more targets for the development of antiviral drugs. In our immune system, pathogen-associated molecular patterns (PAMPs) of pathogens, which are distinct from the host, are detected by pattern recognition receptors (PRRs).⁹ This recognition activates downstream signaling pathways that the production of IFN and inflammatory factors.¹⁰ PRRs play a key role as the first step in pathogen-induced interferon production in host cells. This review highlights the host factors that regulate the production of IFNs induced by viral infection via PRRs (Table 1 and Table 2).

RIG-I-Like Pattern Recognition Receptors (RLRs)

RIG-I-like pattern recognition receptors include RIG-I, MDA5, and laboratory of genetics and physiology 2 (LGP2), which are expressed in most cells and exhibit strong immune responses in bone marrow cells, epithelial cells, and central nervous system cells. RIG-I and MDA5 contain two N-terminal caspase activation and recruitment domains (CARDs), which activate the innate immune signaling pathway. A central DExD/H RNA helicase domain promotes ATP hydrolysis and RNA binding, and a C-terminal RNA binding helicase domain (CTD) assists in the recognition and specific binding of RNA ligands. RIG-I and MDA5 act as pattern recognition receptors to recognize exogenous RNA viruses and induce a common signaling pathway to produce interferon. However, whether LGP2 serves as a pattern recognition receptor is

Table 1 PRRs Affected by Positive Regulatory Factors

PRRs	Host Factors	Functions	Reference
RIG-I	TRIM25, TRIM4, RNF135, MEX3C, hHB, miR-526a	Catalyzing RIG-I K63-linked ubiquitination and RIG-I K63-linked ubiquitination is critical for RIG-I activation	[11–17]
RIG-I	USP4, OTUB1	Eliminating the K48-linked ubiquitin chains conjugated to RIG-I and promoting the RIG-I activation	[18,19]
RIG-I	TRIM38	SUMOylation at K43/K865 of RIG-I and promoting the RIG-I activation	[20]
RIG-I	NEAT1, LINC02574	Facilitating RIG-I expression	[21,22]
RIG-I	miR136	Immune agonist of RIG-I	[23]
MDA5	PPI	Dephosphorylates MDA5, resulting in the activation of the downstream signaling	[24–26]
MDA5	TRIM65, ZCCHC3	Facilitating MDA5 K63-linked ubiquitination and activation	[27,28]
MDA5	I4-3-3η chaperone protein	Reducing the immunostimulatory potential of viral dsRNA within the MDA5 activation signaling pathway	[29]
MDA5	pOASL	As an MDA5-interacting protein, is a coactivator of MDA5-mediated IFN induction to exert anti-CSFV actions	[30]
MDA5	LncITPRIP-1	Promoting the oligomerization and activation of MDA5	[31]
MDA5	LINC02574	Facilitating MDA5 expression	[22]
MDA5	LINC1392	Promoting the activation of MDA5	[32]
MDA5	ZCCHC3	Enhancing the binding of MDA5 and RIG-I to dsRNA	[28]
RIG-I	TRIM3, Mex3B	Facilitating TLR3 K63-linked ubiquitination and activation	[33,34]
TLR3	BTK	Promoting the tyrosine phosphorylation of TLR3 upon ligand binding	[35]
TLR3	Mex3B, ZFYVE1	Increasing the dsRNA-binding activity of TLR3.	[36,37]
cGAS	TRIM56, TRIM41	Promoting cGAS monoubiquitination	[38,39]
cGAS	RNF185	Catalyzing the K27-linked poly-ubiquitination of cGAS	[40]
cGAS	USP14, USP27X, USP29	Cleaving K48-linked poly-ubiquitin chains from cGAS	[41–43]
cGAS	TRIM38	Maintaining the SUMOylation of cGAS at Lys217 and Lys464 residues, which prevented K48-linked cGAS polyubiquitination and degradation	[42]
cGAS	SEN7	deSUMOylates cGAS, which turns on the activation of cGAS	[44]
cGAS	KAT5	Increasing cGAS binding with DNA and activity	[45]
cGAS	CCP5, CCP6, G3BP1	Regulating the glutamylation of cGAS, facilitating the formation of cGAS complexes	[46,47]

Table 2 Negative Regulatory Factors on PRRs

PRRs	Host Factors	Functions	Reference
RIG-I	TRIM40, RNF125, Parkin	Mediating the K48 linked polyubiquitination of RIG-I and promoting the degradation of RIG-I	[48–50]
RIG-I	FAT10	Decreasing the solubility of the RIG-I protein	[51]
RIG-I	USP21, CYLD, SDC4, USP3, USP14, USP27X	Deubiquitinating the K63-linked ubiquitin of RIG-I and inhibiting the RIG-I activation	[52–57]
RIG-I	ISG15	Decreasing the RIG-I protein level by ISGylation	[58]
RIG-I	Lnc-Lsm3b	Decreasing RIG-I binding with viral RNAs	[59]
RIG-I	LncATV, miR485, miR218, miR-4423-3p, miR92a	Negative regulator of full-length RIG-I	[60–64]
RIG-I, MDA5	CCDC50	Specifically recognizes K63-polyubiquitinated RLRs, which deliver the activated RIG-I/MDA5 for autophagic degradation	[65]
MDA5	TRIM40	Promoting K27- and K48-linked polyubiquitination of MDA5, which led to proteasomal degradation of the protein	[48]
MDA5	hHB	Suppressing the MDA5-dsRNA interaction	[16]
MDA5	TRIM13	Inhibiting the activity of MDA5	[66]
MDA5	RIOK3	Phosphorylating the CTD of MDA5 and inhibiting MDA5-mediated cytokine expression	[67]
MDA5	miR203	Target the MDA5–3'UTR sequence and inhibit the expression of MDA5	[68]
TLR3	RNF170	Mediating the K48-linked polyubiquitination of TLR3 and promoting the degradation of RIG-I	[69]
cGAS	AKT, CDK1, AKB	Governing cGAS phosphorylation to control cGAS activation	[70–72]
cGAS	BLK	Retaining cGAS in the cytoplasm for cytosolic DNA sensing	[73]
cGAS	miR-23a/b	Dampening cytosolic DNA-induced innate immune responses	[74]

