

Tripartite Motif Family

Subjects: [Immunology](#) | [Virology](#) | [Oncology](#)

Contributor: Shunbin Ning

The tripartite motif (TRIM) family comprises at least 80 members in humans, with most having ubiquitin or SUMO E3 ligase activity conferred by their N-terminal RING domain. TRIMs regulate a wide range of processes in ubiquitination- or sumoylation-dependent manners in most cases, and fewer as adaptors. Their roles in the regulation of viral infections, autophagy, cell cycle progression, DNA damage and other stress responses, and carcinogenesis are being increasingly appreciated, and their E3 ligase activities are attractive targets for developing specific immunotherapeutic strategies for immune diseases and cancers.

TRIMs

ubiquitination

PRR

IFN-I

IRFs

1. Introduction

In mammals, interferons (IFNs) include three types, type I, II, and III. Type I IFNs (IFN-I) include the majority of 26 isoforms of IFN α that are encoded by 13 genes, and one IFN β that is encoded by the single gene IFNB, as well as other minor subtypes, including IFN ϵ , IFN κ , IFN ω , IFN δ , IFN τ , and IFN ζ . IFN α s are mainly secreted by plasmacytoid dendritic cells (pDCs) and IFN β is mainly secreted by fibroblasts. All IFN-I signal through the integral membrane IFNAR1 and -2 heterodimer, and play crucial roles in the first line of innate immune response and subsequent adaptive immune response in response to viral or bacterial infections ^[1].

Importantly, recent studies have shown that IFN-I play a dual role in chronic viral infections. At the early stage of infection, they have potent antiviral activity. However, at late stages, a low level of prolonged IFN-I signaling, exemplified by chronic infection of viruses such as HIV and HCV ^{[2][3][4]}, triggers long-term chronic immune activation that proceeds to T cell exhaustion and inflammaging/immunosenescence in both direct and indirect manners ^{[5][6]} and therefore serves as a bridge that links innate and adaptive immune responses ^{[4][5][7][8][9][10]}. For example, the engagement of TLR7 in HIV-infected CD4⁺ T cells induces anergy/unresponsiveness, accounting for the impaired T cell function by chronic HIV infection ^[11]. A prolonged IFN-I response also facilitates the establishment of TME (tumor microenvironment) ^{[4][5][7][12][13][14]}. IFN-I also play crucial roles in cellular development and homeostasis ^{[5][6][15][16][17]}. Aberrant production of IFN-I is associated with many types of diseases, including autoimmune disorders and cancers ^{[6][18][19][20]}. Therefore, it is of fundamental importance to understand the precise mechanisms of how IFN-I are regulated in different biological contexts ^{[21][22]}.

Ubiquitination is a pervasive theme equally important to phosphorylation of proteins in myriad processes. Ubiquitin (Ub) is a 76-amino acid protein that is ubiquitously distributed and highly conserved throughout eukaryotic organisms. The Ub protein can be free or conjugated to a lysine site of a protein substrate through its 3'-end. This

conjugation process involves E1 activating enzyme, E2 conjugating enzyme, and E3 ligase, with the E3 ligase determining the specificity of the substrate. Ub itself has seven internal lysine residues (K6, K11, K27, K29, K33, K48, and K63), and each can serve as the Ub target to link another Ub. If only a single Ub is conjugated to each lysine site of the substrates, it is called mono (also only one lysine site on the substrate) or multi (more than one lysine site on the substrate) ubiquitination. If the substrate is Ub itself, polyubiquitin chains will be formed on the substrate. Usually, a polyubiquitin chain contains more than 4 Ub molecules. In the last decade, non-canonical ubiquitination types on serine, threonine, and cysteine sites other than lysine site have been identified, and their importance in specific cellular functions has been recognized [23][24].

The most well-understood type of ubiquitination is K48-linked polyubiquitination, which is principally known as the major process whereby proteins are targeted for proteasomal degradation through the 26S proteasome. Later, nonproteolytic types of polyubiquitination (represented by K63-linked polyubiquitination), monoubiquitination, and linear ubiquitination have been gradually identified [25][26][27]. More recently, other ubiquitination-like modifications (e.g., sumoylation, acetylation, ISGylation, neddylation, palmitoylation, and UFMylation) have also been discovered. The roles of these posttranslational modifications (PTMs) in a myriad of cellular processes, such as receptor internalization (endocytosis), vesicle trafficking, immune response and inflammation, DNA damage response, autophagy, and cell death, have been greatly appreciated [27][28][29][30][31][32][33][34][35].

IFN-I production is controlled at multiple layers to ensure appropriate mounting of antiviral and antitumor immune responses. It is clear that both host and viral ubiquitin systems play pivotal roles in IFN-I-mediated innate immunity and in cellular transformation mediated by oncogenic viruses represented by EBV (Epstein-Barr Virus), KSHV (Kaposi's sarcoma-associated herpesvirus), and HPV (human papillomavirus) [36][37][38][39][40][41].

