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TRIM Proteins and Their Roles in Antiviral Host Defenses

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Abstract

Tripartite motif (TRIM) proteins are a versatile family of ubiquitin E3 ligases involved in a multitude of cellular processes. Studies in recent years have demonstrated that many TRIM proteins play central roles in the host defense against viral infection. While some TRIM proteins directly antagonize distinct steps in the viral life cycle, others regulate signal transduction pathways induced by innate immune sensors, thereby modulating antiviral cytokine responses. Furthermore, TRIM proteins have been implicated in virus-induced autophagy and autophagy-mediated viral clearance. Given the important role of TRIM proteins in antiviral restriction, it is not surprising that several viruses have evolved effective maneuvers to neutralize the antiviral action of specific TRIM proteins. Here, we describe the major antiviral mechanisms of TRIM proteins as well as viral strategies to escape TRIM-mediated host immunity.

INTRODUCTION

Tripartite motif (TRIM) proteins are a family of >80 distinct members in humans that have a conserved structural arrangement of three N-terminal domains: RING–B-box–coiled-coil (1). TRIM proteins can be found in most eukaryotes, with the total number of TRIM genes correlating with the evolutionary degree of the organism (e.g., ~64 members in mice, ~20 in worms, <10 in flies), indicating extensive evolution (2).

The really interesting new gene (RING) domain, which is present in most TRIM proteins, contains a zinc finger motif and is known to possess E3 ubiquitin ligase activity (3). TRIM proteins are able to conjugate a wide range of different polyubiquitin linkage types, which determine the fate of the modified target protein. For example, whereas K48-linked ubiquitination induces proteasomal degradation of the substrate, K63-linked polyubiquitin often modulates the substrate's activity, its subcellular localization, or its ability to interact with other proteins (4). In addition to attaching ubiquitin to their targets, several TRIM proteins catalyze the conjugation of ubiquitin-like (UBL) proteins, such as ISG15 or SUMO, demonstrating enzymatic flexibility of the RING domain. Activity of the RING domain is crucial for the antiviral activity of most TRIM proteins because it allows them to modulate the function of a wide variety of substrates—both host and virus derived—via ubiquitin or UBL modifications. A few TRIM proteins, however, lack a RING domain, and in at least one TRIM protein, TRIM20, the N-terminal RING domain is replaced by a PYRIN domain (5). TRIM proteins generally contain one or two B-box domains that also contain zinc-binding motifs similar to the RING domain (6). Whereas the functional role of the B-box domains remains enigmatic, they have been shown to modulate higher-order self-assembly, E3 ligase activity, and/or protein interactions of certain TRIM proteins. The coiled-coil domain (CCD) directly mediates homomeric self-association of TRIM proteins and in some instances also heteromeric assemblies, which for several TRIM proteins are crucial for their antiviral activities (7).

TRIM proteins can be classified into several subgroups based on their overall domain structure and distinct C-terminal domains (**Figure 1**). The C-terminal domain usually acts as a protein-protein interaction scaffold but can also have enzymatic activity or bind nucleic acids (2). Most commonly found are the ~61 amino acid long PRY domain and the ~140 amino acid long SPRY domain, either in combination (PRY-SPRY) or individually. SPRY domains are found in other human protein families as well and are evolutionarily conserved in mammals, plants, and fungi. In contrast, the PRY-SPRY fusion domain (also referred to as B30.2) is found only in vertebrates (8). The SPRY and PRY-SPRY domains usually serve as protein-protein interaction platforms and exhibit remarkable protein-binding specificities. In addition, the PRY-SPRY domains can have Fc receptor–like properties, as seen with TRIM21 (9), or can mediate binding to RNA molecules (10, 11). The C-terminal subgroup one signature (Cos) domain usually mediates binding to the cytoskeleton, in particular the microtubule network (12). Furthermore, several TRIM proteins possess NHL repeats, which are composed of a six-bladed β propeller and are generally thought to mediate protein-protein interactions (13). Other C-terminal domains found in TRIM family members are fibronectin type 3 (FN3) domains, which can contain binding sites for DNA and heparin; plant homeodomains (PHDs), which bind nuclear substrates; bromodomains, which recognize acetylated lysine residues; meprin and tumor necrosis factor receptor–associated factor homology (MATH) domains, which can mediate self-association; and filamin domains, which have actin cytoskeleton–binding capability (2). Unique among the TRIM proteins is TRIM23, which is the only known family member that encodes an ADP-ribosylation factor (ARF) domain, harboring GTPase activity (14).

TRIM proteins have been implicated in many cellular processes, including signal transduction, oncogenesis, gene regulation, regulation of cell death, and antimicrobial immunity. In this

Figure 1

Domain structure of tripartite motif (TRIM) proteins. The TRIM, consisting of a really interesting new gene (RING) domain, a B-box 1 and/or B-box 2 domain, and a coiled-coil domain (CCD), is followed by distinct C-terminal domains: SPRY-associated domain (PRY), SPIa and the ryanodine receptor domain (SPRY), C-terminal subgroup one signature domain (Cos), fibronectin type 3 domain (FN3), plant homeodomain (PHD), bromodomain (BROMO), acid-rich region (AR), filamin domain, NHL repeats (NHL), transmembrane domain (TM), ADP-ribosylation factor domain (ARF), and meprin and tumor necrosis factor receptor–associated factor homology domain (MATH). Numbers indicate individual TRIM proteins.

review, we discuss the mechanisms that are used by TRIM proteins to mediate an antiviral host response in mammalian cells. The antiviral strategies employed by TRIM proteins fall into three broad categories: modulation of innate immune sensing or signaling, direct restriction of viruses, and regulation of autophagy-mediated antiviral defenses. Finally, we detail how viral pathogens antagonize the antiviral function of specific TRIM proteins to evade host immunity.

