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New Developments in the Study of the Mechanisms by Which RNA Viruses Evade Natural Immunity

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Abstract: *Viral infection triggers an immune response through signal transduction. Cyclic guanosine-adenylate synthetase (cGAS) recognises viral DNA and interacts with the interferon gene stimulating protein (STING) to mediate the production of interferon type 1 (IFN1). The retinoic acid-inducible gene 1 (RIG-1) receptor recognises viral RNA and activates IFN1 by triggering the RIG-1 signalling pathway via the mitochondrial antiviral signalling protein (MAVS). STING not only serves as a DNA viral signalling pathway protein, but also interacts with MAVS and participates in the RNA viral signalling pathway. However, the proteases of RNA viruses, such as dengue virus and hepatitis C virus, escape from the immune system by interacting with STING and inhibit IFN production. In this paper, we review the interaction mechanism between STING and MAVS, and the escape of RNA viruses from the immune system through STING, in order to provide new ideas for the study of viral escape from the natural immune regulation mechanism. Cellular autophagy is a metabolic process widely found in eukaryotic organisms, which is mainly involved in maintaining cellular homeostasis and cellular material recycling by degrading damaged organelles and macromolecules in cells. It has been found that autophagy can participate in the infection process of RNA viruses, and the viruses have evolved a certain mechanism to regulate autophagy to promote their own proliferation. In this paper, we also review the progress of the interaction between RNA virus infection and cellular autophagy in recent years, with a view to providing some reference for antiviral research.*

Keywords: *Stimulator of Interferon Genes, Mitochondrial Antiviral Signalling Protein, Natural Immunity, RNA viruses, Autophagy*

1. Introduction

Natural immunity, also known as innate immunity, is the first line of defense against foreign invasion that organisms have gradually developed over a long period of evolution. The natural immune system recognizes pathogen-associated moleoular pattern (PAMP) through pattern recognition receptor (PRR), which activates the signal transduction pathway to induce interferon (IFN), inflammatory factors to establish an effective defense in the host. Currently, the discovered cellular PRRs mainly include Toll-like receptor (TLR), nucleotide-binding oligomerisation domain (NOD)-like receptor (NLR), and NOD-like receptor (NLR) and retinoic acid-inducible gene 1 (RIG-1)-like receptor (RLR) [1]. Three types of RLRs have been reported, namely RIG-1, melanoma differentiation associated gene 5 (MDA5) and LGP2 (laboratory of genetics and physiology 2) [2]. Viral RNAs entering the host are mainly recognized by two types of PRRs, endosomally located TLRs (e.g., TLR3, TLR7, etc.) and cytoplasmic RLRs (e.g., RIG-1, MDA5, etc.), with RIG-1 and MDA5 being the major receptor proteins for intracellular viral RNAs. In addition, viral DNA is also a signalling molecule of the innate immune system, which has been poorly investigated until the discovery of DNA PRRs and their downstream effectors, especially the stimulator of interferon genes (STING), which has opened up a new way of studying the innate immunity triggered by viral DNA.

2. MAVS Mediates the Viral RNA-induced Signaling Pathway

MAVS is also known as CARD adaptor inducing IFN-β (CARDIF), IFN-β promoter stimulator 1 (IPS-1) or virus-induced signaling adapter (VISA) [3]. MAVS mainly consists of three structural domains:

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the N-terminal CARD, the intermediate proline protein, the N-terminal CARD, the intermediate proline protein, and the intermediate proline protein. MAVS consists of three main domains: the N-terminal CARD, the intermediate proline domain, and the C-terminal conserved hydrophobic transmembrane domain (transmembrane, TM) [4]. MAVS is localized in the outer mitochondrial membrane through its own TM region, and it is the first mitochondrial innate immunity-associated protein found in mitochondria.