2. PRR Signaling Pathways to IFN-I Production

IFN-Is are produced downstream of the signaling pathways of host germline-encoded pathogen recognition receptors (PRRs), which are expressed on the cell membrane or in the cytoplasm of the cells of the innate immune system, in response to pathogen-associated molecular patterns (PAMPs) that include pathogenic nucleic acids, LPS, and proteins, or in response to host damage-associated molecular patterns (DAMPs), such as self-nucleic acids, heat-shock proteins, and HMGB1. Recognition of PAMPs or DAMPs by PRRs triggers signal cascades that activate the transcription factors, including NFκB, Interferon regulatory factors (IRFs), and AP1, or activate caspase-mediated cell death and inflammation.

PRRs include the well-known transmembrane Toll-like receptors (TLRs) (Figure 1) and an increasing pool of “Toll-free” receptors [22]. Endosomal TLRs (TLR3, -7, -9, and murine TLR8) and endocytic TLR4, as well as cytoplasmic RIG-I and cGAS, amongst others, are able to recognize pathogenic or host cell nucleic acids (LPS for TLR4) to activate IRFs in addition to NFκB and AP1, which induce IFN-Is and also pro-inflammatory cytokines [42]. Self-nucleic acids are derived from the nucleus or mitochondria of the cells suffering from endogenous or exogenous stresses, such as DNA replication, oxidative stress, DNA damage, and cell death [43][44][45][46][47]. While the

transcription of IFN α s is solely dependent on IRFs, full transactivation of the IFN β promoter requires the cooperation of IRFs, NF κ B, and other co-factors in the transcriptional complex named enhanceosome [48].

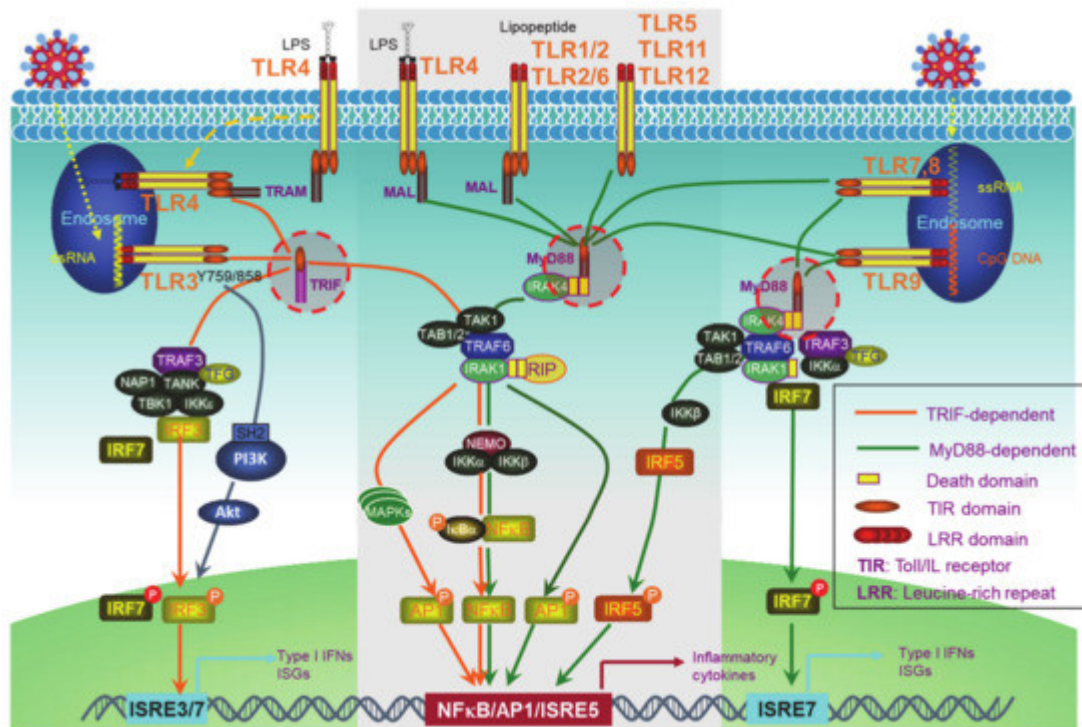


Figure 1. Toll-like receptor (TLR) signaling pathways. The TLR family has 13 members, among which, endosomal TLR3, -7, -9, and murine TLR8, and endocytic TLR4 are able to trigger signaling for IFN-I production. TLRs that cannot trigger the activation of Interferon regulatory factors (IRFs) (The middle part in the gray frame) do not contribute to IFN-I production. All the TLRs have a TIR domain in the cytoplasm, which recruits adaptor proteins also with a TIR domain at their C-terminus. TRIF and MyD88, two adaptor proteins, bridge all TLRs to downstream signaling molecules, leading to the activation of NF κ B, IRFs, and AP1. IRF1, -3, -5, -7, and -8 are the transcription factors for both IFN α and IFN β transcription in different cell contexts, but a full IFN β transcription requires the enhanceosome complex that contains NF κ B, IRF3, -7, ATF-2/c-Jun, and HMGIY (high mobility group I(Y)). ISRE: Interferon-stimulated response element. ISRE3/7: ISRE that binds to IRF3/7. ISRE7: ISRE that binds to IRF7.

