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## Intrinsic Cellular Defenses (TRIMS) in Modulating Viral Infection and Immunity

**Adolfo García-Sastre**, Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; Global Health and Emerging Pathogens Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; and Department of Medicine, Division of Infectious Diseases, Icahn School of Medicine at Mount Sinai, NY, USA

**Lisa Miorin**, Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; and Global Health and Emerging Pathogens Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

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### Glossary

**B-box** A zinc-binding protein domain defined by a series of conserved Cys and His residues.

**Coiled-coil domain** A structural domain that mediates protein dimerization or oligomerization. It typically consists of two or more alpha-helices that wrap around each other to form a supercoil.

**E3 ubiquitin ligase** An enzyme that catalyzes transfer of ubiquitin to a specific substrate resulting in monoubiquitination or polyubiquitination. E3 ligases act together with a ubiquitin-activating enzyme (E1) and a ubiquitin-conjugating enzyme (E2).

**Inflammatory cytokines** Secreted proteins that promote inflammatory and immune responses. Examples include TNF, IL-1 $\beta$ , and IL-6.

**Pathogen-associated molecular patterns (PAMPs)** Molecular patterns that are found in pathogens but not in mammalian cells.

**Phosphorylation** Posttranslational modification of a protein by the addition of phosphate (PO<sub>4</sub>) group.

**Polyubiquitin chain** A string of ubiquitin molecules that are attached to each other by covalent bonds between the

C-terminus of one ubiquitin and any of the seven lysine residues of the adjacent ubiquitin.

**Positive selection** Process of natural selection that increases the frequency of beneficial mutations in a population.

**Restriction factor** A host cell protein whose expression restricts or inhibits the viral life cycle.

**RING domain** Domain of approximately 60 amino acids with conserved Cys and His residues that coordinate two zinc ions. This domain is found in RING-type E3 ligases and mediates binding to the E2-conjugating enzyme.

**Type I IFN** A family of cytokines that includes interferon- $\alpha$  (IFN $\alpha$ ; which is encoded by 13 functional genes in humans and 14 in mice) and IFN $\beta$ .

**Ubiquitination** Covalent attachment of ubiquitin, a 76 amino acid protein, to substrates. Typically ubiquitin's carboxy-terminal glycine is joined to the  $\epsilon$ -amino group of the acceptor lysine residue of the substrate.

**Unanchored ubiquitin chains** Ubiquitin chains that are not attached to substrates.

**Uncoating** Removal of the protein capsid from a virus to release its genome.

### Abstract

The prompt and tightly controlled induction of type I interferon is a central event of the immune response against viral infection. This response relies on the recognition of incoming pathogens by cellular pattern recognition receptors (PRRs), which then trigger various signaling cascades that result in proinflammatory cytokines and interferon production. Tripartite motif (TRIM)-containing proteins recently emerged as a large family of RING-finger E3 ubiquitin ligases with essential regulatory roles during many phases of the antiviral response, either acting as restriction factors or by modulating PRR signaling. In this article, we discuss recent advances in understanding the role of TRIMs in conferring direct antiviral activity as well as in regulating immune signaling pathways.

### Introduction

To effectively control viral infection, eukaryotes have evolved a highly organized and integrated defense network that comprises our innate and adaptive immune response. The innate immune response constitutes the first line of defense against invading pathogens and plays a critical role in the early control of viral dissemination until the slower but specific adaptive response is engaged to resolve infection (Akira et al., 2006; Ivashkiv and Donlin, 2014). Type I interferon (IFN) is an integral component of this system, and its prompt production depends on the recognition of conserved