RIG-1 and MDA5 are both RNA deconjugating enzymes consisting of two N-terminal CARDs, an RNA deconjugating enzyme structural domain and a C-terminal repressor structural domain. Upon RNA virus infection, RNA deconjugase (RIG-1/MDA-5) recognises virus-derived RNA ligands and activates the ATP hydrolysis enzyme of RIG-1/MDA-5, resulting in a conformational change of CARDs, and the exposed CARDs are polyubiquitylated to form K63 linkages in the presence of ubiquitin ligases TRIM56 and RNF135 [5]. Subsequently, the conformationally altered RIG-1/MDA-5 translocates to the mitochondrial outer membrane and interacts with the CARD motifs of MAVS, while the MAVS protein TM structural domain mediates its own dimerisation, and the activated MAVS recruits downstream signalling molecules [6]. On the one hand, through the C-terminal tumour necrosis factor receptor associated factor (TRAF) structural domain binding with TRAF3 to form a functional complex, activating two important downstream kinases TANK-binding kinase 1 (TBK1) and nuclear factor κB (NF-κB) kinase ε inhibitor (inhibitor of kappa light polypeptide gene enhancer in B cells, kinase epsilon kinase, IKBKE). Interferon regulatory factor 3 (IRF3) and IRF7 are phosphorylated and dimerised by TBK1/IKK-i, and then rapidly enter the nucleus and bind to the corresponding cis-acting elements to induce IFN1 production [7]. On the other hand, MAVS binds to the signalling protein TRAF6, an essential regulator upstream of the IKKα/β/γ kinase complex, through two TRAF6 binding motifs, and the signal-induced production of polyubiquitinated TRAF6 forms a complex that includes transforming growth factor- activated kinase 1 (TAK1) and TAK1-binding protein 2 (TAB2). TAK1 degrades IKKγ of the IKKα/β/γ complex through the ubiquitin pathway and activates IKKβ, which phosphorylates, ubiquitinates, and degrades the inhibitor of NF-κB (IκB) by the proteasome, and ultimately removes inhibitor of NF-κB [8], inducing the transcription of related genes.

3. STING Mediates Viral DNA-induced Signalling Pathways

STING is also known as mediator of interferon regulatory factor 3 activation (MITA), endoplasmic reticulum interferon stimulator (ERIS) or transmembrane protein 173 (TMEM173), is an important junction protein in the natural immune signalling pathway that regulates the production of IFN1, and it is mainly located on the endoplasmic reticulum (ER) and mitochondria [9]. The N-terminus consists of about 137 amino acids, forming four transmembrane structural domains (TM1 to TM4), which enable STING to be anchored to the ER. The C-terminus (amino acids 138 to 379) consists of a dimerisation domain (DD) and a cytoplasmic-oriented structural domain, with amino acids 341 to 379 being called the C terminal tail (CTT), which is an important part of IFN1 production [9].

Host double-strand DNA (dsDNA) pattern recognition receptors are divided into two categories: membrane receptors and intracellular receptors. It has been found that PRRs that recognize dsDNA and produce IFN1 intracellularly are articulated through STING, but how signaling activates STING has not been fully elucidated. The discovery of a novel DNA recognition protein, cyclic GMP-AMP synthase (cGAS) [10], provides a new way of thinking about the involvement of STING in novel antiviral immunomodulation. In the presence of Mg^{2+}, cGAS binds to viral dsDNA using a zinc finger structure and a positively charged surface, induces its own conformational transition that catalyses the formation of a 2'-5' GpA linkage and a 3'-5' ApG linkage, ultimately formatting 2'-3' cGAMP (cyclic GMP-AMP) [11,12]. cGAMP is recognised as a second messenger by STING, a junctional protein localized to the ER, which forms a K63-linked ubiquitination modification by the E3 ubiquitin ligase TRIM56, and undergoes membrane trafficking, translocating from the ER through the Golgi to the perinuclear puncta, a type of membrane structure [13], where the C-terminal end of STING serves as a scaffold for the recruitment of IRF3 and TBK1. Activated TBK1 phosphorylates several serine sites of STING (Ser358, Ser353, Ser379), enhances the affinity of STING for IRF3, and causes IRF3 to phosphorylate, dimerise and rapidly enter into the nucleus, thereby inducing the expression of IFN1 [14].

4. STING Interacts with MAVS to Recognize Viral RNA, Triggering Innate Immunity

STING not only recognizes viral DNA, but also plays an important role in the innate immune response induced by viral RNA. RNA viruses interact with STING through two different recognition mechanisms:

the replication intermediates and stem-loop structure of viral dsRNAs as well as the 5'-3p RNAs are recognized by RIG-1, which binds to STING via the C-terminal end of the MAVS to form a complex that activates STING [15, 16]. The second is that positive-stranded RNA can be recognized by cGAS, which generates cGAMP to activate STING [17], but the specific recognition mechanism is still unclear. In the first recognition mechanism, after the intracellular PRR RIG-1 is stimulated by viral RNA, the conformational change exposes the CARD structural domain, which transmits signals downward by interacting with the CARD of the MAVS, and STING, as a novel junction protein of the MAVS, can be activated by cGAMP [17]. As a new type of MAVS junction protein, STING binds to the C-terminus of MAVS at its N-terminus to form the MAVS-STING complex, and interacts with IRF3 to form the STING-IRF3 complex [18]. The two complexes are bound together by STING dimerization, and the complex moves from the ER, through the Golgi apparatus, to the perinuclear punctate structure and binds to TBK1 kinase, which phosphorylates and dimerises IRF3, and finally the IRF3 dimer enters the nucleus to activate the downstream IFN1 secretion signalling pathway.