3. The TRIM Family

The tripartite motif (TRIM) family of proteins is large and includes at least 80 members in humans, with most having E3 ligase activity for target-specific ubiquitination, and plays crucial roles in innate immunity, transcription, autophagy, and carcinogenesis [49][50]. The N-terminal TRIM motif includes the conserved RBCC domain that comprises of three subdomains: 1 RING domain that confers with E3 ligase activity (8 human TRIMs do not have the RING domain), 0–2 B-box ZNF domains (B1+B2 or B2 alone), and 0–1 coil-coil region that is associated with B-boxes. According to the diversity of the C-terminuses and genomic organization, TRIM proteins are grouped into Group1 and Group 2. Members in Group 1 possess a variety of C-terminal domains (COS, FN3, ACID, PRY, PHD-BROMO, FIL, NHL, MATH, ARF, and TM) and exist in both vertebrate and invertebrates, and those in Group 2

possess a C-terminal SPRY domain, and they are absent in invertebrates (Figure 2) [49][50][51]. The SPY-SPRY domain is critical for TRIM proteins' interaction with their substrates.

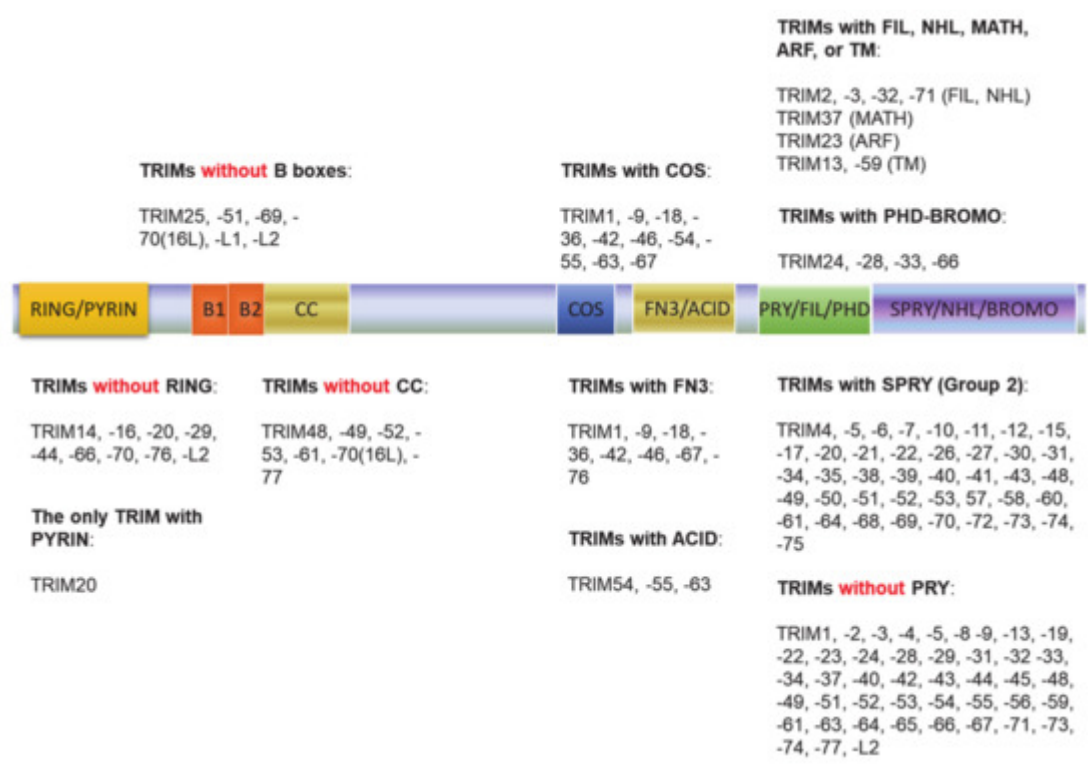


Figure 2. The tripartite motif (TRIM) family protein domain alignment. The TRIM family includes at least 80 members in humans. The N-terminal TRIM motif includes the conserved RBCC domain that comprises of three subdomains: 1 RING domain that confers with E3 ligase activity (8 TRIMs in humans do not have the RING domain), 0~2 B-box ZNF domains (B1+B2 or B2 alone), and 0~1 coil-coil region that is associated with B-boxes. According to the diversity of the C-terminuses and genomic organization, TRIM proteins are grouped into Group1 and Group 2. Members in Group 1 possess a variety of C-terminal domains (COS, FN3, ACID, PRY, PHD-BROMO, FIL, NHL, MATH, ARF, and TM) and exist in both vertebrate and invertebrates, and those in Group 2 possess a C-terminal SPRY domain, and they are absent in invertebrates.