TRIM PROTEINS MODULATING INNATE SIGNALING

The innate immune system plays a vital role in sensing incoming viruses and limiting their replication, as well as inducing a tailored adaptive immune response that ultimately controls or eradicates the infection. This process starts with the recognition of conserved pathogen-associated molecular

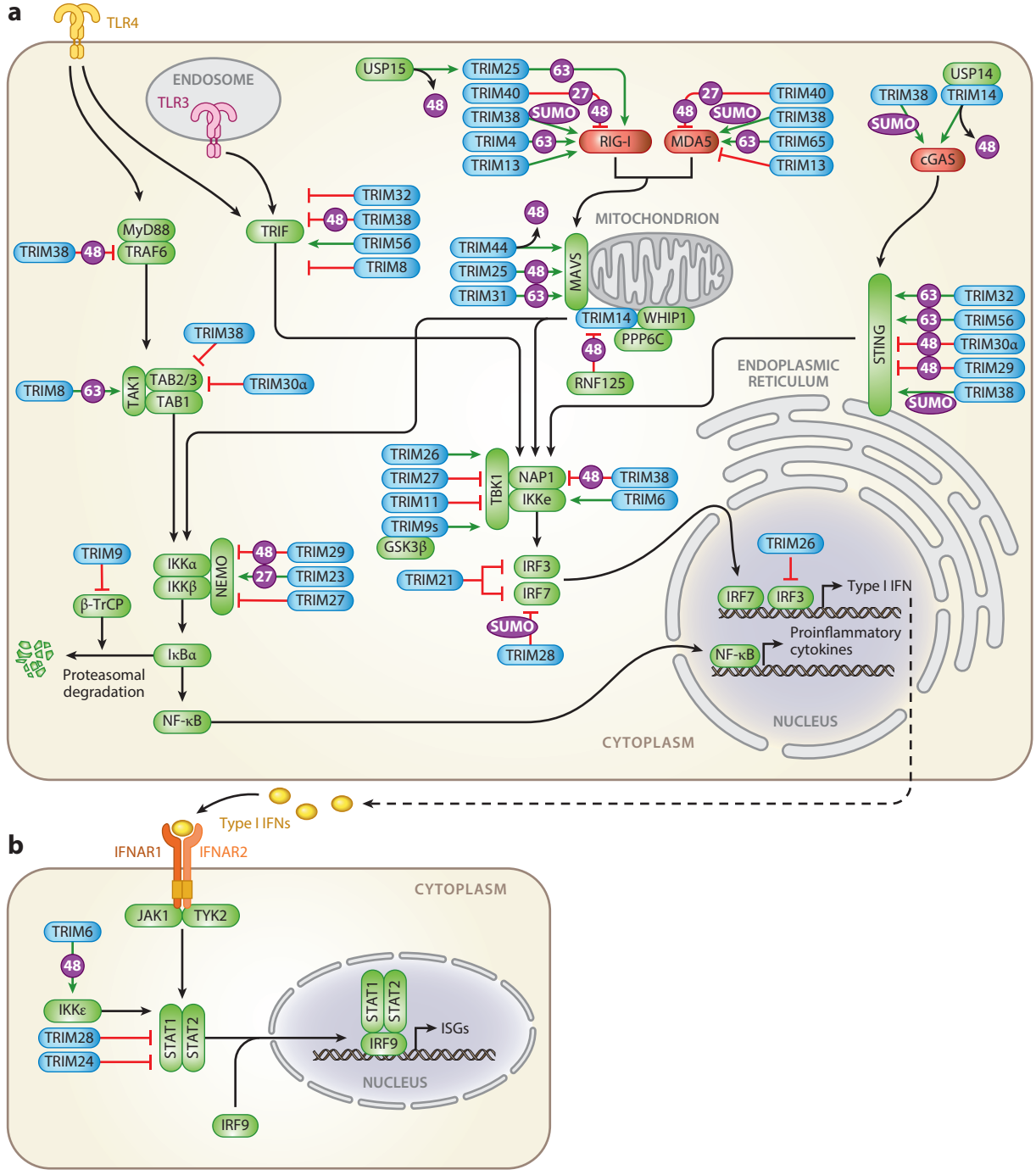
patterns (PAMPs) by pattern-recognition receptors (PRRs) (15). Through a series of highly regulated phosphorylation and ubiquitination events of adaptor molecules and kinases, stimulation of PRRs results in the activation and nuclear translocation of the transcription factors IRF3/7 and NF-κB, which in turn induce transcriptional upregulation of type I interferons (IFNs; predominantly IFNα/β) and proinflammatory cytokines (15). Type I IFNs are of paramount importance in the establishment of an antiviral state by inducing the expression of a plethora of IFN-stimulated genes (ISGs) that can have direct antiviral activity or alter cellular processes to establish an environment hostile to viral replication (16). Over the past decade, TRIM proteins have emerged as important positive and negative regulators of PRR signaling pathways. In this section, we detail the role of TRIM proteins in modulating four major innate signaling pathways, namely, the ones initiated by RIG-I-like receptors (RLRs), the DNA sensor cGAS, Toll-like receptors (TLRs), and the IFNα/β receptor (IFNAR) (**Figure 2**).

TRIM Proteins Regulating RLR Signaling

DExD/H-box RNA helicases of the RLR family are essential sensors of RNA virus infection that are expressed in most cell types and transcriptionally upregulated following viral infection (17). While the prototypic sensor retinoic acid-inducible gene-I (RIG-I) recognizes 5′-triphosphorylated viral RNA with short dsRNA stretches, the closely related RLR member melanoma differentiation-associated protein 5 (MDA5) detects longer dsRNA or viral RNA aggregates. Several studies have demonstrated the importance of RIG-I and MDA5 in innate sensing of a wide spectrum of RNA viruses as well as some DNA viruses (18, 19). RIG-I and MDA5 contain a central helicase domain and a C-terminal domain (CTD), which are both required for RNA binding, as well as two N-terminal caspase activation and recruitment domains (CARDs) essential for downstream signaling (15). Following activation, RIG-I and MDA5 undergo conformational changes and are recruited to their common adaptor mitochondrial antiviral signaling protein (MAVS). MAVS in turn recruits the IKK-related kinases IKKε and TBK1 to activate IRF3/7, as well as the canonical IKKα/β/γ complex, to promote degradation of the NF-κB inhibitor IκBα, leading to NF-κB activation (15). The activity of RIG-I and MDA5 is strictly regulated by posttranslational modifications to allow rapid RLR activation yet prevent excessive immune activation (20). Several TRIM proteins have emerged as key regulators of these modifications and are imperative in the tight control of the RLR-triggered antiviral response (**Figure 2*a***).

TRIM25 was the first immunomodulatory TRIM protein identified; it controls RIG-I antiviral activity by decorating its CARDs with K63-linked polyubiquitin (21). This nondegradative type of ubiquitination induces RIG-I oligomerization and its recruitment to MAVS to trigger downstream antiviral gene expression. In addition, RIG-I can be activated by noncovalently attached K63-linked ubiquitin chains synthesized by TRIM25 (22). TRIM25 protein stability is regulated by the deubiquitinating enzyme USP15, which reverses K48-linked ubiquitination and subsequent degradation of TRIM25 (23). Besides TRIM25, TRIM4 (as well as the E3 ligases Riplet and MEX3C) reportedly modifies RIG-I with K63-polyubiquitin to facilitate its activation and antiviral response (24). Whether these E3 ligases play redundant roles in RIG-I regulation, or whether they have cell type–specific or tissue-specific roles, remains to be determined.