Both ER retention and mitochondrial localization signals are present on STING, and it is presumably through this association that STING and MAVS continue to interact. Virus infection can transfer a tryptophan-aspartate repeat protein, WD40-repeatprotein (WDR5), from the nucleus to the mitochondria, where it binds to the C-terminal TM structural domain of MAVS [19]. Wang et al. [20] infected WDR5 knockdown cells with virus and found that RIG-1, MAVS and STING were inhibited, while TBK1-mediated signalling pathway was not inhibited, suggesting that WDR5 acted downstream of RIG-1 and STING, and upstream of TBK1, and revealing that WDR5 is a key molecule in recruiting RIG-1 and STING to the mitochondrial outer membrane of MAVS protein.

5. RNA Viruses Escape Immune System Surveillance through STING

While the innate immune system fights against viruses, some viruses have evolved mechanisms to escape or suppress innate immunity in favor of their own replication. For example, RNA viruses, such as hepatitis C virus (HCV), dengue virus (DENV), and severe acute respiratory syndrome-related coronavirus (SARS-CoV) have been identified proteases that can interact with the immune pathway junction protein STING to block signal transduction and inhibit IFN production.

5.1 Inhibition of IFN1 Production by Interaction Between HCV NS4B and STING

In 2006, Cheng et al. found that NS34A, a nonstructural (NS) protein with serine protease activity in HCV, could block the RIG-1-mediated signalling pathway and inhibit the expression of the IFN gene. It has also been shown that NS34A binds to MAVS in mitochondria, causing MAVS to break at cysteine 508, and the detached MAVS loses its ability to dimerise and bind to other intracellular signalling proteins (e.g., STING), which ultimately affects the production of IFN1 [21]. RNA viruses can directly interact with STING to escape the immune system and inhibit IFN production [22]. Parera et al. [23] and Nitta et al. [24] used bimolecular fluorescence complementation assay to co-transfect HEK293T cells with a tagged protein vector of NS4B N-terminal domain and C-terminal domain and a STING expression vector, demonstrated that the NS4B protease of HCV can specifically bind to STING. Among them, the NS4B N-terminal domains from 1 to 48 amino acids (NS4Bt1 to 84) and the C-terminal domains from 85 to 261 amino acids (NS4Bt85 to 261) were homologous to the structure of STING. Subsequent experiments using HEK293T cells co-transfected with STING and NS4Bt1-84, NS4Bt85-261 and IFN-β-Fluc vectors confirmed that NS4B directly interacts with STING through the N-terminal NS4Bt1-84 homologous domain to interfere with its binding to TBK1, inhibits the phosphorylation of IRF3 and weakens the production of IFN-β, but has no effect on the protein expression of STING itself. STING itself had no significant effect on protein expression and dimerisation. At the same time, it is also confirmed that NS4B affects the function of STING through direct interaction with STING, while NS34A and MAVS indirectly affect the function of STING, and finally block RIG-β. It also confirmed that NS4B affects the function of STING through direct interaction with STING while NS34A indirectly affects the function of STING through its interaction with MAVS, and ultimately blocks the RIG-1-mediated signalling pathway and inhibits the production of IFN1, which results in the formation of a different mechanism for HCV to inhibit the production of IFN.

5.2 Inhibition of STING by DENV Non-structural Proteins

DENV belongs to a subgroup of the genus *Flavivirus* in the family *Flaviviridae*, and there are four types, DENV1 to 4, with slightly different mechanisms of infection. The genomic RNA of DENV

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encodes not only structural proteins, but also seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5), which play different functions in the process of viral replication, among which NS2A, NS2B, NS3 are mainly involved in hydrolysis of polyproteins, NS2A, NS2B and NS3 are mainly involved in the hydrolysis of polyproteins, while NS4A and NS4B are related to RNA replication [25].

