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Research paper

E3 ubiquitin ligases, the powerful modulator of innate antiviral immunity

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ABSTRACT

During viral infection, the innate immune system represents the first defense line of the human body. The pathogen associated molecular patterns (PAMPs) from the viruses are recognized by pattern recognition receptors (PRRs) of the host cell, especially from those of the immune cells. Sensing of PAMPs by PRRs elicits an elegant signal transduction system, ultimately leading to the production of type I interferons (IFNs) and proinflammatory cytokines. Ubiquitination, with its versatile functions, plays a central role in modulating almost every single step of this signaling cascade. Ubiquitin ligases, which catalyze different types of ubiquitination correlating with multiple functions, are the key participant in fine-tuning antiviral signal transduction. In this review, we focus on summarizing the ubiquitin ligases that regulate the key signaling molecules in antiviral innate immunity.

1. Introduction

The first step in innate immunity signaling is the recognition of PAMPs by their corresponding PRRs. The signature PAMPs in viruses are the viral nucleic acids including double-stranded RNA (dsRNA), single-stranded RNA (ssRNA), and dsDNA [1]. The viral PAMPs are mainly recognized by three kinds of PRRs, including Toll-like receptors (TLRs), RIG-I-like receptors (RLRs), and cytosolic DNA sensors (CDSs) such as cyclic GMP-AMP synthase (cGAS). TLRs are the membrane-bound PRRs, while RLRs and CDSs belong to the cytoplasmic PRRs.

The interaction between the PAMPs and the PRRs initiates the signal transduction cascade. The receptors perceive viral nucleic acids, resulting in the recruitment and activation of the adaptor protein including Toll/interleukin-1 receptor domain-containing adaptor protein inducing interferon beta (TRIF) [2], myeloid differentiation factor-88 (MyD88) [3], mitochondrial antiviral signaling protein (MAVS) [4], and stimulator of interferon genes protein (STING) [5], respectively. The adaptor proteins act as a scaffold, recruiting and activating the kinases including inhibitor of nuclear factor kappa-B [IκB] kinase (IKK) family and TANK-binding kinase-1 (TBK1). Furthermore, IKK family and TBK1 are responsible for the activation of transcription factors nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and interferon-regulatory factor 3 (IRF3), respectively. IKK family, including IKKα, IKKβ, and IKKγ (NEMO), phosphorylates IκBα and leads to its ubiquitination and proteasomal degradation, which releases the sequestered NF-κB (p65/p50) and leads to its translocation from cytoplasm to the nucleus [6]. The translocated NF-κB is then engaged in the production of the proinflammatory cytokines. TBK1 cooperates with IKK-related kinase IKKε to phosphorylate and activate IRF3, leading to its dimerization and translocation. The translocated IRF3 mediates the induction of the genes encoding type I IFNs and IFN regulatory factors in the nucleus [7] (Fig. 1).

Ubiquitin is an 8.5 kDa protein composed of 76 amino acids. The addition of ubiquitin to a substrate protein is called ubiquitination, which is completed through three distinct classes of enzymes: ubiquitin-activating enzymes (E1s), ubiquitin-conjugating enzymes (E2s), and ubiquitin ligases (E3s) [8]. Since there are limited numbers of E1 and E2 enzymes, the substrate specificity relies mainly on the E3 ubiquitin ligase. E3s are divided into three types according to their domain structure, HECT (homologous to E6-associated protein C-terminus), RING (Really Interesting New Gene), and RBR (RING-IBR-RING) [9]. HECT type E3s contain HECT domain at their C terminus, while the RING E3s are characterized by their RING or U-box fold catalytic domain. Different from both of them, RBR E3s are defined by a homologous sequence, encompassing two predicted RING fingers (RING1 and RING2) and a central in-between-RINGs (IBR) zinc-binding domain [9].

Conjugation of ubiquitin to substrates occurs at lysine residues of the substrate proteins. Lysine residues of the substrate can be modified with a single ubiquitin moiety (monoubiquitination) or chains of ubiquitin (polyubiquitination). Polyubiquitin chains are formed through the covalent binding of C-terminal glycine of one ubiquitin molecule with the lysine or methionine of another ubiquitin molecule [8].

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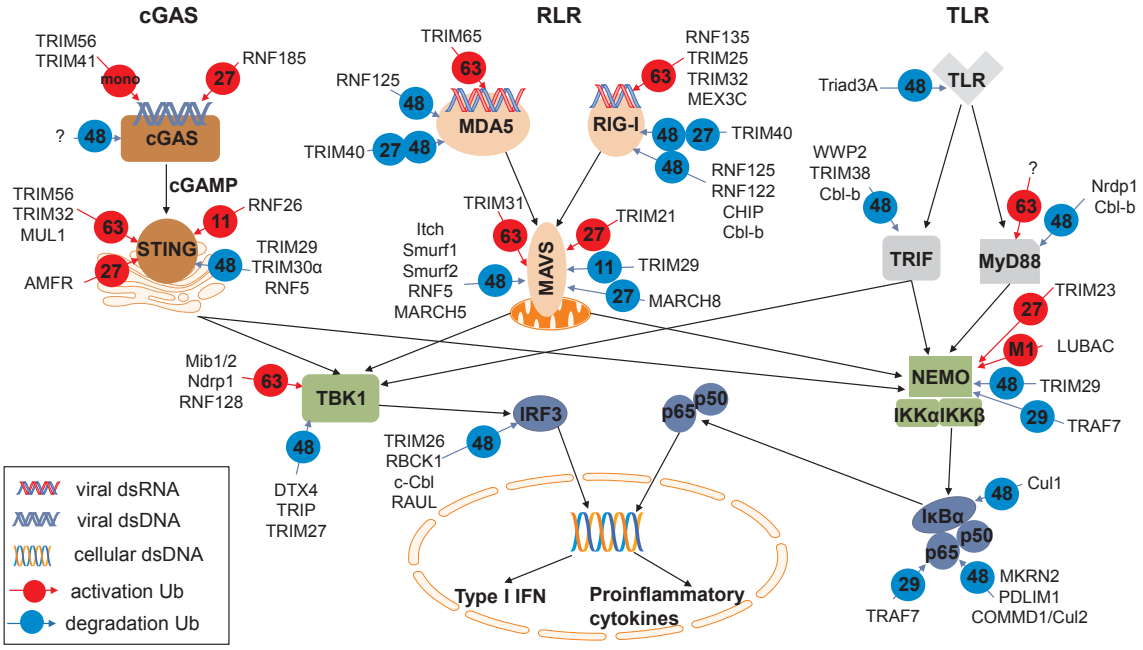

Fig. 1. Diagram presentation of antiviral innate immunity pathway, the E3 ubiquitin ligase and ubiquitin chains regulating the signaling molecules.