controversial due to the lack of CARD domains that are required for signal transmission. RIG-I and MDA5 CARD domains interact with other proteins that have CARD domains,^{75,76} such as mitochondrial antiviral protein (MAVS, also known as IPS-1/VISA/Cardif). Binding of the CARD-CARD domain activates MAVS,^{77–79} recruits, phosphorylates and activates TBK1 and IKK- ϵ kinases, which phosphorylate downstream transcription factors, such as IRF3. These transcription factors form dimers and translocate from the cytoplasm to the nucleus to induce interferon expression via binding to interferon promoters. Activated MAVS also activate the downstream transcription factor NF- κ B, after the phosphorylation and activation of IKK α /IKK β , and transport it from the cytoplasm to the nucleus to induce the expression of inflammatory factors.^{80–82} The expression and activation of RLRs play fundamental roles in eliminating invading RNA viruses and maintaining immune homeostasis. Among the many types of posttranslational modifications, ubiquitination and phosphorylation directly regulate the activation of RLRs and CARD-mediated downstream signaling. SUMOylation and ISGylation are newly discovered posttranslational modification modes of RLR regulation.^{83–86}

Retinoic Acid Inducible Gene-I (RIG-I)

RIG-I is involved in the identification of paramyxovirus families, such as Newcastle disease virus (NDV), Sendai virus (SeV), respiratory syncytial virus (RSV), rhabdoviruses, herpes stomatitis virus (VSV), and rabies virus. The Orthomyxoviridae family includes influenza A, influenza B viruses (IAV, IBV), flaviviruses, hepatitis C virus (HCV), Japanese encephalitis virus (JEV), filovirus, and Ebola virus.^{87–90} RIG-I was initially used as a dsRNA mimic poly (I:C) ligand to induce interferon.⁹¹ Later, it was discovered that RIG-I was also a pattern recognition receptor for innate immune signaling pathways.^{92,93} RIG-I typically recognizes the 5' triphosphate terminus of RNA sequences,⁹⁴ which distinguishes host RNA from viral RNA. The 5'ppp domain of mature host tRNA and rRNA is covered by ribosomal proteins, and the host RNA is not recognized by RIG-I.^{95,96} The DNA analog poly(dA:dT) also induces interferon production via RIG-I-dependent signaling because intracellular RNA polymerase III, which transcribes DNA into RNA, is recognized by RIG-I. Some DNA viruses, such as herpesvirus-1, adenovirus, Epstein–Barr virus, and vaccinia virus

(VV), also induce interferon production via RIG-I-dependent signaling pathways. Notably, the intracellular Gram-negative bacterium *Legionella pneumophila* also activates the RIG-I signaling pathway.^{97,98} The CARD and helicase domains of RIG-I envelop the RNA binding site in cell resting states, which causes RIG-I to be in an inhibitory state. As a virus PAMP, RIG-I undergoes conformational changes by hydrolyzing ATP, which exposes the RNA binding domain. RIG-I binds to viral RNA via closer interactions and is activated to interact with MAVS.⁹⁹

Positive Regulatory Factors on RIG-I

Posttranslational modification is crucial for controlling RIG-I-mediated signaling. Numerous host factors, including ubiquitin ligases and protein kinases, regulate RIG-I (Figure 1). The SPRY domain of TRIM25 at the carboxy terminus interacts with the N-terminal CARD domain of RIG-I, which promotes K63-linked ubiquitination and significantly enhances RIG-I-induced signaling pathways.^{11,12} TRIM4 also plays a crucial role in controlling virus-triggered IFN induction by facilitating the K63-linked ubiquitination of RIG-I.¹³ RNF135 is another ubiquitin ligase that preferentially binds to the RIG-I CTD and facilitates the polyubiquitination of K63 at K788, K849, K851, K888, K907, and K909. Elimination of RNF135 leads to significant impairments in the body's natural antiviral immune reaction, including reduced production of type I IFN and decreased survival rates in mice infected with the virus. RNF135-driven RIG-I ubiquitination plays a vital role in natural antiviral immune responses.¹⁴ RNF135 enhances the interaction of TRIM25 with RIG-I, which increases the activation of RIG-I via TRIM25.^{100,101} NDR2 enhances the antiviral immune reaction by promoting the activation of RIG-I in macrophages via TRIM25.¹⁰² MEX3C is an E3 ubiquitin ligase that aligns with RIG-I within the stress granules of cells infected by viruses, and its increased expression triggers the lysine-63-linked ubiquitination of RIG-I, which activates the IFN- β promoter.¹⁵ Human hemoglobin subunit beta (hHB) amplifies the RIG-I-mediated antiviral reactions via the promotion of RIG-I ubiquitination, which is contingent on hHB-induced reactive oxygen species (ROS).¹⁶ In addition to the Lys63-linked ubiquitin of RIG-I, several deubiquitinating enzymes participate in the regulation of RIG-I activity. USP4 and ovarian tumor-domain-containing ubiquitin aldehyde-binding protein 1 (OTUB1) help stabilize RIG-I proteins by removing the K48-linked ubiquitin chains attached to RIG-I.^{18,19}