In 2009, Barber's team found that the serine protease NS4B of yellow fever virus (YFV) inhibited IFN1 production through STING, but the mechanism of action was not elucidated [26]. 2012, Aguirre et al. [27] infected dendritic cells derived from human monocytes with DENV, and found that its protease NS2B3 could bind to STING, leading to STING degradation and thus reducing the phosphorylation level of IRF3 [28]. In 2012, Aguirre et al. [27] infected human monocyte-derived dendritic cells with DENV and found that its protease, NS2B3, could bind to STING, leading to degradation of STING, thereby reducing the phosphorylation level of IRF3 and inhibiting IFN1 production. In addition, in addition to its protease activity, NS3 also plays the roles of deconjugating enzyme, nucleoside hydrolase and 5'triphosphatase in the process of viral RNA replication. 2015 Nadine [28] and others demonstrated that there are two ways in which DENV inhibits the production of IFN1, one is to block the downstream pathway through inhibition of MAVS. The other is to inhibit IFN gene expression by directly interacting with STING. The other is directly interacting with STING to inhibit the expression of IFN gene, and the NSs in different DENVs have different functions.NS2A and NS4B of DENV1, DENV2 and DENV4 inhibit the phosphorylation of TBK1 kinase and IFN synthesis by blocking the signalling of RIG-1, MDA5 and MAVS. In addition, NS4A of DENV1 alone also inhibited TBK1. NS2B3 of DENV2 and DENV4 blocked the downstream immune pathway by directly binding to STING, but did not interfere with the direct activation of TBK1 pathway. The interaction of STING with MAVS enables DENV to diversify in the pathways that inhibit IFN production.

5.3 Papain-like Proteases (PLP) of SARS-CoV Inhibits STING Dimerisation

In 2012, the antagonistic mechanism between coronavirus PLP and STING was also discovered [29, 30], among which the PLP of SARS-CoV was more clearly identified. Devaraj et al. [31] found that the PLP of SARS-CoV prevented the production of IFN1 by inhibiting the phosphorylation and dimerization of IRF3, and its transport to the nucleus, but did not find that this inhibitory effect was related to STING, and the inhibitory effect was not related to PLP activity, i.e. inactive PLP could also inhibit the production of IFN1. Devaraj et al. [31] found that PLP from SARS-CoV prevented IFN1 production by inhibiting IRF3 phosphorylation and dimerization and transport to the nucleus, but they did not find that this inhibitory effect was related to STING, and the inhibitory effect was not related to the activity of PLP, which means that inactive PLP could also inhibit IFN1 production. In 2014, Chen et al [32], by overexpressing STING or TBK1, which caused IRF3 phosphorylation, found that PLP still reduced its phosphorylation, proving that PLP of SARS-CoV directly interacted with STING to prevent STING from ubiquitylation, dimerisation and binding to the signalling molecule MAVS, and blocked the regulation of downstream IRF3 by STING-TRAF3-TBK1. STING-TRAF3-TBK1, blocking the regulation of downstream IRF3 and inhibiting the production of IFN1.

In summary, HCV, DENV and SARS-CoV interact with STING via the proteases NS4B, NS2B3 and PLP, respectively, to escape immune system surveillance and suppress IFN production. However, the activation and increased expression of STING by RNA virus infection implies that STING is a limiting factor for RNA virus infection.

6. Autophagy Promotes RNA Virus Replication and its Possible Mechanisms of Action

6.1 Autophagy Promotes RNA Virus Replication

Autophagy was originally thought to be an ancient host resistance mechanism (to invading pathogens) in eukaryotic cells. A growing body of research suggests that disease-causing microbes have evolved an ingenious system to escape this cellular degradation mechanism and even to use the induction of autophagy to promote their own replication [33]. Poliovirus (PV) infected cells can induce autophagy, which in turn promotes viral replication. There was a 3-fold increase in viral titer in Rapamycin (autophagy activator) pretreated cells, while there was a significant decrease in viral titer in 3-MA (autophagy inhibitor) pretreated cells [34]. The down-regulation of the expression of the autophagy-related gene Atg12 resulted in the inhibition of cellular autophagy, while the intracellular viral titer decreased 3-fold and the extracellular viral titer decreased 9-fold. These results suggest that cellular autophagy is favorable for virus synthesis and release [34].

HCV infection of host cells can induce autophagy and promote viral replication [35]. Suppression of the expression of Atg4B, a key protein molecule in the formation of autophagy, resulted in a 100-fold decrease in extracellular viral titers and deletion of the expression of Beclin-1 essentially completely inhibited extracellular viral production, all of which suggest that autophagic mechanisms are required for HCV replication and translation [35].

In addition to the above two viruses, a large number of other RNA viruses can also use autophagy to promote the completion of their own life cycle. The use of autophagy inhibitors or down-regulation of autophagy genes can, in turn, inhibit the proliferation of viruses and spread [33].