Ubiquitin itself contains eight amino groups for another ubiquitin molecule to conjugate with: the ε-amino groups of seven lysine residues (K6, 11, 27, 29, 33, 48, and 63) and the α-amino group of the *N*-terminal methionine residue. Among them, the K48- and K63-linked polymeric chains are the best described. K48-based polyubiquitin chains are the canonical signal to target protein for the proteasome-dependent degradation, while K63-based chains regulate signal transduction, protein endocytosis, trafficking, and enzymatic activity [10]. There are emerging studies suggesting the involvement of atypical types of ubiquitin chains in innate immunity [10]. For example, M1-linked chains, which are catalyzed by a linear ubiquitin chain assembly complex (LUBAC), are essential for the NF-κB activation and regulation of IFN production [11,12]. Besides M1-linked chains, K11-, K27-, K-29 polyubiquitin chains are also suggested to play role in the modulation of innate immunity.

In the signaling cascade of innate immunity, most of the receptor proteins, adaptor proteins, and kinases are modified by ubiquitination to activate and transduce the downstream signaling for efficient production of the IFN and proinflammatory cytokines to combat the pathogens. For example, the K-63 linked ubiquitination of RLRs is essential for their oligomerization and activation [13,14]. At the meanwhile, after the elimination of the invading microbes, the host cells must shut down the signal transduction properly to prevent the aberrant autoimmunity. In this case, the ubiquitination can negatively regulate the signal transduction by facilitating the degradation of signaling protein. For example, K-48 linked polyubiquitination of RLRs and MAVS by RNF125 lead to their proteasomal-dependent degradation [15]. Therefore, E3 ubiquitin ligases responsible for catalyzing the ubiquitination on their substrates are the major players of accurately initiating and terminating transduction program of innate immunity. In this review, we summarize the E3 ubiquitin ligases, especially the most recently identified, which regulate the function and stability of the key signaling molecules in antiviral innate immunity (Table 1).

2. TLR signaling

TLRs are type I transmembrane domain proteins with a tripartite structure: an *N*-terminal extracellular domain essential for ligand recognition, a single transmembrane spanning region, and a cytoplasmic C-terminal globular Toll/interleukin-1 (IL-1) receptor (TIR) domain accountable for signal transduction [16]. TLR3, TLR7, TLR8, and TLR9 are responsible for sensing endosomal nucleic acids derived from the enclosed microbes. TLR3 and TLR7/8 recognize dsRNA and ssRNA, respectively. For TLR9, it detects unmethylated CpG DNA species [17].

The TLRs employ their TIR domain to interact with two adaptor proteins, TRIF and MyD88, to relay the distinct downstream signaling. TRIF interacts with TLR3, whereas MyD88 binds with TLR7/8/9. In TLR3-TRIF pathway, TRIF associates with the ubiquitin E3 ligase Tumor Necrosis Factor (TNF) receptor-associated factor 3 (TRAF3) to activate TBK1 and IKKε [18]. Activated TBK1 and IKKε then phosphorylate IRF3 to drive the expression of type I IFN [7]. On the other hand, TRIF also interacts with TRAF6 and Receptor-interacting serine/threonine-protein kinase 1 (RIP1) [19], leading to the activation of TGF-β-activated kinase 1 (TAK1) and subsequent IKK complex. The activation of classical IKK complex, as aforementioned, can phosphorylate IκBα and lead to its proteasome-dependent degradation. Therefore the sequestered NF-κB is liberated from the cytoplasm and translocated to the nucleus [20]. MyD88-dependent TLR pathways typically are engaged in leading to the production of proinflammatory cytokines. Recruitment of downstream molecules such as kinases interleukin-1 receptor-associated kinase 4 (IRAK4), IRAK1, and ubiquitin ligase TRAF6 by MyD88 results in the activation of TAK1 [20]. Upon activation, TAK1 phosphorylates IKKβ in the classical IKK complex, which ultimately causes the activation of NF-κB and subsequent expression of proinflammatory cytokines such as TNF, interleukin 6 (IL-6), and IL-12.

2.1. E3 ubiquitin ligases regulating the TLRs, TRIF, and MyD88

Several E3 ubiquitin ligases have been indicated to regulate the stability of TLR receptors as well as adaptor proteins MyD88 and TRIF through ubiquitination and proteasome-dependent degradation. Triad3A (RNF216) enhances the ubiquitination and degradation of TLR4 and TLR9 but does not affect the protein level of TLR2 [21]. Both TRIF and MyD88 are targeted by the E3 ligase Cbl-b. The interaction between Cbl-b and adaptors is mediated by the integrin CD11b and dependent on the phosphorylation of TRIF and MyD88 [22]. Another E3 ligase Nrdp1 interacts with MyD88 and facilitates its K-48 linked polyubiquitination as well as degradation [23]. Consistently, *Nrdp1*−/− mice exhibited less production of proinflammatory cytokines with the TLR agonist stimulation [23]. Of note, E3 ligase Pellino in

Table 1
Summary of the E3 ubiquitin ligases, ubiquitin chain types, ubiquitination sites, and references for the corresponding signaling molecules.