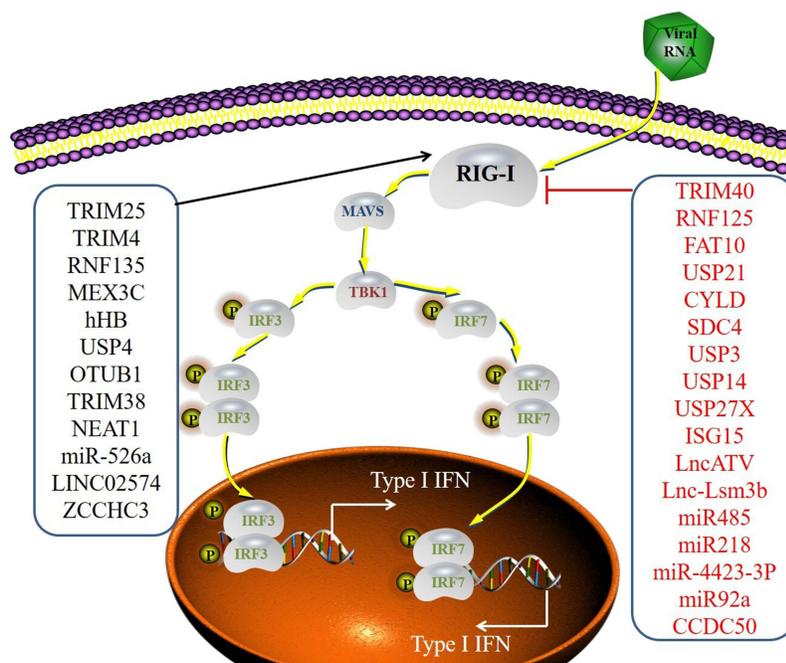


Figure 1 The regulator of the RIG-I signaling pathway. RIG-I recognizes RNA derived from actively replicating RNA viruses. RIG-I contains CARD-like structures that mediate interactions with the adaptor MAVS. MAVS initiates signaling pathways leading to IRF3 and IRF7 via TBK1. Activated IRF3 and IRF7 form dimers and translocate to the nucleus to induce the production of type I IFN. RIG-I is regulated by various mechanisms, such as PTMs (phosphorylation, ubiquitylation, SUMOylation and ISGylation) and small non-coding RNAs.

SUMOylation inhibits the K48-linked degradation of RLRs. TRIM38 actively controls RIG-I and MDA5 via SUMOylation at K43/K865 and K96/K888, respectively.²⁰

LncRNA also enhances the function of RIG-I in a positive manner. For example, the lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1) stimulates the RIG-I-IRF7 signaling pathway by enhancing RIG-I expression, which suppresses Hantaan virus (HTNV) infection.²¹ LINC02574 inhibits IAV replication by increasing the expression of RIG-I, MDA5 and TLR3 and promoting the phosphorylation of IRF3, which beneficially modulates the innate immune reaction.²²

Recent research suggests that miRNAs help control RLR signaling. MiR-136 is an immune agonist for RIG-I that leads to the buildup of IL-6 and IFN- β in A549 cells, and ultimately to the inhibition of IAV infection.²³ RNA virus infection upregulates the production of miR-526a via IRF-dependent pathways. Therefore, miR-526a positively regulates the production of virus-induced type I IFN and prevents virus replication, primarily via the amplification of RIG-I K63 ubiquitination by miR-526a, which is achieved by inhibition of CYLD expression.¹⁷

Negative Regulatory Factors on RIG-I

K48-linked polyubiquitination controls the expression of RIG-I, which is a widely recognized process for protein degradation that is reliant on proteasomes. A number of E3 ligases that inhibit RIG-I have been reported (Figure 1). For example, TRIM40 attaches to RIG-I, which facilitates its polyubiquitination linked to K27 and K48 via its E3 ligase function and promotes the degradation of RIG-I by the proteasome to ultimately suppress the production of IFN.⁴⁸ Parkin is an E3 ubiquitin-protein ligase that facilitates mitophagy, which inhibits the activation of RIG-I and MDA5 via the direct interaction and catalysis of K48-linked polyubiquitination and leads to the degradation of RIG-I and MDA5.⁵⁰ RNF125 is an ubiquitin ligase that facilitates the K48-linked polyubiquitination of RIG-I, which leads to the degradation of RIG-I via proteasomes and a reduction of RIG-I-triggered IFN- β synthesis.⁴⁹ During the advanced phase of infection, SUMO-specific protease 2 (SEN2) promotes the de-SUMOylation of RIG-I and MDA5, which lead to their K48-linked polyubiquitination and degradation.²⁰ The process of ubiquitination is reversible. Multiple additional mechanisms that block the activation of RIG-I via inhibition of the K63-linked polyubiquitin chains on RIG-I have been demonstrated. USP21 is an enzyme responsible for deubiquitination, and it eliminates the K63-linked polyubiquitin chain from RIG-I, which suppresses innate immune reactions.⁵² CYLD is a different enzyme involved in deubiquitination, and it eliminates the K63-linked polyubiquitin chain from RIG-I to act as a negative regulatory factor.⁵³ Syndecan-4 (SDC4) is a transmembrane (TM) protein that forms complexes with RIG-I and CYLD and facilitates the CYLD-driven deubiquitination of RIG-I, which inhibits the IFN signaling pathway.⁵⁴ USP3, USP14, and USP27X remove K63-linked ubiquitin from RIG-I, which hinders RIG-I function.^{55–57} In addition to deubiquitinating enzymes and ubiquitin ligases, the regulatory mechanism of RIG-I via modifications similar to ubiquitin has been reported. Preliminary research indicated that conjugation of the IFN-inducible ubiquitin-like protein ISG15 (ISGylation) to RIG-I suppressed the expression of RIG-I.⁵⁸ Earlier research indicated that the non-covalent attachment of FAT10 to RIG-I reduced the solubility of the RIG-I protein, which decreased RIG-I-mediated IFN expression.⁵¹