TRIM65 promotes K63-linked ubiquitination of the MDA5 helicase domain, thereby enhancing IRF3 activation and IFN production in response to MDA5 agonists or encephalomyocarditis virus (EMCV) infection (25). *TRIM65*-deficient mice were more susceptible to EMCV infection and showed compromised IFN production. Furthermore, TRIM13 was shown to suppress MDA5-mediated IFN production (26). *TRIM13*$^{-/-}$ mice and cells showed increased cytokine production upon EMCV infection compared to wild-type mice and cells (26). In contrast, TRIM13 appears to



(Caption appears on following page)

Figure 2 (*Figure appears on preceding page*)

TRIM-mediated regulation of innate immune signaling pathways. Overview of the TRIM proteins (*blue*) that positively (*green arrows*) or negatively (*red lines*) regulate (*a*) PRR-mediated induction of type I IFNs and proinflammatory cytokines or (*b*) IFNAR-induced expression of ISGs. Intracellular receptors are illustrated in red. Signaling intermediates or transcription factors are illustrated in green. Abbreviations: 27, K27-linked polyubiquitination; 48, K48-linked polyubiquitination; 63, K63- linked polyubiquitination; cGAS, cyclic GMP-AMP synthase; IFN, interferon; IFNAR, IFNα/β receptor; IRF, interferon regulatory factor; ISG, interferon-stimulated gene; MAVS, mitochondrial antiviral signaling protein; MDA5, melanoma differentiation-associated protein 5; PRR, pattern- recognition receptor; RIG-I, retinoic acid-inducible gene-I; STAT, signal transducer and activator of transcription; STING, stimulator of interferon genes; SUMO, SUMOylation; TLR, Toll-like receptor; TRIM, tripartite motif protein; USP, ubiquitin-specific peptidase, WHIP, Werner helicase interacting protein 1.

positively regulate RIG-I signaling through an unknown mechanism (26, 27). TRIM40 modifies both RIG-I and MDA5 with K27- and K48-linked polyubiquitin, leading to proteasomal degradation of the sensors and inhibition of antiviral signaling (28). *TRIM40* deficiency enhanced RNA virus–induced IFNβ production in mice and improved survival following vesicular stomatitis virus challenge (28). TRIM38 was recently identified as an E3 SUMO ligase for RIG-I and MDA5. SUMOylation of the sensors prevents their K48-polyubiquitin-dependent degradation, improving RLR stability and thereby potentiating antiviral responses (29). Furthermore, SUMOylation of specific lysine residues in the CARDs of RIG-I and MDA5 was shown to be essential for their subsequent dephosphorylation by PP1 (29). Dephosphorylation by PP1 is required for activation of both RIG-I and MDA5 (30), which in the case of RIG-I licenses TRIM25-mediated ubiquitination. At the later stages of infection, deSUMOylation of RIG-I and MDA5 by SENP2 aids in terminating the antiviral response (29).

TRIM14, which lacks an E3 ubiquitin ligase domain, forms a complex with Werner helicase interacting protein 1 (WHIP) and the phosphatase PPP6C that is constitutively associated with MAVS at the outer mitochondrial membrane (31). Upon RIG-I activation, WHIP binds to and stabilizes dsRNA-bound, K63-ubiquitinated RIG-I, promoting its translocation to the mitochondria. Dephosphorylation of RIG-I by PPP6C further amplifies RIG-I-mediated antiviral signaling (31). TRIM14 has been reported to recruit the adaptor protein IKKγ/NEMO to the MAVS signalosome, bridging RIG-I to the downstream transcription factors IRF3 and NF-κB (32). The stability of TRIM14 is regulated by the ubiquitin ligase RNF125, which induces its proteasomal degradation (33). Recently, TRIM31 was reported to catalyze K63-linked polyubiquitination of MAVS at K10, K311, and K461, which promoted MAVS aggregate formation and type I IFN induction upon RNA virus infection (34). TRIM44 counteracts the K48-linked polyubiquitination and proteasomal degradation of MAVS, potentiating antiviral responses (35). TRIM44 contains an atypical ubiquitin-binding zinc finger UBP domain and may act as a deubiquitinase rather than an E3 ligase. Another study suggested that K48-linked polyubiquitination and destabilization of the larger MAVS isoform by TRIM25 led to the release of downstream signaling components, thereby enhancing IFN production (36).

Several TRIM proteins regulate signaling by RLRs (and also other sensors) by targeting downstream kinases or IRFs. For example, the short isoform of TRIM9, TRIM9s, promotes TBK1 phosphorylation and IRF3 activation by bridging TBK1 with GSK3β, a protein that aids in the oligomerization of TBK1 (37). At the same time, TRIM9s suppresses NF-κB activation and proinflammatory cytokine production upon vesicular stomatitis virus or herpes simplex virus 1 (HSV-1) infection, essentially biasing the innate response to type I IFN production (37). Interestingly, the longer isoform of TRIM9 (TRIM9l) was previously shown to inhibit NF-κB responses by interfering with β-TrCP-mediated IκBα degradation (38). TRIM11 interacts with TBK1 and inhibits IRF3-mediated IFNβ production (39). TRIM26 reportedly also interacts with TBK1 and restricts RNA virus infection by bridging TBK1 and NEMO to facilitate downstream signaling

(40). However, TRIM26 was also shown to negatively regulate antiviral IFN production by promoting K48-linked polyubiquitination and proteasomal degradation of phosphorylated, nuclear IRF3 (41). TRIM28 specifically targets IRF7 for inhibitory SUMOylation (42), while TRIM23 has been suggested to modify NEMO with K27-linked polyubiquitin, thereby enhancing innate signaling by RIG-I, MDA5, and TLR3 (43). Finally, a comprehensive cDNA screen by Versteeg et al. (27) showed that roughly half of the 75 tested TRIM family proteins regulated RIG-I signaling. Another overexpression screen identified 16 TRIMs that induced NF-κB and/or AP1 activation (44), strengthening the concept that TRIM proteins are key regulators of innate and proinflammatory signal transduction.