Signaling molecules	E3 ubiquitin ligase	Ubiquitin type &function	Ubiquitination sites	Ref.
TLR4/9	Triad3A	K-48 degradation	Not identified	[21]
MyD88	Not identified	K-63 activation	K231	[27]
	Cbl-b	K-48 degradation	Not identified	[22]
	Nrdp1			[23]
TRIF	Cbl-b	K-48 degradation	Not identified	[22]
	WWP2			[25]
	TRIM38			[26]
RIG-I	TRIM25	K-63 Activation	K172	[13]
	RNF135(Riplet)		K849/851/888/907/909	[44]
	TRIM4		K154/164/172	[43]
	MEX3C		K48/99/169	[42]
	RNF125	K-48 degradation	Not identified	[15]
	RNF122		K115/146	[56]
	CHIP		Not identified	[57, 58]
	c-Cbl		K813	[59]
	TRIM40	K-48/K-27 degradation	Not identified	[60]
MDA5	TRIM65	K-63 activation	K743	[48]
	RNF125	K-48 degradation	Not identified	[15]
	TRIM40	K-48/K-27 degradation	K23/43/68	[60]

Table 1 (*continued*)

MAVS	TRIM31	K-63 activation	K10/311/461	[54]
	TRIM21	K-27 activation	K325	[55]
	RNF125	K-48 degradation	Not identified	[15]
	AIP4(Itch)		Not identified	[63]
	Smurf1		Not identified	[62]
	Smurf2		Not identified	[61]
	RNF5		K362/461	[64]
	MARCH5		K7/500	[65]
	TRIM29	K-11 degradation	K371/420/500	[66]
	MARCH8	K-27 degradation	K7	[67]
cGAS	RNF185	K-27 activation	K173/384	[75]
	TRIM56	Mono activation	K335	[76]
	TRIM41		Not identified	[77]
	Not identified	K-48 degradation	K414	[82]
STING	TRIM56	K-63 activation	K150	[78]
	TRIM32		K20/150/224/236	[79]
	MUL1		K224	[80]
	AMFR	K-27 activation	K137/150/224/236	[81]
	RNF26	K-11 protection	K150	[84]
	TRIM29	K-48 degradation	K288/337/370	[85, 86]

(*continued on next page*)

Table 1 (*continued*)

	TRIM30α		K275	[87]
	RNF5		K150	[83]
TRAF3	RNF166	K-63 activation	Not identified	[88]
	HECTD3		K138	[89]
	Triad3A	K-48 degradation	Not identified	[95]
TRAF6	RNF166	K-63 activation	Not identified	[88]
	TRIM38	K-48 degradation	Not identified	[96]
TBK1	Mib1/2	K-63 activation	Not identified	[90]
	Nrdp1		Not identified	[23]
	RNF128		K30/401	[91]
	DTX4	K-48 degradation	K670	[97]
	TRIP		Not identified	[98]
	TRIM27		K251/372	[99]
NEMO	TRIM23	K-27 activation	K105/309/325/326/344	[92]
	LUBAC	M-1 activation	K285/309	[12]
	TRAF7	K-29 degradation	Not identified	[101]
	TRIM29	K-48 degradation	K183	[100]
IRF3	TRIM26	K-48 degradation	K70/87	[103]
	RBCK1		Not identified	[102]
	c-Cbl		Not identified	[104]
	RAUL		Not identified	[105]
p65	MKRN2	K-48	Not identified	[108]
	PDLIM1	degradation		[109]
	COMMD1/Cul2			[110]
	TRAF7	K-29 degradation		[101]

Red color background indicate the ubiquitination and E3 ligases responsible for activation or protection of signaling molecules, while the blue color background point to the ubiquitination and E3 ligases responsible for degradation of signaling molecules.

Drosophila also enhances the ubiquitination and degradation of MyD88, functioning as a negative regulator in Toll-mediated innate immunity [24]. In addition to Cbl-b, stability of TRIF is also under the regulation of a HECT type E3 ligase WWP2 and a RING-type E3 ligase TRIM38. A mass spectrometry study identified WWP2 as the E3 ubiquitin ligase for TRIF [25]. Stimulation of TLR3 with poly(I:C) enhanced the association between WWP2 and TRIF, leading to a preferable K-48 linked polyubiquitination and degradation of TRIF. Furthermore, production of both IFNβ and pro-inflammatory cytokines such as Chemokine (C−C motif) ligand 5 (CCL5), TNFα, and IL-6 was elevated in *Wwp2−/−* bone marrow-derived macrophages (BMDMs) upon the treatment of poly(I:C). More importantly, *in vivo* study suggested that the sera concentration of IFNβ and proinflammatory cytokines in *Wwp2−/−* mice were significantly enhanced in response to poly(I:C), leading to earlier inflammatory death compared with WT mice [25]. TRIM38 is another E3 ubiquitin ligase for TRIF [26]. Treatment of HeLa cells with poly(I:C) induced the expression of TRIM38, causing the delivery of the K48-linked polymeric chains on TRIF and its proteasomal-dependent degradation [26]. Even though these E3s have been demonstrated to regulate the protein level of TLR, TRIF, and MyD88 under specific circumstances, the exact role of these E3s during viral infection still needs to be further examined.

The K-63 linked ubiquitination of MyD88 was found to be induced following *nontypeable Haemophilus influenzae* infection, which is reversed by the deubiquitinase CYLD [27]. K-63 linked ubiquitination at K231 of MyD88 was required for the efficient production of proinflammatory cytokines upon bacterial infection. However, whether the same modification of MyD88 also occurs during viral infection and the E3 ubiquitin ligase for MyD88 require further investigation.