Long noncoding RNAs (lncRNAs) influence innate immune reactions by controlling RIG-I. The IFN-triggered lncRNA Lnc-Lsm3b competes with viral RNAs for binding to RIG-I monomers, which leads to the deactivation of RIG-I innate function in the advanced phase of the innate immune response.⁵⁹ Analogous to Lnc-Lsm3b, the lncRNA inhibitor of antiviral signaling (lncATV) is a strong inhibitor of RIG-I, which suppresses the synthesis of IFN-I and IFN-stimulated genes (ISGs) to avoid excessive activation of signaling pathways.⁶⁰

The host generates miR-485, which targets and eliminates RIG-I mRNA to slow the antiviral reaction and increase viral multiplication.⁶¹ A correlational study pinpointed miR-218 as an innovative viral-triggered miRNA triggered that disrupted RIG-I expression and hindered interferon production to aids in viral immune evasion.⁶² MiR-4423-3p significantly enhances HCV infection by inhibiting the RIG-I/IFN pathway via direct attachment to RIG-I mRNA.⁶³ MiR-92a specifically targets RIG-I and diminishing its expression to decrease the VSV-induced activation of TBK1 and IRF3, which are vital for initiating the transcription of type-I IFN genes.⁶⁴

Melanoma Differentiation-Associated Gene 5 (MDA5)

MDA5 exhibits a similar sequence and structural resemblance to RIG-I. In contrast to RIG-I, MDA5 shows amino acid similarities of 23% and 35% in the N-terminal tandem CARD and C-terminal helicase domains, respectively. MDA5 is primarily identifies members of the small RNA virus family. However, there is growing evidence that the types of viruses identified by MDA5 are not specific. MDA5 also identifies Dengue, West Nile, respiratory enteroviruses and murine noroviruses. The viruses identified by MDA5 are not limited to RNA viruses. Recent studies have shown that MDA5 also identifies HDV. Various processes govern the function of MDA5, including posttranslational modifications (PTMs) and immunomodulatory noncoding RNAs⁹⁹ (Figure 2).

Positive Regulatory Factors on MDA5

Earlier research demonstrated that multiple types of PTMs regulated MDA5 activity, including phosphorylation, ubiquitylation, SUMOylation and ISGylation. Phosphorylation of the 2 CARDS and the CTD of MDA5 inhibit abnormal activation in resting cells.^{24,67} Once a viral RNA is identified by MDA5, phosphatase 1 (PP1) removes phosphate groups from MDA5, which triggers the activation of its subsequent signaling pathways.^{24,25} Excessive activation of MDA5 leads to systemic lupus erythematosus-like autoimmune diseases. Therefore, the phosphorylation of MDA5 is likely to be crucial for the prevention of harmful MDA5 activation in cells without infection.

The MDA5 protein exhibits polyubiquitination. Similar to the RIG-I protein, K63-linked polyubiquitin chains bind to the CARD domain of MDA5.²⁶ The K174 residue of the MDA5 CARD domain is vital for this binding. A ubiquitination-defective K174A mutant of MDA5 did not trigger type I IFN expression. TRIM65 facilitates ubiquitination linked to K63 at Lys743 of MDA5, which increases the oligomerization of MDA5 on dsRNAs.²⁷ The ISGylation of MDA5 is similar to K63-linked ubiquitination, and it is controlled by phosphorylation, which facilitates the oligomerization of CARDS and the assembly of MDA5 filaments.¹⁰³ Current research identified multiple proteins that interact with MDA5 and modulate its function. Pulldown and coimmunoprecipitation assays of glutathione S-transferase revealed that porcine 20–50-oligoadenylate synthetase-like protein (pOASL) binds to MDA5, which amplified MDA5-driven type I IFN signaling.³⁰ The chaperone protein 14-3-3 η enhances antiviral innate immunity by aiding in the

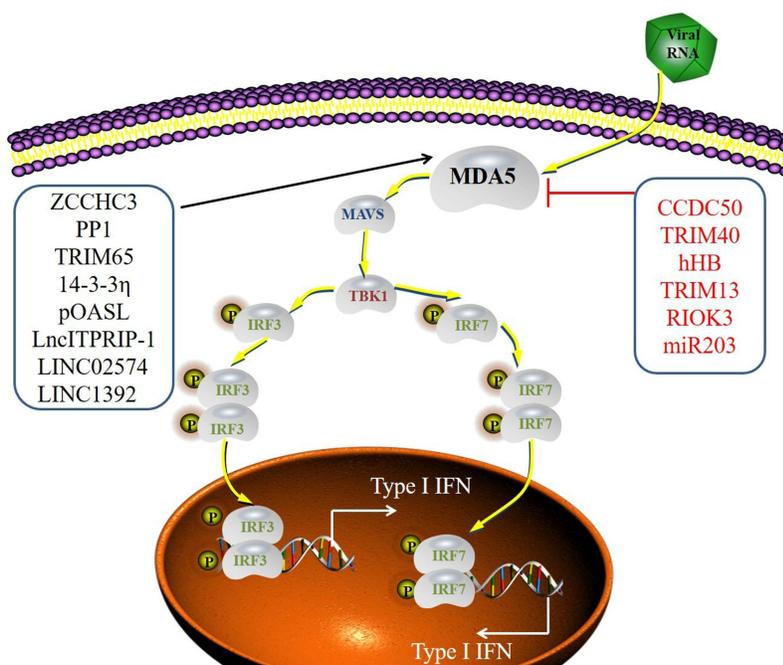


Figure 2 The regulator of the MDA5 signaling pathway. MDA5 recognizes RNA derived from actively replicating RNA viruses. MDA5 contains CARD-like structures that mediate interactions with the adaptor MAVS. MAVS initiates signaling pathways leading to IRF3 and IRF7 via TBK1. Activated IRF3 and IRF7 form dimers and translocate to the nucleus to induce the production of type I IFN. RIG-I is regulated by various mechanisms, such as PTMs (phosphorylation, ubiquitylation, SUMOylation and ISGylation) and small non-coding RNAs.