6.1.1 Autophagy Suppresses the Antiviral Immune Response

Autophagy plays an important role in intrinsic antiviral immunity, and the Atg5-Atg12 conjugation complex can be directly coupled to RIG-I and IFN-β promoter stimulator 1 (IPS-1). Ke et al. [36] found that HCV-infected hepatocellular carcinoma cells could induce unfolded protein response (UPR) and autophagy and inhibit pathogen-associated molecules. Autophagy inhibits pathogen-associated molecular pattern (PAMP)-mediated activation of IFN-β, which in turn promotes viral replication. Shrivastava et al. [37] also reported that Beclin-1 and Atg7 down-regulated expression could inhibit autophagy and thus reduce HCV replication, while increased expression levels of the antiviral proteins IFN-β, OAS1, and IFN-α mRNA were observed, which suggest that the activation of autophagy may inhibit the expression of antiviral proteins and thus favoring viral replication. In addition, DENV infection can induce autophagy, while autophagy-associated proteins Atg5-Atg12 can inhibit IPS-1-mediated activation of interferon stimulated genes (ISGs) and promote viral replication [38].

6.1.2 Autophagy Provides Attachment Sites for Viral Replication

The replication of RNA viruses is closely related to intracellular membrane structure, and it has been shown that the double-layered vesicular structure of autophagic vesicles provides anchoring and aggregation sites for replication complexes [39]. The non-structural proteins of DENV viruses, NS1 and dsRNAs, can be co-localized with autophagy marker molecules, LC3, and ribosomal proteins, L28, suggesting that some of the replicative/translational processes of DENV could be completed on the autophagic vesicles [40]. In enterovirus A71 (EV-A71) infected mouse neurons, co-localization of coat protein VP1 and autophagosomes was observed [41]. Co-localization of non-structural protein 3A, coat protein VP1 and autophagosomes in encephalomyocarditis virus (EMCV) infected cells was observed [42]. In foot and mouth disease virus (FMDV) infected cells, non-structural proteins 2B, 2C, 3A and LC3 co-localize, and structural proteins VP1 and Atg5 co-localize [43]. Chikungunya virus (ChikV) toxin particles are localized to autophagosome-like vesicle-like luminal surfaces (ultra-structural analysis) [44]. In addition, rubella virus (RV) replication has been shown to originate from the endomembrane system, where RV regulates autophagosome formation by interfering with cellular autophagosome membrane-forming signalling pathways (the Ras/Raf/MEK/ERK and PI3K/Akt signalling pathways), thus promoting viral replication [45].

6.1.3 Autophagy Involved in Non-cleavage Release of Viruses

Autophagy has been shown to promote the non-cleavage release of some positive-stranded RNA viruses. PV is usually thought to release the viral particles by lysing cells. However, PV viral particles can also be released in a non-cleavage manner [34]. In PV-infected cells, expression of viral proteins 2BC and 3A induces the formation of autophagosomal bilayer membranes, and down-regulation of Atg8 expression inhibits non-cleavage release of PV [34]. Similar membrane structures can also be detected in rhinoviruses 2 (RV-2) and FMDV infected cells [43]. In coxsackievirus B3 (CVB3) infected cells, microvesicles secreted into the extracellular compartment contained three to four viral particles, and the presence of esterified LC3 and the exosome marker molecule flotillin-1 was detected on these microvesicles [46]. These results suggest that viruses of the picornavirus family may use Atg-dependent double-layered membrane vesicles to encapsulate mature virus particles for non-cleavage release.

6.1.4 Autophagy Involved in the Metabolism of Cellular Substances

Autophagy has been shown to be involved in cellular metabolic regulatory processes, and it can participate in lipid metabolism by regulating the degradation of triglycerides in lipid droplets, a process known as lipophagy [47]. In DENV-infected cells, lipid droplets can appear co-localized with autophagic lysosomes [48]. DENV-induced autophagosomes can transport lipid droplets to lysosomes where triglycerides are consumed and free fatty acids are released. The released free fatty acids undergo oxidation in the mitochondria to produce ATP, which provides energy for multiple processes of DENV replication [48]. In addition, inhibition of AMPK signalling pathway activity decreases lipophagy and

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DENV replication [48]. These studies suggest that DENV may alter lipid metabolism in host cells through autophagy induction, which in turn promotes viral infection.

6.1.5 Autophagy Inhibits Apoptosis

Early apoptosis induction is considered an important antiviral mechanism. The relationship between autophagy and apoptosis is close and complex, and the induction of autophagy is often accompanied by inhibition of apoptosis. DENV-2-induced autophagy has been shown to inhibit apoptosis, and down-regulation of autophagy can inhibit the protective effect of autophagy on cell death [49]. HCV infection is more likely to cause cell death in cells in which autophagy is inhibited, suggesting that autophagy plays an important role in extending cell survival and establishment of successful cell infection [37]. In CVB4-infected cells, inhibition of cellular autophagy (3-MA treatment) triggers caspase activation and apoptosis. Inhibition of apoptosis (pan-caspase inhibitor treatment) increases autophagosome formation [50]. In HCV-infected hepatocytes, HCV can activate autophagy through unfolded protein response, while inhibiting apoptosis and promoting viral replication [51].