3. RLR signaling of RNA virus

RLRs, a family of DExD/H-box RNA helicases, participate in the recognition of viral RNA species in the cytosol of infected cells. The two well-characterized RLR members are retinoic acid-inducible gene-I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5), both of which harbor two tandem *N*-terminal caspase activation and recruitment domains (CARDs), a central helicase domain, and a C-terminal domain (CTD) [28]. CARD domain is critical for transducing downstream signaling, while helicase domain and CTD are responsible for binding with RNA. RIG-I and MDA5 detect different RNA species. RIG-I can detect 5′ triphosphorylated ssRNA, short dsRNA, whereas MDA5 is accountable for recognition of long dsRNA [29]. The *in vivo* functional studies have suggested that RIG-I is essential for sensing of RNA viruses including paramyxoviruses, influenza virus, and Japanese encephalitis virus, whereas MDA5 is indispensable for picornavirus detection [30]. The third RLR member LGP2 (laboratory of genetics and physiology 2), lacking the CARD domain critical for activation of downstream signaling, was suggested to be a physiological negative feedback regulator [31]. But a recent study suggests that LGP2 may play a positive role through regulating MDA5-RNA interaction [32].

In the absence of ligand RNA, 2CARD of RIG-I is masked by the intramolecular interaction with the helicase domain, showing auto-repressed state [33,34]. But upon viral RNA binding, 2CARD of RIG-I is exposed to interact with the CARD domain of MAVS (also known as Cardif, IPS-1 or VISA) on mitochondria [4,35–37]. The CARD-CARD interaction between RLRs and MAVS leads to the conformational change of MAVS, converting MAVS on the outer membrane of mitochondria to form a prion-like structure and activate the downstream signaling [38]. The prion-like structure of MAVS recruits the TRAF2, 5, and 6 to activate kinases TBK1 and IKK complex [39]. Besides these TRAFs, the previous study also demonstrated that TRAF3 is essential for type I IFN production by interacting with MAVS [40]. These TRAF proteins play a redundant role, but deletion of TRAF2, 3, 5, and 6 at the same time absolutely abolishes MAVS-mediated signaling [41]. MAVS-TRAFs complex associates with TBK1/IKKε for their activation. The activated TBK1/IKKε phosphorylate and activate IRF3 to trigger transcriptional activation of type I IFN. In addition, MAVS aggregates also activate the classical IKK complex, ultimately eliciting the production of proinflammatory cytokines as aforementioned.

3.1. E3 ubiquitin ligases regulating aggregation and activation of RIG-I and MDA5

In the past decade, multiple studies have demonstrated that K63-linked polyubiquitination plays a fundamental role in activating RLR signaling. The function of K63-linked ubiquitin chains in the regulation of RIG-I has been particularly investigated. TRIM25 is the first identified enzyme to catalyze the conjugation of K-63 polymeric chains at K172 on second CARD domain of RIG-I [13]. *Trim25−/−* mouse embryonic fibroblasts (MEFs) showed remarkable increase in replication of

Newcastle disease virus (NDV) or vesicular stomatitis virus (VSV) compared with WT MEFs, suggesting the positive regulation of K-63 linked ubiquitination mediated by TRIM25 [13]. Besides TRIM25, E3 ubiquitin ligases TRIM4 and MEX3C also facilitate the conjugation of K-63 linked polyubiquitin chains at the CARD domain of RIG-I [42,43]. Moreover, the production of IFNβ, IL-6, and IL-12 after infection with NDV or VSV was abrogated in *Mex3c*−/− peritoneal macrophages, conventional dendritic cells (cDCs), and MEFs [42]. Different from the E3s mentioned above, RNF135 (Riplet) catalyze the conjugation of K-63 polymeric chains at multiple lysine residues in the CTD domain of RIG-I [44]. *Rnf135*−/− MEFs, macrophages, and cDCs produced severely impaired amount of IFNβ and IL-6 following influenza A virus and VSV infections comparing with WT counterparts. Furthermore, *Rnf135*−/− mice were more susceptible to VSV infection compared with WT mice [44]. Studies have suggested that TRIM25, TRIM4, and MEX3C work synergistically to ubiquitinate multiple lysine residues in CARD domain of RIG-I to robustly activate the IFN response [45,46]. Of note, the ubiquitination of multiple lysine residues in CTD of RIG-I likely is a prerequisite for the ubiquitination of CARD domain, supported by the observation that knockout of RNF135 alone abolished the polyubiquitination of endogenous RIG-I [44,47].

Theoretically, MDA5 is supposed to be ubiquitinated for its activation since it contains the functional domain akin to RIG-I. A previous study suggested that TRIM25 was not involved in covalent K-63 ubiquitination of MDA5 [13]. Recently, another TRIM family member TRIM65 is identified to specifically interact with the helicase domain of MDA5 and facilitate K63-linked polyubiquitination at K743 of MDA5, which is crucial for MDA5 aggregation and subsequent activation [48]. More importantly, *Trim65*−/− BMDMs and MEFs produced much less IFNα/β upon EMCV infection compared with the WT counterparts, suggesting the crucial role of TRIM65 mediated polyubiquitination of MDA5 [48]. Structural work has demonstrated that the filament assembly of MDA5 along the dsRNA axis is essential for its dsRNA recognition since monomeric MDA5 binds to dsRNA with poor affinity [49]. K743 is located on the surface of MDA5 monomer [50] and likely required for the formation and stability of MDA5 filament. The structural study of MDA5 also suggested that CARD domain oligomerizes in a concentration-dependent manner, and oligomerization of MDA5 CARD induces the aggregation of MAVS [50]. Interestingly, the K-63 linked ubiquitination catalyzed by TRIM65 is located in the helicase domain instead of CARD domain. Whether ubiquitination of CARD domain is required for MDA5 oligomerization and the E3 ligase responsible for this modification still need to be further investigated.