TRIM Proteins Modulating cGAS-STING Signaling

In recent years, various cytosolic viral DNA sensors have been identified, most prominently cyclic GMP-AMP synthase (cGAS) (45). Many studies have established that cGAS is crucial for sensing DNA viruses, and more recently, cGAS has been shown to act antivirally against retroviruses and several positive-strand RNA viruses. Upon activation by DNA binding, cGAS produces the second messenger cGAMP, which activates the stimulator of interferon genes (STING) to induce transcriptional upregulation of type I IFNs (46). Although the characterization of posttranslational modifications that regulate the cGAS-STING pathway is still in its infancy (20), recent studies have demonstrated that several TRIM proteins modulate cGAS-STING-dependent antiviral signaling via regulatory modifications (**Figure 2*a***).

TRIM14 was shown to be upregulated upon viral infection and to recruit the deubiquitinating enzyme USP14 to revert degradative ubiquitination of cGAS, improving its stability and enhancing the antiviral response against HSV-1 (47). Analogous to its role in RIG-I and MDA5 SUMOylation, TRIM38 was found to induce SUMOylation of cGAS and STING (48). TRIM38 catalyzed multiple SUMOylation events of cGAS to prevent its K48-linked polyubiquitination and proteasomal degradation. Similarly, SUMOylation of STING by TRIM38 prevented STING degradation by the chaperone-mediated autophagy pathway (48). Together, these modifications ensure robust IRF3 activation and production of antiviral effectors, and *TRIM38* deficiency severely impaired the antiviral response to HSV-1 in vivo (48). TRIM56 and TRIM32 were found to induce K63-linked polyubiquitination of STING upon cytosolic DNA stimulation to facilitate the induction of an antiviral response (49, 50). However, more recent studies suggested that instead of directly ubiquitinating STING, TRIM56 and TRIM32 may synthesize unanchored polyubiquitin chains that activate NEMO and, together with IKKβ and TBK1, ultimately induce IRF3 and NF-κB activation (51, 52). TRIM29, which is specifically expressed in lung alveolar macrophages and airway epithelial cells, was reported to negatively regulate innate immune responses to DNA viruses by mediating degradative ubiquitination of STING (53). Similarly, mouse-specific TRIM30α promotes degradation of STING through K48-linked polyubiquitination (54).

TRIM Proteins Modulating TLR Signaling

TLRs sense pathogen-derived nucleic acid, lipid, or protein components at the cell surface or in endosomal compartments (55). Major TLRs involved in virus recognition are endosomally localized TLR3, TLR7, TLR8, and TLR9. Upon ligand binding, TLRs dimerize and activate signaling cascades that ultimately lead to NF-κB- and IRF-mediated induction of proinflammatory cytokines. All TLRs except TLR3 signal through the adaptor molecule MyD88, which recruits the kinases IRAK1/4 and E3 ubiquitin ligase TRAF6. Autoubiquitination of TRAF6 is recognized by TAB2, which activates the kinase TAK1, ultimately inducing IKKα/β/γ and NF-κB activation

(55). Alternatively, TLR3 (and also TLR4) can activate TRIF-mediated signaling, which results in activation of IRF3 and IRF7 via TRAF3 and TBK1/IKKε (55). Several steps in TLR signaling pathways are regulated by TRIM proteins (**Figure 2*a***).

TRIM38 negatively affects TLR signaling through destabilization of several signaling intermediates required for TBK1/IKKε and IRF3/7 activation, including TRAF6 (56), TRIF (57), TAB2/3 (58), and NAP1 (59). Similarly, TLR signaling is suppressed by murine TRIM30α, which is induced upon TLR stimulation and promotes lysosomal degradation of TAB2/3 (60). TRIM32 negatively regulates TLR3/4 responses by inducing autophagy-mediated degradation of TRIF (61). Conversely, TRIM56 was reported to interact with TRIF and play a positive role in TLR3-mediated IFN/ISG production (62), while TRIM62 was shown to promote activation of the TRIF branch of TLR4 signaling (44). TRIM21 functions as a negative feedback modulator by promoting ubiquitination and proteasomal degradation of IRF3/7 following viral TLR stimulation (63, 64). Upregulation of TRIM27 in response to viral infection was shown to inhibit antiviral responses by targeting the IKK complex and TBK1 (65–67). TRIM29 acts as a negative regulator of proinflammatory cytokine production in alveolar macrophages by inducing NEMO degradation (68). Finally, TNFα signaling and IL-1β signaling, which activate the same MyD88-dependent pathway as TLRs, are potentiated by TRIM8 through K63-linked ubiquitination of TAK1 (69), while TRIM8 suppresses TRIF-mediated responses by disrupting the TRIF-TBK1 interaction (70).

TRIM-Mediated Regulation of IFNAR Signaling

Secreted type I IFNs induce signal transduction pathways in an autocrine and paracrine fashion through binding to the IFNα/β receptor, a heterodimer of IFNAR1/2 that is expressed on virtually all nucleated cells (71). Receptor ligation activates the kinases JAK1 and TYK2 and induces phosphorylation of signal transducer and activator of transcription (STAT)1 and STAT2, which together with IRF9 form the interferon-stimulated gene factor 3 (ISGF3) complex, which translocates into the nucleus and induces transcription of an extensive set of antiviral ISGs (71). TRIM6, TRIM24, and TRIM28 have been implicated in regulation of IFNAR signal transduction (**Figure 2*b***). Besides its role in the IFN induction pathway, IKKε is also required for optimal IFNAR signaling and ISG production (72). TRIM6 was found to interact with IKKε and synthesize atypical unanchored K48-linked ubiquitin chains that are vital for optimal IKKε activation and subsequent STAT1 phosphorylation (73). In contrast, TRIM24 and TRIM28 negatively regulate IFNAR signaling. Whereas TRIM24 suppresses transcription of STAT1 by binding to the STAT1 promoter (74), TRIM28 associates with STAT1 and inhibits STAT1-mediated IRF1 gene expression (75).