Many TRIMs are inducible by IFN-Is, and play crucial roles in IFN-I-mediated innate immune regulation, with the involvement of ubiquitination and sumoylation in most cases [50][52][53][54][55][56][57][58]. These TRIMs can target most if not all components of the PRR and Jak-STAT1 IFN-I pathways, including different ligands (PAMPs and DAMPs); the receptors such as TLRs, cGAS, and DDX41; the adaptors MyD88, TRIF, STING, and TRAF6 and -3; the kinases IKKs and TAK1; and the transcription factors IRF3 and -7 and NFκB (Table 1). TRIM genes evolve parallelly with the immune system, further supporting their roles as regulators of immune responses [51][53].

Table 1. TRIMs in the regulation of Interferon (IFN)-I-mediated innate immune network.

* NA: not assayed. Question marks (?) refer to “very likely but not experimentally revealed”.

TRIM	Synonym	Targets in the IFN-I Network	Ub Conjugation Type	Outcome of Conjugation	Selected References
TRIM3	RNF97	TLR3	K63	Promotes ESCRT-mediated TLR3 sorting to endosomes	[59]
TRIM4	RNF87	RIG-I	K63	Activation	[60]
TRIM5α	RNF88	HIV Gag	K48	Degradation	[61][62]
		TAK1	K63	Activation	[63]
	TRIM12c in mice	TRAF6	K63 (?)	Activation	[62]
TRIM6	RNF89	Ebola VP35	Poly	Promotes VP35 IFN-I inhibitory activity	[64]
		IKKε	Free K48	Activation of IKKε, leading to STAT1 activation	[65]
TRIM7	RNF90	Zika virus envelope (E)	K63	Enhances virus attachment and entry into the cell	[66]
	GNIP				
		TLR4	NA*	Promotes TLR4 activation	[67]
TRIM8	RNF27	TRIF	K6, K33	Disrupts the TRIF-TBK1 complex	[68]
	GERP				
		TAK1	K63	Activation	[69][70]

TRIM	Synonym	Targets in the IFN-I Network	Ub Conjugation Type	Outcome of Conjugation	Selected References
		IRF7		Protects p-IRF7 from Pin1-mediated proteasomal degradation in the nucleus	[71]
		SOCS1	K48 (?)	Degradation	[72]
			K48	Degradation	[73]
		PIAS3	Interaction (?)	Promotes PIAS3 nucleus-to-cytoplasm translocation	[74]
TRIM9s	RNF91	TBK1	Interaction	Recruits GSK3β and TBK1, leading to TBK1 activation	[75]
	SPRING				
TRIM9		β-TrCP	Interaction	Stabilizes IκBα	[75][76]
	RNF92	TBK1	Interaction	Inhibits TBK1 activation	[77]
TRIM11					
	BIA1	TRIM5	NA*	Degradation	[78]
	RNF77	RIG-I	Interaction	Potentiates RIG-I activity	[79]
TRIM13	RFP2	MDA5	Interaction	Inhibition	[79]
	CAR				
	LEU5	TRAF6	K29	Activation	[80]
	DLEU5	NEMO	K48	Degradation	[81]
TRIM14	KIAA0129	HCV NS5A	K48 (?)	Degradation	[82]

TRIM	Synonym	Targets in the IFN-I Network	Ub Conjugation Type	Outcome of Conjugation	Selected References
		cGAS, TBK1	Interaction	Inhibition of autophagic degradation of cGAS	[83][84][85]
		MAVS	Interaction	Recruitment of NEMO to MAVS signalosome	[84]
TRIM15	RNF93 ZNF178 ZNFB7	MAVS	NA*	Promotes RIG-I-mediated IFN production	[86]
TRIM19	RNF71 PML MYL	HIV genome		Sequesters HIV genome in the cytoplasm, blocking HIV transduction	[87]
		HFV Tas		Represses HFV transcription by preventing Tas binding to viral DNA	[88]
		LCMV Z		Inhibits LCMV replication	[89]
		hCMV IE1	Interaction	IE1 forms a complex with TRIM19-STAT1/2 to impede IFN-I signaling	[90]
		STAT1/2		Induction and stabilization, promoting IFN-I signaling	[90]

TRIM	Synonym	Targets in the IFN-I Network	Ub Conjugation Type	Outcome of Conjugation	Selected References
		Pin1 (by TRIM19IV)		Regulates the cellular distribution of Pin1	[91]
		Ubc9 (The only SUMO E2)		Required for IFN-induced global sumoylation	[92]
		NFκB		Inhibits NFκB-mediated transcription and survival	[93]
				Promotes IKKε-mediated p65 phosphorylation and NFκB activity	[94]
		ROS		Functions as an ROS sensor promoting p53 activation	[95]
TRIM20	Pyrin	p65	Interaction	Promotes p65 nuclear translocation	[96]
	MEFV	IκBα		Promotes IκBα degradation	[96]
TRIM21	RNF81	DDX41	K48	Degradation	[97]
	Ro52	MAVS	K27	Activation	[98]
	SSA1				
		FADD	Interaction	Promotes IRF7 ubiquitination-mediated degradation	[99]