3.2. TRIM31 and TRIM21 polyubiquitinate MAVS for its activation

MAVS is the immediate downstream molecule of RIG-I and MDA5, serving as the adaptor protein in the RLR signaling pathway [4,35–37]. MAVS contains the *N*-terminal CARD domain, a middle proline-rich region, and a C-terminal transmembrane domain (TM) [51]. The CARD domain is required for the interaction with RIG-I/MDA5 and transducing the signaling cascade, whereas TM domain tethers MAVS on mitochondria or peroxisome [52]. A previous study suggested that function of MAVS was regulated by K63-linked ubiquitination and this modification led to the enhanced recruitment of IKKε, ultimately promoting IRF3 activation and expression of IFN stimulated genes (ISGs) [53]. However, the ubiquitin E3 ligase responsible for MAVS ubiquitination was not investigated in this study.

Recently, our lab identified TRIM31 as a bona fide E3 ubiquitin ligase for MAVS through both *in vitro* and *in vivo* study [54]. TRIM31 interacts with the proline-rich domain of MAVS and facilitates the conjugation of K-63 linked polyubiquitin chain at K10, K311, and K461 of MAVS. *In vitro* ubiquitination assay clearly demonstrated that TRIM31 conjugated K-63 linked not K-48 linked ubiquitin chains on MAVS with the E2 UbcH5a. As aforementioned, MAVS forms prion-like aggregates to potently activate downstream signaling after RNA virus infection. Deficiency of TRIM31 or mutation of MAVS ubiquitination sites by TRIM31 abolished the aggregation of the MAVS in MEFs, suggesting the K-63 linked polyubiquitination catalyzed by TRIM31 is crucial for the prion-like aggregate formation of MAVS. Congruently, *Trim31*−/− peritoneal macrophages secreted much fewer IFNβ following SeV or VSV infection. Furthermore, *in vivo* study demonstrated that *Trim31*−/− mice were more susceptible to infection of RNA virus than were WT mice. Of note, TRIM31 was found to be particularly enriched in mitochondria during the infection of RNA virus instead of DNA virus, consistent with the phenomenon that the susceptibility of *Trim31*−/− mice to viral infection was confined to RNA virus. TRIM21, another TRIM family member, specifically interacts with MAVS and facilitates the conjugation of K-27 linked polyubiquitin chain at K325 of MAVS [55]. This modification enhances the interaction between TBK1 and MAVS, therefore promoting the activation of IRF-3 and NF-κB signaling pathways. However, the study was performed in HLCZ01 and Huh7.5.1 cell lines, both of which are hepatoma cells. It would be interesting to investigate the effect of TRIM21 on MAVS in specific immune cells.

3.3. E3 ligases responsible for degradation of RLRs and MAVS

There are multiple E3 ubiquitin ligases promoting the degradation of RIG-I. Two RNF family E3 ligases RNF125 and RNF122 are indicated to regulate the protein stability of RIG-I. RNF125 is the first identified E3 ligase responsible for the K-48 linked ubiquitination and degradation of RIG-I [15]. Besides interacting with RIG-I, RNF125 also associates with both MDA5 and MAVS to facilitate their ubiquitin conjugation [15]. RNF122 interacts with the CARD domain of RIG-I, facilitating the delivery of K-48 ubiquitin chains at K115 and K146 of the CARD domain and leading to the degradation of RIG-I [56]. Knockdown or knockout of RNF122 in mouse peritoneal macrophages significantly enhanced the expression level of IFNβ and proinflammatory cytokines as well as the production of IFNα/β following infection of VSV or SeV instead of HSV-1 [56]. Interestingly, this study also found that RNF122 deficiency did not affect the production of IFNβ and proinflammatory cytokines with the stimulation of RNA viruses in plasmacytoid bone marrow-derived DCs (BMDCs), suggesting that RNF122 exerts its negative regulation of RIG-I in specific immune cell types [56].

Another two RING-type E3 ubiquitin ligases, CHIP and c-Cbl, are also identified to modulate the protein level of RIG-I. Two independent studies demonstrated that CHIP enhanced the K-48 linked ubiquitination and degradation of RIG-I, which is mediated through cytoplasmic STAT5 and MLL5, respectively [57,58]. STAT5 interacts with CHIP and blocks the association between RIG-I and CHIP, while MLL5 enhances the interaction between RIG-I and CHIP [57,58]. Therefore, STAT5 and MLL5 play opposite role in RIG-I-mediated pathway. Furthermore, knockdown of CHIP enhanced the activation of IRF3 and subsequent production of IFNβ upon RNA virus infection in peritoneal macrophages, confirming its inhibitory effect on RIG-I mediated RNA sensing pathway [57]. The effect of c-Cbl on RIG-I is mediated by Siglec-G and SHP2. RNA virus infection leads to the induction of Siglec-G in macrophages, which in turn recruits and phosphorylates SHP2 and E3 ligase c-Cbl. c-Cbl further promotes the conjugation of K-48 polymeric ubiquitin chains at K813 of RIG-I, leading to its proteasomal degradation [59]. Congruent with this, knockout of Siglec-G or knockdown of c-Cbl or SHP2 significantly enhanced the expression level of IFNβ upon the VSV infection in macrophages [59].

A TRIM family E3 ligase, TRIM40 participates in the degradation of both RIG-I and MDA5 [60]. TRIM40 conjugates both K-27 and K-48 linked polymeric chains at the first CARD domain of both RIG-I and MDA5 to facilitate their degradation. Consistent with this, *Trim40*−/− peritoneal macrophages significantly enhanced secretion of IFNβ, TNFα, and IL-6 compared with WT counterparts following SeV or VSV infection. Moreover, *in vivo* study demonstrated that *Trim40*−/− mice mount less viral replication and survived longer compared with their

WT mice. Notably, TRIM40 expression level was markedly down-regulated at the early stage of RNA virus infection, suggesting the host cells modulate its level to boost the immune response in the early infection.