oligomerization of MDA5 and its redistribution within cells.²⁹ The zinc-finger protein ZCCHC3, which acts as a co-receptor for RIG-I and MDA5, attaches to dsRNA and increases the attachment of RIG-I and MDA5 to dsRNA. ZCCHC3 also recruits the E3 ubiquitin ligase TRIM25 to the RIG-I and MDA5 complexes, which aids in its K63-associated polyubiquitination and activation.²⁸

LncRNAs play a role in controlling MDA5 activation, and lncITPRIP-1 amplifies the natural immune reaction to viral infections by encouraging oligomerization and activating MDA5.³¹ LINC02574 suppresses the replication of IAV by increasing the expression of RIG-I, TLR3 and MDA5 and the phosphorylation of IRF3 and the production of IFN.²² LINC1392 enhanced the expression of several interferon-stimulated genes (ISGs), such as IFIT1, IFIT2, and IFITM3, by stimulating MDA5, which hindered the replication of coxsackievirus B5 (CVB5) in vitro.³²

Negative Regulatory Factors on MDA5

TRIM40 attaches to the CARD domain of MDA5 and accelerates the K27- and K48-linked polyubiquitination of MDA5, which results in the proteasomal degradation of MDA5.⁴⁸ Viral infection amplifies the expression of CCDC50, and CCDC50 specifically recognizes RLRs that are K63-polyubiquitinated, which delivers the activated RIG-I/MDA5 for degradation by autophagy and inhibits the type I interferon (IFN) signaling pathway.⁶⁵ The protein kinase RIOK3 phosphorylates the CTD domain of MDA5 and inhibits IFN expression mediated by MDA5. However, RIOK3 does not phosphorylate the CARD domain of MDA5, and a different protein kinase likely phosphorylates the CARDS of MDA5.⁶⁷ The E3 ubiquitin ligase TRIM13 in immune cells shows increased expression in macrophages derived from bone marrow after stimulation with type I IFN inducers. TRIM13 interacts with MDA5 to inhibit the MDA5-mediated production of type I IFN in vitro during EMCV infection.⁶⁶ Human hemoglobin subunit beta (hHB) impedes MDA5-driven antiviral signals by inhibiting the MDA5–dsRNA interaction.¹⁶ The dual-luciferase reporter assay results showed that miR-203 targeted the MDA5–3'UTR sequence, and miRNA-203 may act as an inhibitor of MDA5 in miiuy croaker.⁶⁸

Toll-Like Pattern Recognition Receptors (TLRs)

TLRs are highly expressed in many types of cells, such as macrophages, dendritic cells, neutrophils, natural killer cells, and fibroblasts.¹⁰⁴ TLRs are a class of transmembrane proteins that include an extracellular region, transmembrane region, and the Toll interleukin-1 receptor region (TIR). The extracellular region is a leucine-rich repeat sequence that recognizes PAMPs of pathogens.¹⁰⁵ Transmembrane and TIR regions bind to adaptor proteins to activate downstream signaling pathways. Thirteen toll-like receptors have been reported. TLR1-9 is conserved in humans and mice. TLR10 lost function after retroviral insertion in mic, but TLR11-13 is only expressed in mice.^{106–108}

The localization of TLRs differs. TLR2, TLR4 and TLR5 are located on the outer membrane of the cell, and TLR3, TLR7, TLR8 and TLR9 are located on the endosome. Different TLRs recognize different ligands, which are primary membrane structures of microorganisms, such as lipids, lipoproteins, and proteins. TLR4 recognizes the lipopolysaccharides of Gram-positive bacteria.^{109,110} TLR2 combines with TLR1 or TLR6 to bind various bacterial components, such as peptidoglycan from Gram-positive bacteria, lipopeptides, lipoprotein bacteria, and mycoplasma lipopeptides.^{111–114} TLR3 primarily recognizes double-stranded RNA (dsRNA) during viral replication, such as hepatitis C virus (HCV), Japanese encephalitis virus (JEV), dengue virus (DENV), and enterovirus 71 (EV71).¹¹⁵ TLR5 primarily recognizes the flagella of bacteria.¹¹⁶ TLR7 recognizes synthetic imidazoline-like quinoline molecules, guanosine analogs, or single-stranded RNA (ssRNA) from viruses, such as human immunodeficiency virus type I (HIV-1), vesicular stomatitis virus (VSV), and influenza viruses, as well as certain small interfering RNAs (siRNAs).^{117,118} TLR9 recognizes CpG-DNA sequences in bacteria and viruses.^{119,120} Human TLR8 recognizes single-stranded RNA (ssRNA), but mouse TLR8 is nonfunctional. All TLRs mediate the production of inflammatory cytokines. The activation of TLR3, TLR4, TLR7, TLR8, and TLR9 leads to the production of IFNs, which are important for antiviral immune responses. This review focuses on Toll-like pattern recognition receptor 3, which recognizes viruses (Figure 3).

Toll-Like Pattern Recognition Receptor 3 (TLR3)

Toll-like receptor 3 (TLR3) facilitates the transcriptional activation of type I interferons (IFNs), proinflammatory cytokines and chemokines, which together form an antiviral response in hosts. In contrast to other TLR family proteins,