DIRECT ANTIVIRAL RESTRICTION BY TRIM PROTEINS

Retroviral Restriction by TRIM Proteins

Several TRIM proteins interfere with retroviral infection by directly inhibiting various stages of the infectious cycle (**Figure 3*a***). TRIM5α, which is probably the most well-characterized antiviral restriction factor, interacts with the intact viral capsid lattice and forms a complementary lattice that induces premature virion disassembly, blocking viral infection (76). This process also releases viral PAMPs into the cytosol that may be detected by cytoplasmic innate sensors that in turn promote antiviral responses (77). Additionally, TRIM5α itself reportedly functions as an immune sensor that, upon retroviral capsid binding, catalyzes the synthesis of unanchored K63-linked ubiquitin chains that activate the TAK1-containing complex and AP1- and NF-κB-mediated

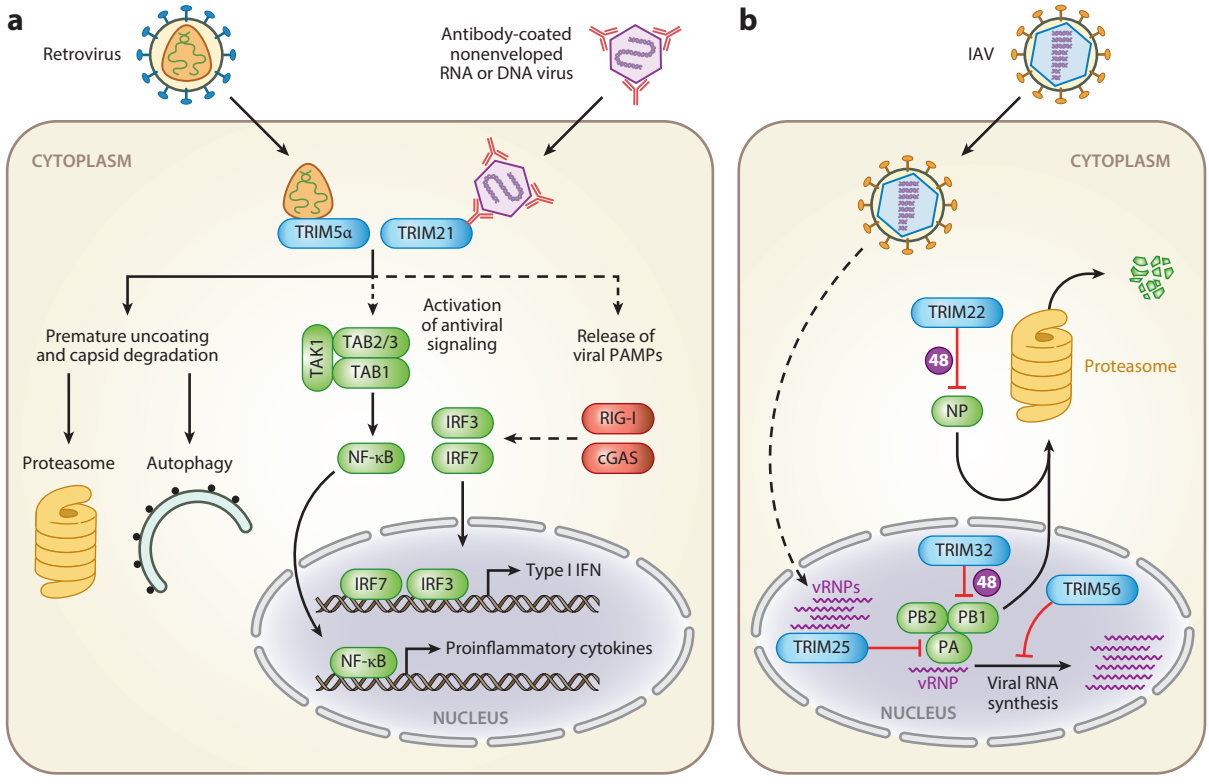


Figure 3

Direct antiviral effects of TRIM proteins. (*a*) TRIM5α restricts retroviral infection by directly interacting with the viral capsid and inducing premature uncoating and capsid disassembly. This process may release viral PAMPs that can be sensed by cytosolic PRRs. Both proteasomal and autophagic degradative mechanisms have been implicated in TRIM5α-mediated virus restriction. In addition, TRIM5α catalyzes noncovalent K63-linked ubiquitin chains that activate the TAK1 signaling complex and thereby activate NF-κB and AP1. TRIM21 is a cytosolic sensor of antibody-opsonized, nonenveloped RNA and DNA viruses. Proposed antiviral mechanisms for TRIM21 include proteasomal degradation of incoming viral particles; activation of signaling pathways leading to NF-κB, AP1, and IRF activation; and release of viral PAMPs for detection by RIG-I or cGAS and potentially other intracellular PRRs. (*b*) Several TRIM proteins directly interfere with IAV replication. TRIM22 induces proteasomal degradation of the viral nucleoprotein NP. In the nucleus, TRIM32 induces proteasomal degradation of the viral polymerase subunit PB1, while TRIM25 interacts with vRNPs to prevent the viral polymerase from accessing the viral RNA template. TRIM56 blocks IAV RNA synthesis through an unknown mechanism. Solid lines indicate direct or well-established interactions. Dashed lines indicate indirect correlations. Abbreviations: 48, K48-linked polyubiquitination; cGAS, cyclic GMP-AMP synthase; IAV, influenza A virus; IFN, interferon; PAMP, pathogen-associated molecular pattern; PRR, pattern-recognition receptor; TRIM, tripartite motif protein; vRNP, viral ribonucleoprotein.

signaling (78). TRIM5α-mediated retroviral restriction is known to be highly species specific (76, 79, 80), but a recent study nuanced the view of TRIM5α's species specificity by showing that human TRIM5α is able to restrict human immunodeficiency virus type 1 (HIV-1) infection in Langerhans cells, a specific dendritic cell subset that represents a primary target of HIV-1 infection (81). Binding of HIV-1 to the surface C-type lectin receptor Langerin, which is uniquely expressed on Langerhans cells, routes HIV-1 into TRIM5α-dependent autophagic degradation and prevents these cells from becoming infected (81). In contrast, HIV-1 entry mediated by the DC-SIGN receptor expressed on conventional dendritic cell subsets was shown to bypass TRIM5α-mediated degradation (81).

TRIM22, which is closely related to TRIM5, suppresses retroviral transcription by regulating binding of the transcription factor Sp1 to the long terminal repeats and by interfering with trafficking of the viral Gag protein to the plasma membrane (82–84). Enhanced TRIM22 expression in peripheral blood mononuclear cells of HIV-1-infected patients was associated with lower viral load (85). In addition to its role in retroviral restriction, several reports have described an antiviral activity of TRIM22 against influenza A virus (IAV) (86), hepatitis B virus (HBV) (87), hepatitis C virus (HCV) (88, 89), and EMCV (90). Several other TRIM proteins, including TRIM11 (91), TRIM28 (92), and TRIM37 (93), directly or indirectly interfere with retroviral infections. Moreover, a screening of 36 human and 19 mouse TRIM proteins for antiretroviral activity revealed ~20 TRIMs that interfered with either the early or the late stage of retroviral replication (94).