There are a couple E3 ubiquitin ligases responsible for the degradation of MAVS through K-48 mediated proteasomal degradation, including RNF125, AIP4 (Itch), Smurf1, Smurf2, RNF5, and MARCH5 [61–65]. In addition to these E3s, TRIM29 is also identified as the E3 ubiquitin ligase to trigger the proteasomal-dependent degradation of MAVS. However, the degradation occurs through K-11 linked polyubiquitination instead of K-48 linked polyubiquitination [66]. Consistently, knockout of TRIM29 resulted in the upregulation of IFNα/β in both BMDCs and BMDMs upon the reovirus infection. Recently, one interesting study also demonstrated that MAVS can also be targeted for degradation through autophagy instead of proteasome [67]. BST2, known for tethering the viral particles on the cellular membranes, can recruit membrane-associated E3 ubiquitin ligase MARCH8 to facilitate the conjugation of K-27 polymeric ubiquitin chains at K7 of MAVS. This modification serves as a recognition signal for NDP52-mediated autophagic degradation, acting as a negative feedback to suppress the sustained activation of RLR mediated IFN signaling [67].

4. cGAS-STING signaling

In the past years, several proteins such as AIM2, DAI, RNA polymerase III, IFI16, DDX41 have been reported to recognize microbial DNA and are regarded as CDSs [68]. However, these proteins are found to be important for sensing of various DNA pathogens in specific cell type or mouse models. Different from the DNA sensors above, cGAS has been identified to detect cytosolic microbial or endogenous aberrant DNA in various cell types [69]. cGAS contains an *N*-terminal regulatory domain (RD), a central nucleotidyltransferase (NTase) domain, and a C-terminal domain (CTD) [70]. In the absence of ligand DNA, cGAS exists in an autoinhibited state [71]. The binding of cGAS with DNA results in a conformational change, allowing access of the nucleotide substrates including GTP and ATP into the active site and subsequent synthesis of cGAMP [70]. The cGAMP acts as a second messenger and binds to the endoplasmic reticulum (ER)-membrane adaptor protein STING [72]. The interaction with cGAMP leads to a conformational change and activation of STING [73]. STING then traffics from ER to an ER-Golgi intermediate compartment and the Golgi apparatus [74]. During this process, STING recruits and activates the kinase TBK1 and IKK complex, eventually resulting in the induction of IFN and NF-κB response, respectively [5].

4.1. E3 ligases accountable for cGAS activation

Different from activation of RLRs by K-63 chains, two different types of ubiquitination, K-27 linked polyubiquitination and mono-ubiquitination, have been indicated to upregulate the function of cGAS. RNF185 is responsible for polyubiquitination of cGAS, while TRIM56 and TRIM41 monoubiquitinate cGAS. RNF185 specifically facilitates the formation of K27-linked polyubiquitin chain at K173 and K384 of cGAS, potentiating the catalytic activity of cGAS. Mutations of these two lysine residues in cGAS or mutation of the RING domain of RNF185 impaired the cGAMP production through *in vitro* enzymatic activity assay. Furthermore, knockdown of RNF185 in L929 fibroblast led to the reduction of IFN production and subsequent less restriction of viral replication following HSV-1 infection [75]. Different from RNF185, TRIM56 induces monoubiquitination of cGAS at K335 of CTD domain [76]. Furthermore, this modification by TRIM56 is required for its oligomerization and DNA binding capacity, but dispensable for the catalytic activity of NTase domain. Congruently, the peritoneal macrophages or BMDMs from *Trim56*−/− mice produced a significantly lower level of IFNβ mRNA upon infection of HSV-1 instead of influenza virus. More importantly, *in vivo* study demonstrated that the blood from *Trim56*−/− mice contained much less level of IFNα/β compared to WT mice, leading to higher death rate compared with WT mice following HSV-1 infection and suggesting the critical role of TRIM56-mediated monoubiquitination on cGAS function [76]. Another TRIM family E3 ligase TRIM41 (RINCK) also monoubiquitinates cGAS and upregulates the activity of cGAS as well as the synthesis of cGAMP [77]. Furthermore, knockout of TRIM41 in U937 cells led to less production of IFNβ and more viral particles upon HSV-1 infection.

4.2. E3 ligases accountable for activation of STING

Until now, there are four identified E3 ubiquitin ligases, including TRIM56, TRIM32, MUL1, and AMFR, to promote the function of STING. Three of them, including TRIM56, TRIM32, and MUL1, facilitate the conjugation of K-63 linked chains, whereas AMFR enhances the K-27 linked polyubiquitination of STING. TRIM56 binds to the C-terminal domain of STING and induces the polyubiquitination at residue K150 of STING, which promotes dimerization of STING as well as its interaction with TBK1 [78]. TRIM32 interacts with the transmembrane domain of STING and facilitates the conjugation of K-63 polymeric chains at K20, K150, K224, and K236 of STING [79]. Knockdown of TRIM32 in THP-1 cells inhibited the expression of IFNβ, TNFα, and IL-1β upon HSV-1 infection, suggesting the positive regulation of STING by TRIM32 [79]. A recent study indicated that MUL1 is accountable for the K-63 linked polyubiquitination at K224 of STING [80]. Knockdown of MUL1 in MEFs generated significantly less IFNβ and more viral particles upon infection of HSV-1 with γ34.5 deletion [80].

AMFR, an ER-associated E3 ubiquitin ligase, is identified as an interacting partner with STING following HSV-1 infection through a proteomic study [81]. Different from the E3s above, AMFR facilitates the formation of K-27 linked polyubiquitin chain at K137, 150, 224, and 236 of STING, and this modification serves as a scaffold to recruit TBK1 through interaction between K-27 polyubiquitin chains and ubiquitin-like domain (ULD) of TBK1. Consequently, the deficiency of AMFR in MEFs attenuated IRF3 activation as well as the production of subsequent IFN and proinflammatory cytokines following HSV-1 infection. Of note, the interaction between AMFR and STING was enhanced by another protein INSIG1. *Insig1*−/− mice produced much fewer IFNβ and were less resistant to the lethal HSV-1 infection, indicating the positive regulation of STING function by AMFR/INSIG mediated K27-linked ubiquitination [81].