TRIM	Synonym	Targets in the IFN-I Network	Ub Conjugation Type	Outcome of Conjugation	Selected References
		TAK1	Free K63	Activates TAK1, leading to the activation of NFκB, AP1, and IRFs	[100] [101]
		IKKβ	Mono-Ub	Autophagic degradation	[102]
		IRF3	Interaction	Protects p-IRF3 from Pin1-mediated proteasomal degradation	[103]
			K48	Targets IRF3 for proteosomal degradation	[104] [105]
		Interacts with ULK1, Beclin1, and p62		Targets IRF3 for autophagic degradation	[106]
		IRF5	Various	Degradation of isoforms V1 and V5, but not V2 or V3	[107]
		IRF7	K48	Degradation	[108]
		IRF8	NA*	Activation	[109]
TRIM22	RNF94	HIV Gag, LTR		Degradation	[110]
	STAF50	Influenza A Virus NP		Degradation	[111]

TRIM	Synonym	Targets in the IFN-I Network	Ub Conjugation Type	Outcome of Conjugation	Selected References
		HCV NS5A	K48 (?)	Degradation	[112]
		TAB2	K48 (?)	Degradation	[113]
		TRAF3	Interaction	Function not clear, likely promoting TRAF3-mediated antiviral activity	[114]
TRIM23	RNF46	TRAF6	Interaction	Activation of NFκB mediated by HCMV UL144	[115]
	ARD1				
	ARFD1	NEMO	K27	Activation	[114]
		TBK1	K27 of TRIM23 (self)	Recruits and activates TBK1, inducing TBK1-mediated autophagy	[116]
		TRAF3	K63	Activation	[117]
TRIM24	RNF82	RARα	Interaction	Inhibits RARα activity and retinoic acid-induced STAT1 expression	[118]
	TIF1A				
		p53	K48 (?)	Promotes p53 ubiquitination and degradation	[119]
TRIM25	RNF147	Influenza virus vRNP		Blocks vRNA chain elongation	[120]
	ZNF147				
		RIG-I	K63	Activation	[121] [122]

TRIM	Synonym	Targets in the IFN-I Network	Ub Conjugation Type	Outcome of Conjugation	Selected References
		MAVS	K48	Degradation	[123]
		ISG15		Functions as an ISG15 E3 ligase	[124]
		ZAP	K48, K63	Critical for ZAP inhibition of viral genome translation	[125]
TRIM26	RNF95	TBK1	K27 of TRIM26 (self)	Bridges TBK1-NEMO interaction, leading to TBK1 activation	[126]
	ZNF173				
	AFP	IRF3	K48	Degradation	[127]
TRIM27	RNF76	TBK1	K48	Degradation	[128] [129] [130]
	RFP	IKK α , IKK β , IKK ϵ	Interaction	Inhibition	[131]
TRIM28	RNF96	IRF7	Sumoylation	Inhibition	[132]
	KAP1				
TRIM29	ATDC	STING	K48	Degradation	[133] [134]
		MAVS	K11	Degradation	[135]

TRIM	Synonym	Targets in the IFN-I Network	Ub Conjugation Type	Outcome of Conjugation	Selected References
		NEMO	K48	Degradation	[136]
		STING	K48	Degradation	[137]
TRIM30α	RPT1				
TRIM31	RNF	TAB2/3		Lysosomal degradation	[138]
	HCG1	MAVS	K63	Promotes MAVS signalosome assembly	[139]
		Influenza PB1	K48	Degradation	[140]
TRIM32	TATIP				
	BBS11	STING	K63	Activation	[141]
	HT2A	TRIF	NA*	Targets TRIF for TAX1BP1-mediated autophagic degradation	[142]
TRIM33	TIF1y	HIV integrase	K48	Degradation	[143]
TRIM35	HLS5	TRAF3	K63	Activation	[144]
	MAIR	IRF7	K48	Degradation	[145]
TRIM38	RNF15	RIG-I, MDA5	Sumoylation	Stabilization	[146]
	RORET	cGAS, STING	Sumoylation	Stabilization	[147]
		TRAF6	K48	Degradation	[148]