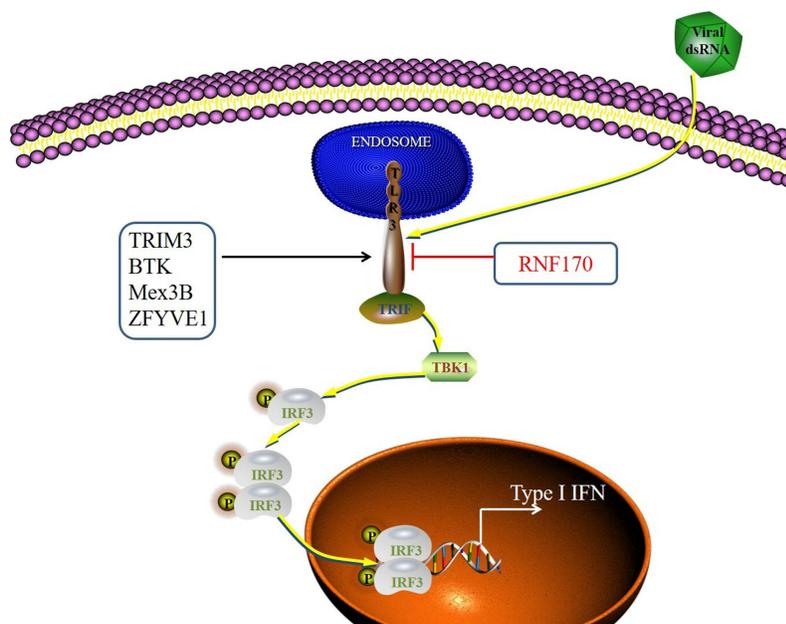


Figure 3 The regulator of the TLR3 signaling pathway. TLR3 recognizes viral dsRNA. TLR3 mediates the interaction with the adaptor TRIF. TRIF initiates signaling pathways leading to IRF3 via TBK1. Activated IRF3 dimerizes and translocates to the nucleus to induce the production of type I IFN. TLR3 is regulated by various mechanisms, such as PTMs.

TLR3 entirely relies on the Toll/interleukin-1 receptor (TIR) domain-containing adaptor inducing IFN- β (TRIF) for RNA sensing.¹²⁰ TLR3 and TRIF interact to recruit TNF receptor-associated factor (TRAF3) and activate two kinases, TANK-binding kinase 1 (TBK) and inhibitor- κ B kinase ϵ (IKK ϵ). Ultimately, the transcription factor IRF3 is activated by phosphorylation and dimerizes. The IRF3 dimer translocates from the cytoplasm to the nucleus where it induces the production of type I IFN.

Positive Regulatory Factors on TLR3

TLR3 activation is linked to K63-linked polyubiquitination. The E3 ubiquitin ligase TRIM3 primarily resides in the Golgi apparatus and is transported to early endosomes when stimulated by the dsRNA analog poly (I:C). TRIM3 facilitates the K63-associated polyubiquitination of TLR3 at K831, a process that intensifies after poly (I:C) stimulation.³³ Bruton's tyrosine kinase (BTK) in macrophages increases the production of inflammatory cytokines and IFN- β via TLR3, which suppresses intracellular dengue virus infection.³⁵ Mex3B is an RNA-binding protein that enhances TLR3-mediated signaling in two distinct manners. The attachment of Mex3B to dsRNA enhances the ability of TLR3 to bind to dsRNA. Mex3B facilitates the proteolytic processing of TLR3, which is essential for its activation.³⁶ Mex3B enhances the innate immune response by facilitating the K63-linked ubiquitination of TLR3.³⁴ The FYVE domain of ZFYVE1 increases TLR3-driven innate immune and inflammatory responses by facilitating the binding of ligands to TLR3.³⁷

Negative Regulatory Factors on TLR3

E3 ubiquitin ligases and deubiquitinase act as master regulators of TLR signaling by co-regulating the dynamic and reversible ubiquitination process.¹²¹ The TLR3-binding E3 ligase RNF170 mediates the K48-linked poly-ubiquitination of K766 in the TIR domain of TLR3. RNF170 selectively inhibits the TLR3-mediated pathway by promoting TLR3 degradation via the proteasome pathway.⁶⁹

Intracellular DNA Sensors

RNA viruses induce immune responses by activating TLR or RLR signaling pathways, and DNA viruses are recognized by other types of pattern recognition receptors, such as DDX41, IFI16, and cGAS. Compared to the regulation of RLRs by PTMs, we know little about PTMs that directly regulate cGAS or IFI16 activity. Recent studies have shown that

phosphorylation, acetylation, and glutamylation play important roles in controlling these sensors. However, the mechanism by which host factors regulate the production of IFN via PTMs on DDX41 and IFI16 has rarely been reported. The following section focuses on the host regulators of the pattern recognition receptor cyclic adenylyl synthetase (cGAS).

Cyclic Adenylyl Synthetase (cGAS)

cGAS contains one nucleotidyl transferase domain and two DNA-binding domains. cGAS is self-inhibited in the resting state. cGAS can bind to DNA in the cytoplasm to form a 2:2 complex, which is activated by conformational changes and catalyzes the cyclization of adenosine triphosphate (ATP) and guanosine (GTP) to form the second messenger cyclic guanosine (cGAMP).^{120,122} cGAMP binds to the adaptor protein STING, located in the ER, to cause a conformational change in STING, which may be the cause of STING activation. Activated STING migrates from the endoplasmic reticulum to the Golgi apparatus.¹²³ During the transfer process, the carboxyl terminus of STING recruits and activates TBK1, which forms dimers after phosphorylation and activation of the transcription factor IRF3. IRF3 migrates from the cytoplasm to the nucleus to induce IFN- β production. STING also activates the IKK complex, and the IKK complex can phosphorylate and ubiquitinate the NF- κ B transcription inhibitor I κ B- α to separate I κ B- α from NF- κ B, which promotes its activation. Translocation to the nucleus induces the production of inflammatory factors, such as TNF, IL- β , and IL-6.^{124,125}

cGAS is activated by double-stranded DNA, such as HSV-1. Its ability to recognize DNA is not sequence specific. The crystal structure of the cGAS and DNA complex indicates that cGAS primarily binds to the sugar-phosphate chain of double-stranded DNA. Single-stranded DNA is also recognized by cGAS via the formation of internal double-stranded structures. The cGAS-STING signaling pathway produces an immune response against the invasion of DNA-containing pathogens and generates an anti-tumor immune response. However, overactivation of the cGAS-STING signaling pathway by DNA may also lead to autoimmune and inflammatory diseases, such as systemic lupus erythematosus. Therefore, proper regulation of the cGAS-STING signaling pathway is crucial for protection against foreign pathogens.¹²⁶ Posttranslational modifications, such as phosphorylation, ubiquitination, SUMOylation, and acetylation, play key roles in cGAS signaling regulation¹²⁷ (Figure 4).