4.3. E3 ubiquitin ligases responsible for the degradation of cGAS and STING

Until now, a specific E3 ligase responsible for the ubiquitination and subsequent degradation of cGAS has not been identified according to our knowledge. But one study suggested that K48-linked polyubiquitination at K414 of cGAS regulates its degradation through the autophagy-lysosome pathway instead of the proteasome-dependent pathway [82]. K48-linked polyubiquitination at K414 of cGAS permits the interaction between cGAS and the ubiquitin associated domain (UBA) of autophagy cargo protein p62, which is important for the transportation of ubiquitinated protein into the autophagosome. In this study, they also found that TRIM14 inhibits this degradation process through recruiting USP14 to cleave the K-48 linked ubiquitin and block the interaction between cGAS and p62 [82].

There are a couple of E3 ubiquitin ligases accountable for the protein stability of STING, including RNF5, RNF26, TRIM29, and TRIM30α. RNF5 targets STING for K-48 linked polyubiquitination at K150 and therefore leads to its proteasome degradation [83]. RNF26, another E3 ubiquitin ligase, catalyzes the ubiquitination of STING and counteracts the effect of RNF5 [84]. RNF26 polyubiquitinates STING with K-11 linked polymeric chain at K150, which in turn protects STING from K-48 mediated degradation by RNF5. TRIM29 has been identified as E3 ligase for STING by two independent groups. One group found that Epstein-Barr virus (EBV) employed TRIM29 in airway

epithelial cells and myeloid dendritic cells to target STING for degradation and lead to the less production of type I interferons, which is beneficial for EBV to establish persistent infection in both cell types [85]. Another group found that deficiency of TRIM29 elevated the type I interferon and proinflammatory cytokines, and *Trim29*−/− mice were more resistant to lethal HSV-1 infection than WT counterparts [86], indicating the inhibitory effect of TRIM29 on STING. TRIM30α interacts with STING and leads to K-48 linked ubiquitination at K275 of STING and its degradation. Furthermore, *Trim30α*−/− BMDCs and peritoneal macrophages elevated the production of type I IFN as well as IL-6 in responses to HSV-1 or transfected DNA compared with WT counterparts. Most importantly, *Trim30α*−/− mice were more resistant to HSV-1 infection than WT mice [87], suggesting its negative regulation of STING-mediated DNA virus-triggered signaling.

5. Common downstream molecules in the antiviral signaling pathway

Even though different antiviral pathways employ distinct adaptor proteins, they converge on common signaling molecules. Among these common downstream signaling molecules are members of the TRAF proteins, especially TRAF3 and 6, the kinases TBK1/IKKε and IKKα/β/γ, and the transcriptional factors IRF3/p65. As aforementioned, these molecules are responsible for transducing the signaling downstream and ultimately inducing the IFN and proinflammatory response. Multiple E3 ubiquitin ligases have been identified to fine-tune these important common signaling molecules.

5.1. E3 ubiquitin ligases for activation of common downstream molecules

RNF166 and HECTD3 have been identified as the E3 ligases catalyzing the K-63 linked polyubiquitination of TRAF proteins. RNF166 enhances the conjugation of K-63 linked polyubiquitination of TRAF3 and TRAF6. Furthermore, knockdown of RNF166 inhibited the production of IFN upon SeV or EMCV infection [88]. HECTD3 promotes the conjugation of K-63 linked polymeric chains at K138 of TRAF3 during bacterial infection [89]. Therefore, the mice with deficiency of HECTD3 were more susceptible to *Francisella novicida, Mycobacterium,* and *Listeria*. Furthermore, *Hectd3*−/− BMDMs produced considerably less expression of IFNβ and ISGs compared with WT counterparts in response to poly(I:C) or dsDNA [89]. But the exact function of HECTD3 during viral infection still needs to be further examined.

Several E3 ubiquitin ligases, including Nrdp1, Mib1, Mib2, and RNF128, promote the K-63 linked polyubiquitination of kinase TBK1 for its activation. These E3s regulate the activation of TBK1 under different stimuli. Nrdp1 facilitates the ubiquitination after LPS treatment [23], whereas Mib1 and Mib2 conjugate the ubiquitination of TBK1 following RNA virus infection [90]. RNF128 is considered as a general regulator of TBK1 ubiquitination, responding to both DNA and RNA viruses [91]. RNF128 has been identified by our lab to facilitate the conjugation of the K-63 linked chains at K30 and K401 of TBK1 [91]. Deletion of RNF128 or mutation of ubiquitination sites in TBK1 drastically impaired its kinase activity and phosphorylation upon viral infection. More importantly, the replication of both VSV and HSV was significantly enhanced in *Rnf128*−/− mice than in WT counterparts. Of note, the protein level of RNF128 was significantly elevated in both mouse primary peritoneal macrophages and THP-1 cells following either RNA or DNA virus infection, suggesting the host cells modulate its level to combat the viral infection.

Activation of NEMO is regulated by the E3 ligase TRIM23 through atypical K-27 linked polyubiquitination occurring at K105/309/325/326/344 [92]. Moreover, knockdown of TRIM23 in MEFs affected the production of IFNβ with SeV infection and enhanced the production of viral particles following VSV infection [92]. Besides K-27 linked modification, NEMO is also conjugated with linear ubiquitin chains catalyzed by a heterotrimeric RBR-family E3 ligase LUBAC complex composed HOIP, HOIL-1L, and Sharpin [93,94]. LUBAC interacts with NEMO and conjugates the linear polyubiquitin chains at K285 and K309 of NEMO. Mutations of K285 and K309 of NEMO abrogated its activation in the NF-κB reporter assay, suggesting the positive role of linear ubiquitination on NEMO in the regulation of NF-κB pathway [12]. However, the linear ubiquitination of NEMO catalyzed by LUBAC exerts the opposite role in IFN response [11]. The linear ubiquitination of NEMO competes with MAVS to interact with TRAF3, therefore affecting the formation of MAVS-TRAF3 signalosome and downstream production of IFNβ. In SHARPIN-deficient MEFs, VSV replication was decreased due to the increase of IFN production.