In conclusion, the antiviral function of autophagy in the life cycle of RNA viruses involves multiple modes of action, either directly on viral replication or indirectly on host antiviral immunity and other related activities. Considering that autophagy plays an important role in a variety of life processes, other functions of autophagy (cell cycle regulation, cell differentiation, gene transcription) may also be involved in and contribute to viral replication, and their related mechanisms need to be further investigated.

7. Conclusions

The above reviews the structure, localization, natural immune signalling pathway and interaction between MAVS and STING, and highlights the facilitating and antagonistic roles of STING in the RNA virus immune pathway. The interaction between STING and MAVS enables the two different junction proteins to be effectively united in the RIG-I antiviral pathway. Conversely, RNA virus proteases inhibit the function of STING and escape from the immune system, making STING a key protein in the immune pathway. With the intensive study of the antiviral natural immune system, several antiviral natural immune signalling pathways have been identified. Nevertheless, the MAVS and STING-mediated intracellular natural immune network still needs to be improved, such as the molecular mechanism of TBK1 activation by STING and the mechanism of STING escape from natural immunity by RNA viruses have not been fully elucidated. The complex escape strategy of positive-stranded RNA viruses indicates that the current research on STING is only the tip of the iceberg, and whether the mechanism of STING on negative-stranded RNA viruses and DNA viruses is similar to that of positive-stranded RNA viruses or what are the differences between the two is also a question that needs to be explored. The revelation of these questions will point the way for future research and help us to further understand the mechanism of viral evasion of host natural immunity and provide new targets and ideas for the treatment of virus-induced diseases.

Cellular autophagy is a lysosome-dependent degradation process that maintains cellular homeostasis, and as part of the body's immune system, it also plays an important role in pathogen resistance. RNA viruses can be directly degraded by cellular autophagy or indirectly eliminated by activating the immune system. Meanwhile, in the long term evolutionary process, RNA viruses can escape autophagy recognition by various mechanisms, and even use cellular autophagy to promote viral replication. The interaction between RNA viruses and autophagy is an extremely complex process. With the deepening of the study on cellular autophagy, the interaction between RNA viral infection and cellular autophagy will become clearer, and the further elucidation of the relevant mechanisms will provide theoretical basis and new ideas for disease prevention, treatment and vaccine development.