pathogen-associated molecular patterns (PAMPs) by germ line-encoded pattern recognition receptors (PRRs) (Goubau et al., 2013). These sensors include, among others, the transmembrane Toll-like receptors (TLRs) that recognize a wide range of PAMPs from various pathogens (Kawai and Akira, 2010, 2011), the retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs), that specifically sense cytoplasmic nonself viral RNA (Loo and Gale, 2011; Patel and Garcia-Sastre, 2014), and the cytoplasmic DNA sensors, such as cGAS, that recognize pathogen-derived DNA in the cytoplasm (Cai et al., 2014; Paludan and Bowie, 2013). Upon recognition, surface and intracellular PRRs engage

downstream signaling pathways that ultimately trigger transcriptional upregulation of type I IFNs and proinflammatory cytokines leading to the establishment of an antiviral state and to the initiation of adaptive immunity (Takeuchi and Akira, 2010; Schneider et al., 2014). In addition to conventional innate and adaptive immune responses, mammalian cells are also equipped with an array of constitutively expressed genes with intrinsic antiviral activity. These proteins, known as restriction factors, inhibit viral replication directly, often before the onset of the IFN response. However, most of these proteins can be further induced by IFN to amplify their activity (Yan and Chen, 2012; Blanco-Melo et al., 2012). The importance of these highly coordinated defense mechanisms for the resolution of infection is further emphasized by the fact that viruses have developed multiple tricks to escape or at least counteract innate immune responses (Bowie and Unterholzner, 2008; Versteeg and Garcia-Sastre, 2010; Garcia-Sastre, 2011).

However, these normally beneficial responses might have harmful consequences for the host if they are not tightly controlled by multiple regulatory mechanisms (Eisenacher and Krug, 2012; Jefferies et al., 2011; Ivashkiv and Donlin, 2014). Notably, protein posttranslational modifications (PTMs), such as phosphorylation and ubiquitination, constitute a versatile and efficient strategy to orchestrate an appropriate immune response by regulating the stability, activity, and localization of target proteins.

In this article, we will discuss recent findings that reveal the important role of the tripartite motif (TRIM) E3 ligase family of proteins in conferring direct antiviral activity as well as in regulating immune signaling pathways.

### TRIM Protein Structure

TRIM proteins constitute a large family of really interesting new gene (RING)-finger E3 ubiquitin ligases that have been implicated in a broad range of biological processes including cell differentiation, development, oncogenesis, and antiviral immunity. Since the description of *Xenopus laevis* nuclear factor 7 as the first identified TRIM-containing protein (Reddy et al., 1991), the TRIM family has grown significantly. To date, more than 70 members have been identified in the human genome, and many of these exist as multiple isoforms (Versteeg et al., 2013). However, only a few of them have been well characterized thus far. Interestingly, the evolution and expansion of TRIM-containing proteins nicely parallels with the evolution of the IFN system suggesting that these protein families may have in part coevolved (Flajnik and Du Pasquier, 2004; Versteeg et al., 2014).

TRIM proteins are characterized by the presence of a highly conserved N-terminal RBCC motif that consists of a RING domain, one or two B-boxes, and a coiled-coil domain, but differ in their C-terminal regions that confer function specificity (Reymond et al., 2001; Meroni and Diez-Roux, 2005; Ozato et al., 2008).

The RING domain is a cysteine-histidine-rich domain that coordinates two atoms of zinc and is typically located in TRIM proteins within 20 amino acids of the protein's first methionine. Functionally, the RING domain of many family

members has been shown to confer E3 ubiquitin ligase activity by directly binding to and activating E2 conjugating enzymes (Deshaies and Joazeiro, 2009; Napolitano et al., 2011). Moreover, several TRIMs with antiviral and immunoregulatory functions are known to require the RING domain for their activity (Versteeg et al., 2013; Rajsbaum et al., 2014; Uchil et al., 2013; Pertel et al., 2011; Tsuchida et al., 2010; Gack et al., 2007; Arimoto et al., 2010; Liu et al., 2014). However, whether or not all TRIM proteins possess intrinsic E3 activity still remains to be experimentally demonstrated.