TRIM21, an Intracellular Antibody Receptor

TRIM21 is a high-affinity intracellular antibody receptor that binds the Fc portion of immunoglobulin (Ig) molecules through its PRY-SPRY domain, thereby contributing to the restriction of various nonenveloped viruses such as adenoviruses and rhinoviruses (95–98) (**Figure 3*a***). The important role of TRIM21 in the antiviral response was illustrated by the fact that mice lacking *TRIM21* succumbed to an otherwise nonlethal dose of mouse adenovirus 1 (95). As for TRIM5α, multiple mechanisms have been proposed for how TRIM21 restricts viral infection. Following viral entry, TRIM21 neutralizes infection by targeting viral particles for degradation by the proteasome in conjunction with the ATPase p97 (99, 100). Additionally, TRIM21 acts as an innate immune sensor that, upon recognition of opsonized virions, activates NF-κB, AP1, and IRF signaling through the generation of unanchored K63-linked polyubiquitin (101, 102). Moreover, a delayed and more specific induction of immune pathways is achieved by TRIM21-mediated premature uncoating of the virus particle and release of viral PAMPs for exposure to RIG-I, cGAS, and potentially other intracellular sensors (102).

TRIM19/PML

TRIM19, or promyelocytic leukemia (PML) protein, is a key component of PML nuclear bodies, which are dynamic protein aggregates containing many proteins including PML, hDaxx, Sp100, and ATRX. They have been implicated in a multitude of cellular processes, such as cell cycle regulation, apoptosis, senescence, the DNA damage response, and intrinsic resistance to viral infection (103). PML nuclear bodies are known to restrict many DNA viruses, including herpesviruses, adenoviruses, papillomaviruses, and parvoviruses, as well as RNA viruses such as IAV, vesicular stomatitis virus, and HIV-1 (104–106). The mechanisms of PML nuclear body–mediated virus restriction have been most extensively characterized for herpesviral infections and include engulfment and epigenetic silencing of incoming viral genomes, as observed for HSV-1 and human cytomegalovirus, or entrapment of newly synthesized nucleocapsids, as in the case of varicella zoster virus (107, 108). Besides conferring these direct antiviral functions, PML is also emerging as a positive regulator of IFN induction during retroviral and herpesviral infections (reviewed in 109).

TRIM25 and ZAP

Recently, TRIM25 was identified as an important regulator of zinc finger antiviral protein (ZAP) (110, 111). Originally described to suppress retroviral infections, ZAP has now been shown to confer antiviral activity against several other viruses, including alphaviruses, filoviruses, and HBV

(112). Although the exact antiviral mechanism employed by ZAP remains somewhat elusive, ZAP was shown to recruit the exosome to target viral RNA for degradation, inhibit translation of incoming viral genomes, and promote RIG-I-mediated IFNβ induction (reviewed in 112). Two recent studies have identified that TRIM25 acts as a key regulator of ZAP's antiviral activity by mediating both K48- and K63-linked polyubiquitination of ZAP (110, 111). Furthermore, RNA binding by TRIM25 was suggested to be required for licensing TRIM25-mediated ZAP ubiquitination (11).

Other TRIM Proteins Directly Restricting Viral Infections

Several other TRIM proteins were shown to directly target viral components to restrict replication (**Figure 3*b***). For example, TRIM32 targets the polymerase subunit PB1 of several IAV strains for ubiquitination and subsequent proteasomal degradation (113). TRIM25 was recently suggested to interact with viral ribonucleoproteins of IAV in the nucleus and to inhibit mRNA chain elongation by preventing access of the viral polymerase to the viral RNA template (114). Furthermore, IAV infection is restricted by TRIM56, which blocks IAV RNA synthesis (115), and TRIM22, which induces proteasomal degradation of the viral nucleoprotein NP (86).

Other viruses are also directly targeted by TRIM proteins. TRIM52 targets the NS2A protein of Japanese encephalitis virus for proteasomal degradation (116). TRIM56 was reported to restrict infection by the flaviviruses bovine viral diarrhea virus, yellow fever virus, and dengue virus, as well as human coronavirus OC43 and HIV-1 (117–119). TRIM14 suppresses HCV replication by targeting the NS5a protein for degradation (120). Moreover, a cDNA screen identified multiple TRIM proteins that interfered with HBV infection (121), although the molecular mechanisms of TRIM-mediated HBV restriction remain to be determined.

TRIM PROTEINS REGULATING VIRUS-INDUCED AUTOPHAGY

A major cellular homeostatic process mediating destruction of damaged organelles, surplus proteins, and even viral cargo is autophagy. During autophagy, cytoplasmic contents are engulfed by double-layered membranes called autophagosomes and degraded upon fusion with the lysosome. Initially, autophagy was described as a nonspecific cellular response toward nutrient depletion, but it has become evident that autophagy also mediates degradation of cargos via specific receptors such as p62 or NDP52 (122). Autophagy is implicated in diverse physiological functions, including inflammation, cancer, and antimicrobial activities (123). In regards to viral infection, autophagy can have either a proviral or antiviral role, dependent on the virus, cell type, and host organism. Whereas autophagy promotes the replication of several positive-strand RNA viruses, it restricts HSV-1, Sindbis virus, and HIV-1. Multiple mechanisms for autophagy-mediated antiviral restriction have been identified, including the direct degradation of viral components, leading to virus clearance, and the exposure of PAMPs to PRRs, promoting innate immune signaling.

Several recent studies demonstrated that TRIM proteins are important modulators of both nonviral and virus-induced autophagy. In a cDNA screen, 31 out of 62 tested TRIM proteins induced autophagy (124). Furthermore, individual depletion of 24 TRIM proteins interfered with IFNγ-induced autophagy (125), and silencing of 22 TRIM proteins diminished autophagy upon mTOR inhibition (126). The precise mode of action in the autophagy pathway, however, has been determined for only a few TRIM proteins. Whereas some TRIM proteins act as key regulators of the core autophagy machinery, others function as viral cargo receptors in a highly virus-specific manner.