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References

[1] Kumar H,Kawai T,Akira S.Pathogen recognition by the innate immunesystem[J].Int Rev Immunol, 2011,30(1) : 16-34.
[2] Bruns A M,Horvath C M.LGP2 synergy with MDA5 in RLR-mediated RNA recognition and antiviral signaling[J].Cytokine,2015,74(2) : 198-206.
[3] Seth R B,Sun L,Ea C K,et al.Identification and characterization of MAVS,a mitochondrial antiviral signaling protein that activates NF-kappaB and IRF3[J].Cell,2005,122(5) : 669-682.
[4] Xu H,He X,Zheng H,et al.Structural basis for the prion-like MAVS filaments in antiviral innate immunity[J]. Elife,2014,3 (2) :e01489.
[5] Zeng W,Sun L,Jiang X,et al.Reconstitution of the RIG-I pathway reveals a signaling role of unanchored polyubiquitin chains in innate immunity[J].Cell,2010,141(2) : 315-330.
[6] Yoneyama M,Onomoto K,Jogi M,et al.Viral RNA detection by RIG-I like receptors[J].Curr Opin Immunol, 2015,32: 48-53.
[7] Saha S K,Pietras E M,He J Q,et al.Regulation of antiviral responses by a direct and specific interaction between TRAF3 and Cardif[J].EMBO J,2006,25(14) : 3257-3263.
[8] Wang X A,Zhang R,She Z G,et al.Interferon regulatory factor 3 constrains IKKβ/NF-κB signaling to alleviate hepatic steatosis and insulin resistance[J].Hepatology,2014,59(3) : 870-885.
[9] Li Z,Liu G,Sun L,et al.PPM1A regulates antiviral signaling by antagonizing TBK1-mediated STING phosphorylation and aggregation[J /OL].PLoS Pathog,2015,11(3) : e1004783.
[10] Gao D,Wu J,Wu Y T,et al.Cyclic GMP-AMP synthase is an innate immune sensor of HIV and other retroviruses[J].Science,2013,341(6148) : 903-906.
[11] Civril F,Deimling T,de Oliveira Mann C C,et al.Structural mechanism of cytosolic DNA sensing by cGAS[J].Nature,2013,498 (7454) :332-337.
[12] Andrea A,Marion G,Taner C,et al.cGAS produces a 2'-5'-linked cyclic dinucleotide second messenger that activates STING[J].Nature,2013,498(7454) : 380-384.
[13] Tsuchida T,Zou J,Sation T,et al.The ubiquitin ligase TRIM56 regulates innate immune responses to intracellular double-stranded DNA[J].Immunity,2010,33(5) : 765-776.
[14] Tanaka Y,Chen Z J.STING specifies IRF3 phosphorylation by TBK1 in the cytosolic DNA signaling pathway[J /OL].Sci Signal,2012,5(214) : ra20.
[15] Baum A,Sachidanandam R,Garcia Sastre A.Preference of RIG-I for short viral RNA molecules in infected cells revealed by next-generation sequencing[J].Proc Natl Acad Sci USA,2010,107(37) : 16303-16308.
[16] Liu S,Cai X,Wu J,et al.Phosphorylation of innate immune adaptor proteins MAVS,STING,and TRIF induces IRF3 activation[J].Science,2015,347 (6227): aaa2630.
[17] Atianand M K,Fitzgerald K A.Molecular basis of DNA recognition in the immune system [J].J Immunol,2013,190 (5) :1911-1918.
[18] Zhong B,Yang Y,Li S,et al.The adaptor protein MITA links virus-sensing receptors to IRF3 transcription factor activation[J].Immunity,2008,29(4) : 538-550.
[19] Wysocka J,Swigut T,Milne T A,et al.WDR5 associates with histone H3 methylated at K4 and is essential for H3 K4 methylation and vertebrate development[J].Cell,2005,121(6) : 859-872.
[20] Wang Y Y,Liu L J,Zhang B,et al.WDR5 is essential for assembly of the VISA-associated signaling complex and virus-triggered IRF3 and NF-kappaB activation[J].Proc Natl Acad Sci USA,2010,107(2) : 815-820.
[21] Cheng G,Zhong J,Chisari F V.Inhibition of dsRNA-induced signaling in hepatitis C virus-infected cells by NS3 protease-dependent and-independent mechanisms[J].Proc Natl Acad Sci USA, 2006, 103(22) : 8499-8504.
[22] Maringer K,Fernandez-Sesma A.Message in a bottle: lessons learned from antagonism of STING signalling during RNA virus infection[J].Cytokine Growth Factor Rev,2014,25(6) : 669-679.
[23] Parera M,Martrus G,Franco S,et al.Canine hepacivirus NS3 serine protease can cleave the human adaptor proteins MAVS and TRIF[J /OL].PLoS One,2012,7(8): e42481.
[24] Nitta S,Sakamoto M,Nakagawa M,et al.Hepatitis C virus NS4B protein targets STING and abrogates RIG-I-mediated type I interferon dependent innate immunity[J].Hepatology,2013,57 (1) :46-58.
[25] Zou J,Xie X,Wang Q,et al. Characterization of Dengue virus NS4A and NS4B protein interaction[J]. J Virol,2015,89 (7) :3455-3470.
[26] Ishikawa H,Ma Z,Barber G N.STING regulates intracellular DNA mediated, type I interferon-dependent innate immunity[J].Nature,2009,461(7265) : 788-792.
[27] Aguirre S,Maestre A M,Pagni S,et al.DENV inhibits type I IFN production in infected cells by cleaving human STING[J /OL].PLoS Pathog,2012,8 (10) : e1002934.