The B-box domains have not been found in any other proteins; therefore, they are considered an important determinant of the TRIM family. B-boxes are zinc-binding motifs with ternary structure very similar to that of the RING domain (Reymond et al., 2001; Sardiello et al., 2008). To date, no specific function has been assigned to them. However, because of their structural similarity to the RING, it has been suggested that they could also confer ubiquitin E3 ligase activity. In agreement with this hypothesis, the RING-less TRIM16 protein was recently shown to possess autoubiquitination activity *in vitro* (Bell et al., 2012).

The third component of the RBCC motif is the coiled-coil domain, a region predicted by bioinformatics tools to be hyperhelical. This helical structure is involved in homomeric and heteromeric protein-protein interactions and promotes the formation of high molecular weight complexes both in the nucleus and in the cytoplasm (Reymond et al., 2001). One of the best-known examples is the assembly of discrete subnuclear compartments, also termed nuclear bodies (NBs), by the scaffolding protein promyelocytic leukemia (PML/TRIM19), which has been shown to interfere with the replicative cycle of several viruses (Bernardi and Pandolfi, 2007; Cuchet et al., 2011; Geoffroy and Chelbi-Alix, 2011). In addition, an intact coiled-coil region was also shown to be required for the formation of TRIM6-dependent cytoplasmic TRIM-ubiquitin bodies (TUB) and for their role in IFN signaling (Rajsbaum et al., 2014).

The TRIM is then followed by one or more specific structures that can also be present in unrelated proteins. Based on their C-terminal domain composition, TRIMs have been further classified into 11 different subgroups (Ozato et al., 2008; Figure 1).

The PRY-SPRY domain (also known as B30.2) is present in approximately 60% of human TRIMs and has been proposed to be predominantly involved in protein-protein interactions and/or RNA binding. Interestingly, the number of TRIM genes containing this domain rapidly expanded in higher eukaryotes strongly suggesting that the PRY-SPRY domain has evolved under positive selection (Rhodes et al., 2005; Sardiello et al., 2008). In support of this notion, the PRY-SPRY domain of TRIM5 $\alpha$  has been shown to be critical for binding to the capsid of incoming retroviruses and to contribute to retroviral restriction in various species (Sebastian and Luban, 2005; Sayah et al., 2004; Lukic et al., 2011; Yap et al., 2005; Stremlau et al., 2005). Other domains present in several TRIMs include the C-terminal subgroup one signature (COS) domain that is necessary for microtubule binding (Short and Cox, 2006); the plant homeodomain (PHD), always associated to a bromodomain

Sub group	N-terminal region (RBCC motif)	Variable C-terminal region	TRIM subgroup members
C-I	N- R B1 B2 CC	COS FN3 PRY/SPRY	01, 09, 18, 36, 46, 67
C-II	N- R B2 CC	COS	54, 55, 63
C-III	N- R B1 B2 CC	COS FN3	42
C-IV	N- R B1 B2 CC	PRY/SPRY	04, 05, 06, 07, 10, 11, 15, 17, 21, 22, 25, 26, 27, 34, 35, 38, 39, 41, 43, 47, 48, 49, 50, 53, 58, 60, 62, 64, 65, 68, 69, 72, 75, 14, 16, 20, 51, 70, 1L
C-V	N- R B1 B2 CC		08, 19, 31, 40, 52, 56, 61, 73, 74, 29, 44
C-VI	N- R B1 B2 CC	PHD BRD	24, 28, 33, 66
C-VII	N- R B1 B2 CC	FIL NHL	02, 03, 32, 71
C-VIII	N- R B2 CC	MATH	37
C-IX	N- R B1 B2 CC	ARF	23
C-X	N- R B1 B2 CC	FIL	45
C-XI	N- R B2 CC	TM	13, 59