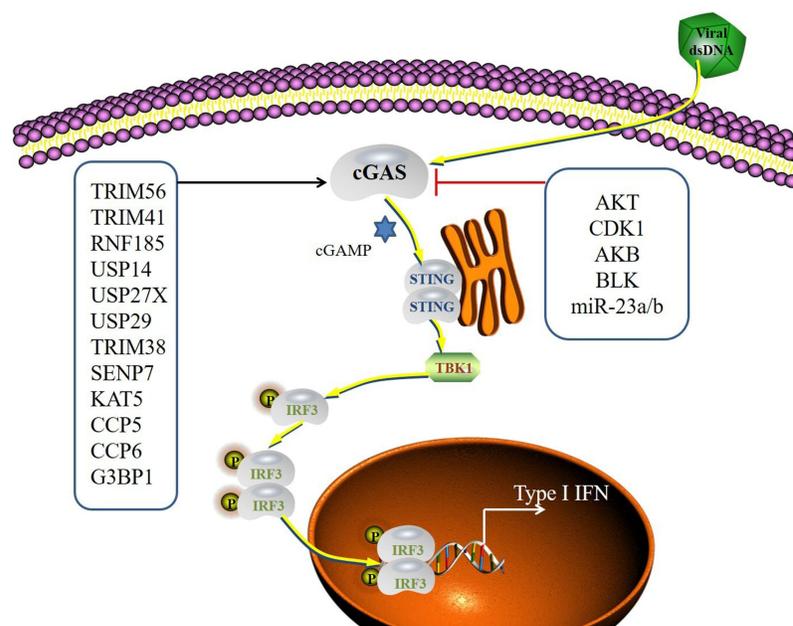


Figure 4 The regulator of the cGAS signaling pathway. cGAS recognizes viral dsRNA and activates a STING-dependent signaling pathway. STING initiates signaling pathways leading to IRF3 via TBK1. Activated IRF3 dimerizes and translocates to the nucleus to induce the production of type I IFN. cGAS is regulated by various mechanisms, such as PTMs (phosphorylation, ubiquitylation, SUMOylation, glutamylation and acetylation) and small non-coding RNAs.

Positive Regulatory Factors on cGAS

Ubiquitination

Several ubiquitin ligases have been identified as regulators of cGAS activity. TRIM56 is an E3 ligase that monoubiquitinates cGAS at Lys335 to significantly enhance its dimerization, DNA-binding ability and cGAMP generation.³⁸ Like TRIM56, TRIM41 also increases the production of IFN by promoting cGAS monoubiquitination.³⁹ RNF185 is an ER ubiquitin ligase that specifically facilitates the K27-linked polyubiquitination of cGAS at K-384 to enhance its enzymatic function and IFN production.⁴⁰ Patients with systemic lupus erythematosus (SLE) exhibit continuous activation of cGAMP-STING signaling¹²⁸ and increased RNF185 mRNA levels. Whether the increase in RNF185 mRNA plays a role in enhancing cGAS-STING signaling is not certain. Reports indicate that during DNA virus infection, TRIM14 enlists USP14 to eliminate K48-linked ubiquitin chains at the Lys414 site in h-cGAS, which results in cGAS stabilization and the enhancement of antiviral innate immunity.⁴¹ Similarly, USP27X⁴² and USP29⁴³ contribute to the stabilization of cGAS proteins via the removal of K48-linked polyubiquitin chains from cGAS, and both of these factors act as enhancers of innate immunity to combat DNA viral infections.

SUMOylation

Similar to ubiquitination, TRIM38 preserves the SUMOylation of m-cGAS at the Lys217 and Lys464 residues (equivalent to Lys231 and Lys479 in hcGAS), which inhibit the K48-linked polyubiquitination and degradation of cGAS.⁴² Another study revealed that SENP7, a protease specific to SUMO, played a positive role in controlling cGAS-mediated signaling. cGAS undergoes SUMOylation at K335, K372, and K382. Because the SUMOylation sites are located on the DNA-binding surface or dimerization interface of cGAS, the SUMOylation of cGAS at these locations hinders its capacity for DNA binding and self-association. Upon HSV-1 infection, SENP7 actively engages with cGAS to deSUMOylate cGAS and consequently activating cGAS.⁴⁴

Acetylation

The acetylation process of cGAS can control its activity in a positive or negative manner depending on the specific acetylation location. Protein acetylation of lysine residues is facilitated by acetyltransferases and deacetylases.¹²⁹ In the resting state, deacetylation of hcGAS at the Lys384, Lys394, and Lys414 residues enhances cGAS activity.¹³⁰ Recently, the lysine acetyltransferase KAT5 was shown to acetylate the N-terminal region of human cGAS at the Lys47/Lys56/Lys62/Lys83 residues. Acetylation enhances the binding of cGAS to DNA and its activity in response to DNA challenge.⁴⁵ Additional functional verification indicated that acetylation at Lys198 enhanced the activation of h-cGAS. Notably, quantitative proteomic analysis revealed a reduction in h-cGAS-Lys198 acetylation following infection by HSV-1 or HCMV (human cytomegalovirus), which suggests that these DNA viruses bypass innate immune monitoring by commandeering the acetylation of cGAS at these locations.¹³¹