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[28] Dalrymple N A,Cimica V,Mackow E R.Dengue virus NS proteins inhibit RIG-I/MAVS signaling by blocking TBK1 /IRF3 phosphorylation: Dengue virus serotype 1 NS4A is a unique interferon regulating virulence determinant[J].MBio,2015,6(3) : e00553.
[29] Sun L,Xing Y,Chen X,et al.Coronavirus papain-like proteases negatively regulate antiviral innate immune response through disruption of STING-mediated signaling[J /OL].PLoS One,2012, 7(2) : e30802.
[30] Yuan L,Chen Z,Song S,et al. p53 degradation by a coronavirus papain-like protease suppresses type I interferon signaling[J].J Biol Chem,2015,290(5) : 3172-3182.
[31] Devaraj S G,Nan W,Zhongbin C,et al Regulation of IRF3- dependent innate immunity by the papain-like protease domain of the severe acute respiratory syndrome coronavirus[J].J Biol Chem,2007, 282(44) : 32208-32221.
[32] Chen X,Yang X,Zheng Yet al. SARS coronavirus papain-like protease inhibits the type I interferon signaling pathway through interaction with the STING-TRAF3-TBK1 complex[J].Protien Cell,2014, 5(5) : 369-381.
[33] Kirkegaard K, Taylor MP, Jackson WT. Cellular autophagy: surrender, avoidance and subversion by microorganisms [J]. Nat Rev Microbiol, 2004, 2 (4): 301-314.
[34] Jackson WT, Giddings TH, Jr, Taylor MP, et al. Subversion of cellular autophagosomal machinery by RNA viruses [J]. PLoS Biol, 2005, 3 (5): e156.
[35] Dreux M, Gastaminza P, Wieland SF, et al. The autophagy machinery is required to initiate hepatitis C virus replication [J]. Proc Natl Acad Sci US A, 2009, 106 (33): 14046- 14051.
[36] Ke PY, Chen SS. Activation of the unfolded protein response and autophagy after hepatitis C virus infection suppresses innate antiviral immunity in vitro [J]. J Clin Invest, 2011, 121 (1): 37-56.
[37] Shrivastava S, Raychoudhuri A, Steele R, et al. Knockdown of autophagy enhances the innate immune response in hepatitis C virus-infected hepatocytes [J]. Hepatology, 2011, 53 (2): 406-414.
[38] Huang X, Yue Y, Li D, et al. Antibody-dependent ehancement of dengue virus infection inhibits RLR-mediated type-I IFN-independent signalling through upregulation of cellular autophagy [J]. Sci Rep, 2016, 6: 22303.
[39] Miller S, Krijnse-Locker J. Modification of intracellular membrane structures for virus replication [J]. Nat Rev Microbiol, 2008, 6 (5): 363-374.
[40] Khakpoor A, Panyasrivanit M, Wikan N, et al. A role for autophagolysosomes in dengue virus 3 production in HepG2 cells [J]. J Gen Virol, 2009, 90 (Pt 5): 1093-1103.
[41] Lee YR, Wang PS, Wang JR, et al. Enterovirus 71-induced autophagy increases viral replication and pathogenesis in a suckling mouse model [J. J Biomed Sci, 2014, 21: 80.
[42] Hou L, Ge X, Xin L, et al. Nonstructural proteins 2C and 3D are involved in autophagy as induced by the encephalomyocarditis virus [J]. Virol J, 2014, 11: 156.
[43] O'Donnell V, Pacheco JM, LaRocco M, et al. Foot-and-mouth disease virus utilizes an autophagic pathway during viral replication [J]. Virology, 2011, 410 (1): 142-150.
[44] Krejbich-Trotot P, Gay B, Li-Pat-Yuen G, et al. Chikungunya triggers an autophagic process which promotes viral replication [J]. Virol J, 2011, 8: 432.
[45] Orosz L, Megyeri K. Well begun is half done: rubella virus perturbs autophagy signaling, thereby facilitating the construction of viral replication compartments [J]. Med Hypotheses, 2016, 89: 16-20.
[46] Li M, Wang X, Yu Y, et al. Coxsackievirus B3-induced calpain activation facilitates the progeny virus replication via a likely mechanism related with both autophagy enhancement and apoptosis inhibition in the early phase of infection: an in vitro study in H9c2cells [J]. Virus Res, 2014, 179: 177-186.
[47] Jeong SJ, Lee MN, Oh GT. The role of macrophage lipophagy in reverse cholesterol transport [J]. Endocrinol Metab (Seoul), 2017, 32 (1): 41-46.
[48] Jordan TX, Randall G. Dengue virus activates the AMP kinase-mTOR axis to stimulate a proviral lipophagy [J]. J Virol, 2017, 91 (11): e02020-16.
[49] McLean JE, Wudzinska A, Datan E, et al. Flavivirus NS4A-induced autophagy protects cells against death and enhances virus replication[J]. J Biol Chem, 2011, 286 (25): 22147-22159.
[50] Yoon SY, Ha YE, Choi JE, et al. Coxsackievirus B4 uses autophagy for replication after calpain activation in rat primary neurons [J]. J Virol, 2008, 82 (23): 11976-11978.
[51] Sir D, Chen WL, Choi J, et al. Induction of incomplete autophagic response by hepatitis C virus via the unfolded protein response [J]. Hepatology, 2008, 48 (4): 1054-1061.