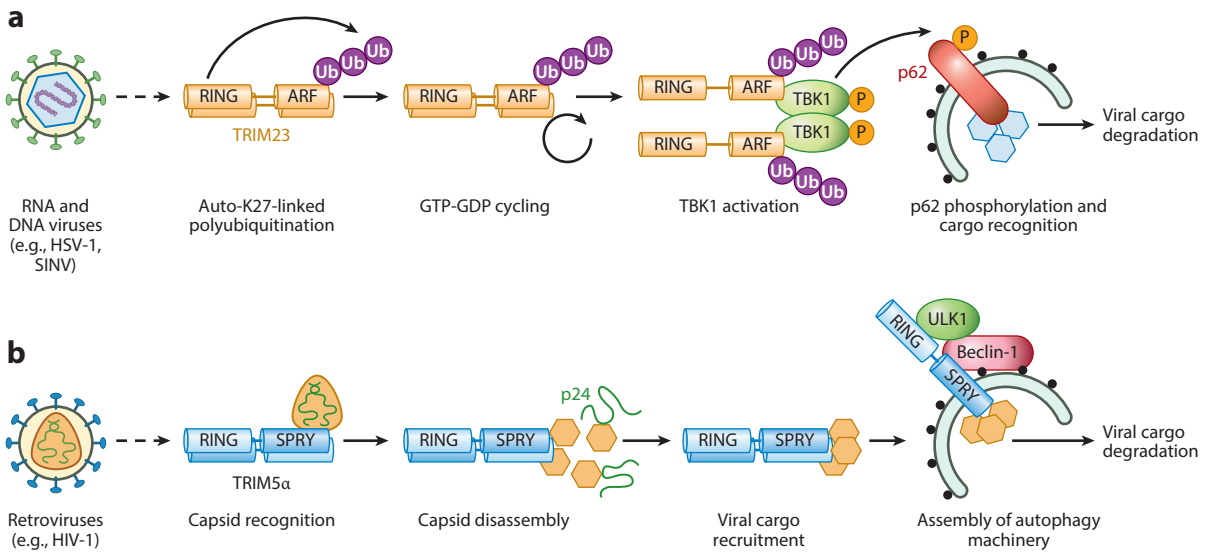


Figure 4

TRIM proteins regulating virus-induced autophagy. TRIM proteins can promote viral autophagy in at least two different ways. For example, TRIM23 (panel *a*) activates key molecules of the autophagic machinery, whereas TRIM5α (panel *b*) recognizes and recruits viral cargo to the autophagic machinery for degradation. (*a*) The E3 enzymatic activity of TRIM23 is activated upon infection by diverse viral pathogens (e.g., HSV-1, SINV), which leads to nondegradative K27-linked autopolyubiquitination of its C-terminal ARF domain. K27-linked ubiquitination in turn stimulates ARF GTPase activity. Upon recruitment of TBK1 to the ARF domain of TRIM23, ubiquitin-induced GTP-GDP cycling of the ARF domain facilitates TBK1 dimerization and *trans*-autophosphorylation and thereby promotes activation of TBK1's catalytic activity. TBK1-mediated phosphorylation of the autophagy receptor p62 enables viral cargo recognition by p62 and ultimately causes degradation of the cargo. (*b*) TRIM5α recognizes the capsid protein of HIV-1 (p24), causing premature virus uncoating, which blocks HIV-1 infection. At least two destructive mechanisms reportedly lead to p24 degradation: the proteasome (not illustrated) and autophagic degradation. Autophagy is induced by the p24-TRIM5α complex in a Beclin-1- and ULK1-dependent manner at budding autophagosomes, ultimately leading to p24 degradation. Abbreviations: ARF, ADP-ribosylation factor; HIV-1, human immunodeficiency virus type 1; HSV-1, herpes simplex virus type 1; RING, really interesting new gene; SINV, Sindbis virus; SPRY, SPIa and the ryanodine receptor; TRIM, tripartite motif protein; Ub, ubiquitin.

TRIM23, a Key Regulator of Core Autophagic Components

While several TRIM proteins have been implicated in virus-induced autophagy, the precise mechanisms of their action in the autophagy pathway have been determined for very few, among them TRIM23 (**Figure 4*a***). *TRIM23* depletion or gene targeting abrogated autophagy induction by several viruses (e.g., HSV-1, Sindbis virus, adenovirus), which correlated with increased replication of these viruses (124). TRIM23 is unique among TRIM family proteins as it exhibits two enzymatic functions: E3 ubiquitin ligase function in the RING domain and GTPase function in the C-terminal ARF domain (14). Upon viral infection, TRIM23 modifies itself at the ARF domain with atypical K27-linked polyubiquitin, which stimulates the GTPase cycling activity of the ARF domain, a process necessary for TRIM23's autophagy function and antiviral activity (124). Following virus-induced autophagy, TRIM23 interacts with TBK1, which is well known to regulate the IFN response and recently has been implicated in autophagy (127). Mechanistically, the GTP-GDP hydrolysis activity of TRIM23 facilitates TBK1 self-association and *trans*-autophosphorylation, thereby activating the kinase (124). TBK1 proceeds to phosphorylate p62 to enhance cargo recognition, ultimately inducing autophagic degradation of viral components (124).

TRIM5α, a Viral Cargo Receptor Triggering Autophagic Degradation

Besides restricting retroviral infection through nondegradative and proteasomal mechanisms, TRIM5α was recently shown to act as a viral cargo receptor inducing autophagic degradation of viral components (**Figure 4*b***). Recognition of the HIV-1 capsid (p24) by the SPRY domain of TRIM5α assembles two key molecules in autophagy, ULK1 and Beclin-1, to induce autophagic flux and thereby cause degradation of p24 (81, 126). However, HIV-1 restriction by TRIM5α still occurs in cells lacking key autophagic components, suggesting that autophagy is not solely responsible for antiviral restriction (128).

VIRAL MANIPULATION OF TRIM PROTEINS

Viruses have evolved strategic maneuvers to antagonize the antiviral function of TRIM proteins, including inhibition of their E3 ligase activity, sequestration of specific TRIM proteins, or induction of their proteasomal degradation. On the other hand, some viral pathogens divert the activity of TRIM proteins or induce their gene expression in a way that directly or indirectly promotes virus replication and/or spread. In this section, we discuss how diverse viral pathogens manipulate TRIM proteins and the impact of these interactions on viral infection and antiviral immunity.