TRIM	Synonym	Targets in the IFN-I Network	Ub Conjugation Type	Outcome of Conjugation	Selected References
		NAP1	K48	Degradation	[149]
		TAB2	K48?	Degradation	[150]
		TRIF	K48	Degradation	[150] [151]
TRIM39	RNF23 TFP	Cactin	NA*	Stabilizes Cactin, inhibiting NFκB and IRFs	[152]
TRIM40	RNF35	RIG-I, MDA5	K27, K48	Degradation	[153]
		NEMO	Neddylation	Inhibition	[154]
TRIM41	RINCK MGC1127	cGAS	Mono-Ub	Activation	[155]
TRIM44	DIPB AN3	MAVS	Interaction	Stabilization of MAVS by preventing its ubiquitination	[156]
TRIM45	RNF99	NFκB	E3 ligase activity not required	Inhibition of TNFα-mediated NFκB activation	[157]
TRIM56	RNF109	Influenza virus RNA	Inhibits vRNA synthesis		[158]

TRIM	Synonym	Targets in the IFN-I Network	Ub Conjugation Type	Outcome of Conjugation	Selected References
		cGAS	Mono-Ub	Activation	[159]
		STING	K63	Activation	[160]
		TRIF	Interaction	Activation	[161]
TRIM59	RNF104 TSBF1 MRF1 IFT80L	ECSIT	Interaction	Inhibition of TLR singling pathways to activate NFκB and IRFs	[162]
TRIM62	DEAR1	TRIF	NA*	Activation	[86]
TRIM65		MDA5	K63	Activation	
TRIM68	RNF137 SS56	TFG	various	Induces TFG lysosomal degradation	[163]

4. TRIMs in Regulating PRR Signaling Pathways to IFN-I Production

Upon binding to PAMPs or DAMPs, PRRs trigger signals that transmit via unique adaptors to the Ub E3 ligase TRAF6 or -3 and then orchestrate to activate the kinase cascades IKKs, IRAKs, and MAPKs for the activation of the transcription factors NFκB, IRFs, and AP1. Ubiquitination regulates the cellular trafficking, stability, complex assembly, and activity of different components in PRR signaling cascades ([Figure 3](#)).

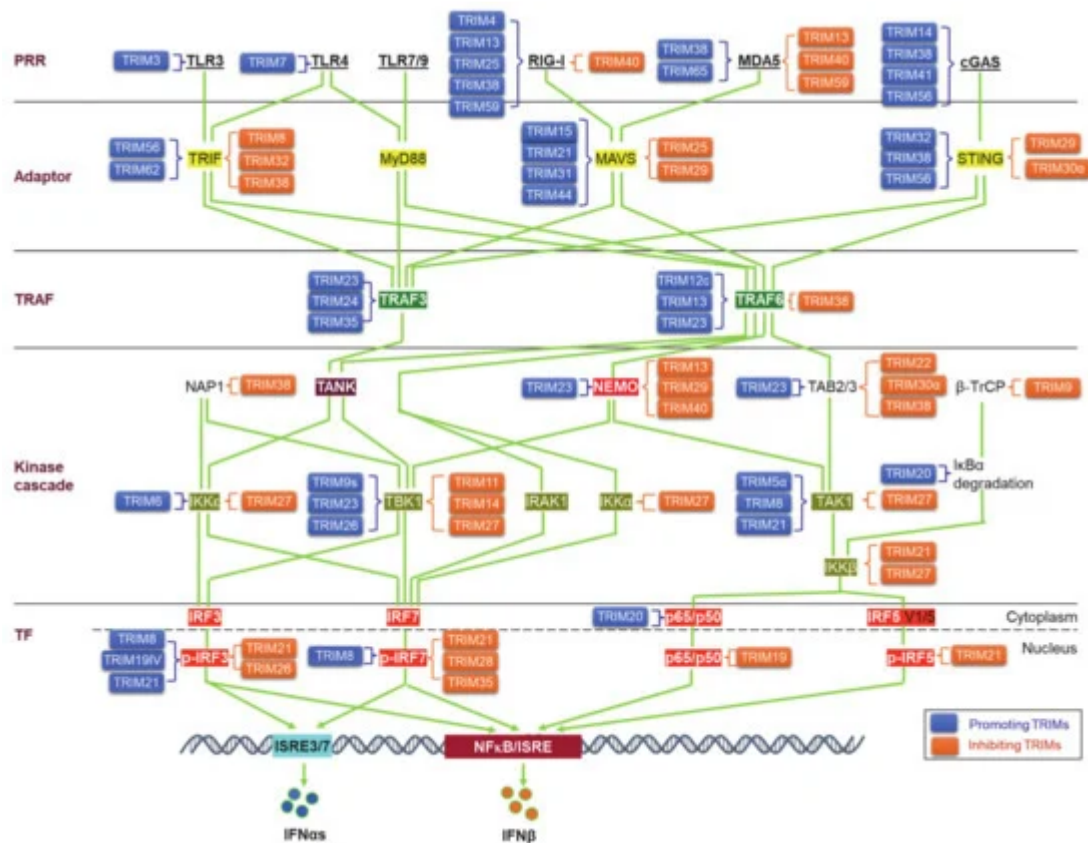


Figure 3. TRIM regulation of pathogen recognition receptor (PRR) pathways. TRIMs are involved in the regulation of the stability and activity of PRR components in all cascades of the signaling pathways, including ligands, receptors, adaptors, TRAFs, kinases and associated regulators, and the final transcription factors (TFs). An increasing pool of regulatory factors of the PRR pathways is also regulated by TRIMs (not shown). TRIMs promoting the stability or activity of the targets are shown on the left of the targets (blue), and those inhibiting the targets are shown on the right of the targets (brown). TRIM19IV and TRIM21 positively regulate phosphorylated IRF3 in indirect manners via Pin1. As such, TRIM8 positively regulates phosphorylated IRF7 in an indirect manner via Pin1. Other indirect regulations of these PRR pathways by TRIMs are not shown. TF: Transcription factor.