5.2. E3 ubiquitin ligases responsible for the degradation of common downstream molecules

Triad3A and TRIM38 were identified as the E3 ligase for the ubiquitination and subsequent degradation of TRAF3 and TRAF6, respectively [95,96]. Traid3A facilitates the conjugation of K-48 linked polyubiquitination on TRAF3, leading to its proteasome-dependent degradation. Consistent with this, knockdown of Triad3A enhanced the expression of IFNβ and ISGs following infection of VSV or SeV [95]. Of note, Triad3A was found to be induced in the late phase of infection by VSV or SeV [95], suggesting a negative feedback of innate immunity by Triad3A in late phase infection. TRIM38 conjugates the K-48 linked polyubiquitin chains on TRAF6, leading to its degradation [96]. Knockdown of TRIM38 in primary macrophages enhanced the protein level of TRAF6 and subsequent production of proinflammatory cytokines including TNFα and IL-6 upon stimulation of TLR agonists [96].

A couple of E3 ubiquitin ligases including DTX4, TRIP, and TRIM27 have been identified to regulate the stability of TBK1. DTX4 facilitates the K-48 linked polyubiquitin chains at K670 of TBK1, which leads to proteasomal-dependent degradation [97]. NLRP4 is required for the interaction between DTX4 and TBK1, which is stimulated with the virus infection. Congruently, knockdown of NLRP4 in THP-1 cells stabilized TBK1, enhancing the expression of IFNβ and restricting viral infection [97]. TRIP, a RING-type E3 ubiquitin ligase, specifically interacts with TBK1 and promotes K-48 linked polyubiquitination and degradation of TBK1 [98]. Furthermore, knockdown of TRIP in mouse peritoneal macrophages enhanced the TBK1 activity and production of IFNβ upon SeV infection, indicating its negative regulation of innate immunity in immune cells. TRIM27 associates with Siglec1, DAP12, and SHP2 to facilitate the polyubiquitination of TBK1. The K-48 linked polyubiquitination occurs at K251 and K372 of TBK1, leading to its degradation. Consistently, knockdown of TRIM27 in macrophages significantly enhanced the production of type I interferon and inhibited the VSV replication [99].

The E3 ligases TRIM29 and TRAF7 modulate the stability of NEMO through proteasome- and lysosome-dependent pathway, respectively. TRIM29 promotes K48-linked ubiquitination at K183 of NEMO, leading to its proteasomal-dependent degradation [100]. Congruent with this, *Trim29*−/− alveolar macrophages (AMs) produced significantly more type I IFN and proinflammatory cytokines following influenza virus or reovirus infection. Furthermore, *Trim29*−/− mice were more resistant to the lethal influenza virus infection compared with the WT mice in the survival assay [100]. Different from TRIM29, TRAF7 facilitates the conjugation of K-29 linked polyubiquitination and subsequent lysosome-dependent degradation of NEMO, playing an inhibitory role in NF-κB pathway [101].

Several E3 ligases including RBCK1, TRIM26, c-Cbl, and RAUL have been identified to be responsible for K-48 linked ubiquitination and degradation of IRF3. Knockdown of RBCK1 in 293 cells affected the VSV replication, suggesting its negative regulation of host immunity [102]. Furthermore, knockdown of TRIM26 or c-Cbl in peritoneal macrophages enhanced the IFNβ production following SeV infection, suggesting both of them negatively regulate the innate immunity against viral infection [103,104]. Interestingly, the degradation of IRF3

through RAUL is hijacked by KSHV to counteract the antiviral response [105]. Of note, there are two contradictory results concerning the effect of TRIM21 on IRF3. One group proposed that TRIM21 induces the ubiquitination and degradation of IRF3 [106], while the other one found TRIM21 stabilizes the IRF3 during viral infection [107]. The exact role of TRIM21 in antiviral immunity requires further examination in the knockout mouse model. p65, the subunit of NF-κB, is also targeted for ubiquitination by a variety of E3 ubiquitin ligases, including PDLIM2, MKRN2, COMMD1/Cul2, and TRAF7. Notably, MKRN2 and PDLIM2 synergistically promote polyubiquitination and degradation of p65 [108,109]. Furthermore, the degradation of p65 by COMMD1/Cul2 complex is phosphorylation and proteasome-dependent [110], while the K-29 linked polyubiquitination induced by TRAF7 leads to lysosomal degradation of p65 [101].

6. Conclusions and perspectives

In the past decades, a myriad of studies have demonstrated that K-63 linked and K-48 linked polyubiquitination play a crucial role in the modulation of key signaling molecules. Meanwhile, emerging studies indicate the participation of atypical ubiquitination in antiviral response. Unlike K-48 or K-63 canonical chains with defined roles, the same atypical ubiquitination in different lysine residues of the same substrate or in different substrate proteins exert quite distinct functions, suggesting the complexity of atypical ubiquitin chains. Illustration of the functional roles of atypical chains and their corresponding E3s will provide new clues for both innate immunity and the other signaling pathways since the atypical ubiquitination has been suggested to participate in a series of physiological processes. Substantial studies have emphasized the importance of ubiquitination and E3 ubiquitin ligases in accurately regulating the antiviral innate immunity. Notably, the key signaling molecules are activated and degraded by a variety of E3s in same or different lysine residues, suggesting that a dynamic, temporal, and spatial modulation is essential for a proper immune defense. Therefore, elucidating the dynamic control of signaling transduction will be employed for the development of novel clinical therapies, both for treating infectious diseases as well as aberrant autoimmunity resulting from inflammatory response.

Conflicts of interest

None declared.

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Appendix A. Supplementary data

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