Glutamylation

Glutamylation is a posttranslational alteration that is facilitated by tubulin tyrosine ligase-like (TTLs) glutamylases and is counteracted by enzymes belonging to the cytosolic carboxypeptidase (CCP) family.¹³² Glutamylation stringently controls cGAS. Mice lacking CCP5 or CCP6 are sensitive to DNA virus infections due to the unsuccessful activation of type I interferons.⁴⁶ This study revealed that polyglutamatergic TTL6 at Glu272 reduces the binding capacity of cGAS for DNA, and monoglutamatergic TTL4 at Glu302 inhibits the enzymatic function of cGAS. Conversely, CCP6 and CCP5, which are analogous to TTL6 and TTL4, respectively, facilitate the deglutamylation of cGAS at glu272 and glu302, which alleviates the inhibitory impact of glutamylation. TTL4, TTL6, CCP5, and CCP6 collaboratively influence cGAS-driven immune reactions by dynamically controlling cGAS glutamylation. However, the mechanism by which these enzymes are activated or controlled to regulate the glutamylation, and deglutamylation of cGAS is ambiguous. Additional research is required to clarify this question and enhance our understanding of cGAS regulation.

In addition to the posttranslational modifications of cGAS, some host factors promote IFN synthesis by directly increasing the formation of cGAS complexes. For example, the GTPase-activating protein SH3 domain-binding protein 1 (G3BP1) plays a pivotal role in DNA detection and the effective activation of cGAS, and G3BP1 enhances the binding of cGAS to DNA by facilitating the formation of cGAS complexes.⁴⁷

Negative Regulatory Factors on cGAS

Phosphorylation

The phosphorylation of cGAS by serine kinases, including serine/threonine protein kinase (AKT), cyclin-dependent kinase-1 (CDK1), and Aurora kinase B (AKB), inhibits cGAS function, which affects the immune response.^{70–72} Infection by HSV-1 in 293T cells triggers AKT activation, which subsequently phosphorylates cGAS at positions S291 (m-cGAS) and S305 (h-cGAS).⁷¹ The phosphorylation of cGAS at positions S291/S301 hindered the production of cGAMP, which affected the generation of type I IFNs.⁷¹ Another study revealed that HSV-1 infection in human primary fibroblasts and HEK293T cells led to the phosphorylation of cGAS at various serine residues (Ser37, Ser116, Ser201, Ser221, and Ser263), which inhibited cGAS function during their posttranslational alteration. However, the specific signaling mechanisms involved in this phosphorylation are not clear.¹³¹ Zhong et al demonstrated a comparable reduction in cGAS activity following phosphorylation at the S305 site by the CDK1-cyclin B kinase complex in cells undergoing mitosis.⁷² Recent findings by Li et al revealed that AKB hyperphosphorylation of the cGAS N-terminus at specific serine and threonine sites (Ser13, Ser37, Ser64, Thr69, Thr91, Ser116, Ser129, and Ser143) inhibited chromatin DNA detection in cells undergoing mitosis.⁷⁰ Therefore, it seems likely that AKT, CDK1, and AKB regulate cGAS phosphorylation to manage cGAS activation in vital cell cycle stages, such as DNA replication and mitotic division. However, the phosphorylation of cGAS by these kinases was counteracted by protein phosphatase 1 (PP1)⁷² or PP6,¹³³ which restored the capacity of cGAS to sense DNA. Notably, cGAS encompasses multiple tyrosine residues whose functions are not known. Research revealed that the phosphorylation of Tyr215 in BLK (B lymphocyte kinase) in hcGAS resulted in the retention of cGAS within the cytoplasm, which is essential for the detection of cytosolic DNA.⁷³

cGAS activity is regulated by miRNAs. Overexpression of miR-23a/b markedly suppresses cytosolic DNA-induced innate immune responses.⁷⁴

Conclusion

Innate immunity is the first line of defense of host cells against the invasion of foreign microorganisms and resistance to the entry of viruses. It plays an important role in the invasion process. There are many host factors that regulate innate immune responses. Host factors promote the immune response and enhance the body's clearance of invading viruses. However, an excessive immune response leads to tissue damage and induces autoimmune diseases. Host factors suppress the immune response, so that the body cannot clear the virus quickly, which results in chronic infection. To balance the immune response induced by viral infection, the immune response was modified, and a complete regulatory mechanism was established. In this review, we focused on the host factors that regulate the IFN signaling pathway induced by virus infection via pattern recognition receptors. Pattern recognition receptors (RIG-I, MDA5, TLR3, and cGAS) are regulated by various mechanisms, such as PTMs (phosphorylation, ubiquitylation, SUMOylation and ISGylation) and small non-coding RNAs. Posttranslational modification is one of the key factors in host antiviral immune defense and viral immune escape, which strictly regulates the activation of the virus-induced innate immune response signaling pathway. Viral infection promotes the expression of host factors, which inhibit interferon production by targeting PRRs and results in immune escape. We found that some host factors regulate the production of IFNs via different PRRs. For example, ZCCHC3 positively regulates the IFN signaling pathway via MDA5 and RIG-I, which suggests crosstalk between different PRR-mediated IFN signaling pathways. Exploring the regulatory role of host factors on PRRs will help us better understand the mechanism of antiviral immune defense in the body and provide targets and a theoretical basis for accurate clinical diagnosis and treatment of virus-related diseases caused by IFNs. Increasing focus has been placed on the functions of PRRs in autoimmune disorders and cancer-fighting immunity, but the regulatory mechanisms of PRRs by environmental, pathogen and host factors are largely unknown. Delving deeper into these inquiries will undoubtedly elucidate our comprehension of PRR-driven PAMP detection pathways and help formulate approaches to avert and manage associated diseases.

Author Contributions

All authors made a significant contribution to the work reported, whether in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all of these areas, took part in drafting, and revising or critically

reviewing the article. All authors gave final approval of the manuscript version to be published, agreed on the journal for submission, and agreed to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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