Viral PAMPs and other viral components can be targeted by the host Ub system, including a subset of TRIMs, for ubiquitination-mediated degradation in most cases, and thus the IFN-I response is blocked at the very beginning to suppress viral replication, with some examples listed in [Table 1](#) [54][58]. Of note, TRIM5α (also TRIM22) targets HIV1 Gag and plays a unique role in restricting HIV1 infection (and other retroviruses), implicating a potential clinical application [61][62]. In fewer cases, TRIMs can promote viral entry and replication by targeting viral proteins. For example, TRIM7 targets Zika virus envelope protein E for K63-linked ubiquitination that enhances viral attachment to the cell surface and promotes viral entry [66]. VP35, the Ebola virus polymerase co-factor, has IFN-I inhibitory activity. TRIM6 promotes VP35 polyubiquitination to enhance viral infection [64].

5. TRIMs in Regulating the Jak-STAT IFN-I Signaling

The level of initial IFN-I_s produced downstream of PRR pathways upon viral infection is relatively low due to the low level of endogenous IRF7 protein; these priming IFN-I_s then secret to outside of the cell in autocrine and paracrine manners, and bind to IFN-I receptor (IFNAR) on other cells, consequently triggering the Jak-STAT IFN-I pathway, which serves as the second phase of antiviral response by inducing the expression of more IRF7, which in turn participates in IFN-I production downstream of PRR signaling, therefore amplifying the IFN-I production in a positive regulatory circuit (Figure 4) [42].