Viral Antagonism of TRIM Proteins

Given the important role of TRIM25 in the RIG-I antiviral pathway, it is not surprising that viruses have evolved a diverse collection of strategies to neutralize TRIM25's activity, thereby preventing RIG-I activation and IFN-mediated immunity. The NS1 protein of IAV forms a complex with TRIM25, which inhibits TRIM25 dimerization and thereby prevents its E3 ligase activity from modifying RIG-I with K63-polyubiquitin (129). Interestingly, the CCDs of different TRIM25 orthologs show high sequence variability, and accordingly, human-, avian-, and mouse-adapted IAV strains bind to TRIM25 in a species-specific fashion (130). The nucleocapsid (N) protein of severe acute respiratory syndrome virus binds to the RIG-I-recruiting module of TRIM25, the C-terminal SPRY domain, thereby interfering with RIG-I binding to TRIM25 (131). This strategy of TRIM25 and RIG-I antagonism is also conserved in the related Middle East respiratory syndrome virus (131), providing a molecular mechanism of how the N proteins of coronaviruses thwart the host immune response. Severe fever with thrombocytopenia syndrome virus (SFTSV) has evolved a completely different mechanism to inhibit TRIM25. Using its nonstructural protein NSs, SFTSV sequesters TRIM25 as well as RIG-I and TBK1 to cytoplasmic structures that colocalize with Rab5 (132). Redistribution of TRIM25, RIG-I, and TBK1 by NSs away from appropriate signaling platforms at mitochondria-associated membranes then dampens type I IFN induction. Intriguingly, at least one virus uses a viral protein–independent strategy to suppress TRIM25 activity and thereby attenuate RIG-I signaling. The subgenomic flavivirus RNA encoded by an epidemic strain of dengue virus that emerged in Puerto Rico in 1994 bound to TRIM25 and interfered with its deubiquitination and stabilization by USP15 (10, 23).

Many viruses encode effector proteins that disrupt TRIM19/PML-containing ND10 subnuclear structures and thereby interfere with intrinsic immunity, and some of these viral antagonists directly target TRIM19. For example, the immediate early protein IE1 of human cytomegalovirus directly binds to the CCD region of TRIM19 to prevent TRIM19 auto-SUMOylation, disrupting nuclear bodies (133, 134). Structural analysis of IE1 revealed that its globular core, which is the region that binds to TRIM19, exhibits features that are highly similar to those of the CCD regions of TRIM proteins, indicating structural mimicry (133). Interestingly, IE1 interacts not only with TRIM19 but also with TRIM5α and TRIM33 (133, 135), suggesting that the unique CCD-like

structure of the IE1 core region allows it to interact with and manipulate multiple TRIM proteins, although this requires further investigation. The related murine gammaherpesvirus 68 uses a different strategy to incapacitate TRIM19. Upon interaction with TRIM19, murine gammaherpesvirus 68 ORF75c induces the ubiquitination and subsequent proteasomal degradation of TRIM19 (136).

Other viruses that target specific TRIM proteins for proteasomal degradation are HSV-1 and Nipah virus. The ICP0 protein of HSV-1 utilizes its own RING E3 ligase activity to induce polyubiquitination and degradation of TRIM27 (137). The matrix protein of Nipah virus targets TRIM6 for degradation, thereby blocking the activation of IKKε and the ensuing type I IFN–mediated antiviral responses (138). Several other henipaviruses (e.g., Hendra, Cedar, and Ghana viruses) also effectively inhibited the IFN response mediated by TRIM6 and IKKε (138).

Viral Commandeering of TRIM Proteins

Viruses use a variety of strategies to commandeer TRIM proteins for promoting their own replication. Conceptually, hijacked TRIM proteins either directly alter the activity of viral proteins or modulate signaling cascades that establish a milieu in the infected host cell that benefits the virus. For example, Japanese encephalitis virus induces transcriptional expression of TRIM21, which then negatively regulates the IFNβ pathway (139). Similarly, Epstein-Barr virus induces the expression of TRIM29, which in turn modifies STING with K48-linked polyubiquitin, inducing its degradation (53). The NS5 protein of yellow fever virus utilizes TRIM23 to promote its own ubiquitination; ubiquitination of NS5 promotes its binding to STAT2 and thereby triggers NS5-mediated interference of the IFNAR signaling cascade (140). Recently, it has been shown that the Ebola virus VP35 protein, which is a major IFN antagonist of the virus and also regulates the activity of the viral polymerase, recruits TRIM6, which in turn ubiquitinates VP35 and promotes both its IFN-antagonistic and polymerase-promoting functions (141). Accordingly, the replication of infectious Ebola virus in *TRIM6*-deficient cells was reduced as compared to wild-type cells, supporting a proviral function of TRIM6 during Ebola virus infection. The UL144 protein of human cytomegalovirus is known to activate NF-κB via TRAF6 and TAK1, ultimately upregulating the expression of macrophage-derived chemokine (or CCL22), which may function to subvert the Th1 immune response (142). UL144 directly interacts with TRIM23, which leads to K63-linked autoubiquitination of TRAF6 and thereby causes NF-κB induction by UL144 (143).

CONCLUDING REMARKS

Over the past decade we have learned many amazing things about TRIM proteins and their roles during viral infection. While it has been well established that TRIM proteins can act as antiviral restriction factors and master immune regulators, completely new functions of TRIM proteins have recently been discovered, such as their ability to regulate autophagy. Interestingly, emerging evidence also suggests that several TRIM proteins influence RNA metabolism or microRNA processing, or even have RNA-binding capacities themselves. For example, TRIM25 has RNA-binding activity (11, 144), and TRIM32, TRIM65, and TRIM71 have been described as regulators of microRNA processing and RNA interference (145–148). It warrants further investigation whether processing of host microRNAs by these TRIMs influences infection biology, and whether some of these TRIMs could even process virus-encoded microRNAs.

Apart from their involvement in antiviral immunity, many TRIM proteins play powerful roles in cancer-related processes, such as modulation of the tumor suppressor protein p53 among many other tumor-related molecules (149, 150). Furthermore, several TRIM proteins (e.g., TRIM11,

TRIM25, TRIM32, and TRIM66) are upregulated in certain cancers. As many oncogenic viruses are known to manipulate critical pathways involved in oncogenesis or cancer progression, it is tempting to speculate that some of these TRIM proteins are involved in virus-induced tumorigenesis as well. Lastly, it remains to be seen whether viruses target specific TRIM proteins to either block autophagy-mediated virus clearance or, on the other hand, promote autophagy for their efficient replication. Elucidating virus-TRIM interactions and their impact on pathogenesis may reveal new molecular targets for preventing and treating viral infectious diseases in humans.

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