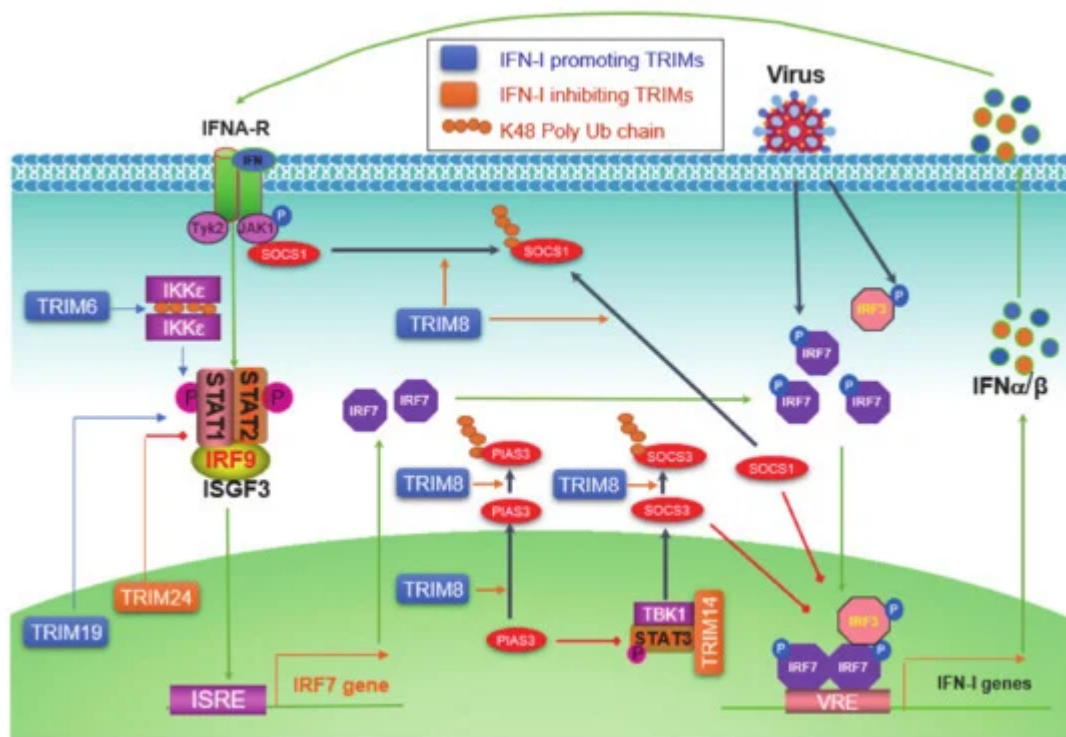


Figure 4. TRIM regulation of the Jak-STAT IFN-I signaling circuit. pathogen-associated molecular patterns (PAMPs) from pathogens activate PRR pathways, leading to the phosphorylation of constitutive high level of IRF3 and low level of IRF7, which induce a low level of IFN-I_s. IFN-I_s secrete from the cell and bind to IFN-I receptors (IFNAR1 and -2) on the cell membrane, followed by the recruitment and activation of Jak1 and Tyk2, leading to the phosphorylation and activation of STAT1 and -2. Phosphorylated STAT1 and -2 bind to IRF9 to form the ISGF3 (IFN-stimulated gene factor) complex, which functions as the transcriptional activator of more than 300 IFN-inducible genes (ISGs), including IRF7 itself. The induced IRF7 proteins then return to be activated by PRR pathways, and therefore constitute a positive regulatory circuit between IRF7 and IFN-I_s, ensuring a potent production of IFN-I_s to fight the invading pathogen. TRIM6 promotes free K48-linked Ub chains that serve as a platform to facilitate IKKε dimerization and activation. TRIM8 regulates the Jak-STAT IFN-I signaling at multiple points. The nuclear TRIM19 potentiates the transcription and activation of STAT1 and -2, and nuclear TRIM24 inhibits RARα-mediated STAT1 promoter activation. ISRE: Interferon-stimulated response element; VRE: Virus-responsive element.

Jak-STAT pathways are well known to be negatively regulated by two families: SOCS (Suppressor of cytokine signaling) and PIAS (Protein inhibitor of activated STAT). TRIM8 can shuttle between the cytoplasm and the

nucleus [74], and has multiple functions to promote IFN-I signaling. TRIM8 promotes proteasomal degradation of SOCS1 and PIAS3 presumably in the cytoplasm, and also nuclear TRIM8 promotes PIAS3 nucleus-cytoplasm translocation to inhibit PIAS3 activity [72][73][74]. SOCS1 not only inhibits Jak1 activity by directly binding to phosphorylated Jak1 in the IFN-I Jak-STAT signaling but also acts as a ubiquitin E3 ligase that targets phosphorylated IRF3 and IRF7 (both also targeted by SOCS3 that recruits the Cul-RBX2 E3 complex) for proteasomal degradation in the nucleus [164]. As such, PIAS3 acts as a SUMO E3 ligase that inhibits IRF1 transcriptional activity through sumoylation in addition to its ability to inhibit STAT3 [165]. TRIM14 negatively regulates IFN-I signaling in mouse macrophage in response to *Mycobacterium tuberculosis* infection by serving as a scaffold that bridges TBK1-STAT3 interaction promoting STAT3 S727 phosphorylation, consequently inducing SOCS3 expression that inhibits IFN-I signaling by targeting phosphorylated IRF3 and IRF7 as well as TBK1 for proteasomal degradation [83]. The nuclear protein TRIM19/PML promotes ISGF3-mediated gene expression by facilitating STAT1 gene transcription and STAT2 protein stabilization, as well as the accumulation of both activated STAT1 and -2 to chromosome [90].

IKK ϵ is not only responsible for the activation of IRF7 and -3 but also plays a role in balancing IFN-I and IFN-II Jak-STAT signaling pathways in immune responses [166]. TRIM6 catalyzes free chains of K48, which promotes IKK ϵ oligomerization and activation to facilitate STAT1 S708 phosphorylation and IFN-I signaling [65]. However, TRIM24 can inhibit retinoic acid-induced STAT1 transcription by interacting with the transcription factor RAR α on the STAT1 gene promoter [118].

IFN-Is establish an antiviral state in both virus-infected cells and uninfected bystander cells, by inducing the expression of over 300 ISGs (IFN-stimulated genes) [6]. Many components of the PRR signaling pathways, such as RIG-I, cGAS, STING, IRF1, and IRF7 belong to ISGs. In addition to these components, many other ISGs, including some TRIMs themselves, are also directly regulated by TRIMs. For example, TRIM11 promotes TRIM5 turnover dependently on its RING domain [78]. Ubiquitination-like modifications, such as sumoylation and ISGylation, are involved in IFN-I-mediated defense mechanisms [30][34][167][168][169][170]. TRIM19/PML mediates global sumoylation [92], and TRIM25 functions as an ISG15 E3 ligase that mediates ISGylation [124]. Further, TRIM25 has been recently reported to be required for the stability of several ISG products [171]. The zinc-finger antiviral protein ZAP, as an ISG, is activated by TRIM25-mediated ubiquitination to inhibit viral genome translation [125]. The tumor suppressor p53 is also an ISG inducible by IFN-Is [172]. TRIM24 promotes p53 ubiquitination and degradation and, in turn, is inducible by p53 [119]. ATM phosphorylates TRIM24 at S768 and promotes its degradation, stabilizing p53 [173]. Numerous TRIMs, in addition to TRIM24, regulate p53 activity and stability in direct or indirect manners [174].

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