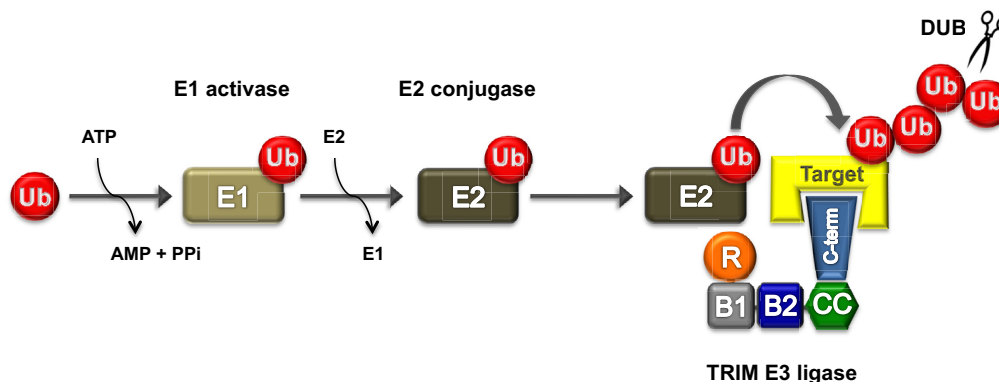
**Figure 1** Classification of TRIM family proteins. TRIM members are categorized into 11 subgroups (C-1 to C-11) based on their C-terminal domains as defined by Ozato et al. (2008). Brown numbers indicate TRIM members lacking at least one key tripartite domain.

(BRD), which are involved in chromatin binding and transcriptional regulation; and the ADP ribosylation factor-like (ARF) domain that regulates intracellular trafficking.

### TRIM Proteins as E3 Ubiquitin Ligases

TRIMs constitute the largest subfamily of RING domain-containing proteins and they have been demonstrated to participate in the ubiquitination process as E3 ubiquitin ligases. Ubiquitination is a reversible PTM that results in the

covalent attachment of ubiquitin to specific lysine residues of the target protein (Figure 2). Three classes of enzymes are involved in this reaction: a ubiquitin-activating enzyme (E1), a ubiquitin-conjugating enzyme (E2), and a ubiquitin ligase (E3). The human genome encodes two E1s, about 40 E2s, and approximately 600 E3s that provide substrate specificity. The ubiquitination reaction begins when ubiquitin is activated in an ATP-dependent manner by the E1, which forms a thioester bond with the ubiquitin C-terminus. The E1 then transfers ubiquitin to the E2 active site cysteine, and ultimately the E3 ligating enzyme brings together the ubiquitin-loaded E2 with



**Figure 2** Schematic representation of the ubiquitination cascade. The ubiquitin-activating enzyme (E1) catalyzes the adenylation of the ubiquitin peptide (Ub). Ubiquitin is transferred to an E2 conjugase through a thiol-ester linkage. Finally, the TRIM E3 ligase interacts with E2 complex (through the RING domain) and the substrate, facilitating the transfer of ubiquitin to a lysine residue in the target protein. DUBs remove conjugated ubiquitin from the target proteins.

the target protein catalyzing ubiquitin transfer. Like other PTMs, ubiquitination is then reversed by deubiquitination (DUB) enzymes that disassemble polyubiquitin chains or remove ubiquitin from target proteins (Komander and Rape, 2012). Substrates can be modified with either a single ubiquitin molecule (monoubiquitination) or with a polyubiquitin chain (polyubiquitination). In a polyubiquitin chain, ubiquitin molecules are linked to each other through one of the seven ubiquitin internal lysines (K6, K11, K23, K27, K33, K48, K63) or through the ubiquitin N-terminal methionine residue (M1), allowing the formation of a diverse array of ubiquitin-mediated signals (Trempe, 2011). Global mass spectrometry analysis of cellular ubiquitin linkages revealed that all different linkages coexist in cells (Peng et al., 2003; Wagner et al., 2011; Komander and Rape, 2012). However, only K48- and K63-linked polyubiquitin chains have been extensively characterized. K48-linked polyubiquitin chains predominantly target substrates for proteasomal degradation. In contrast, K63-linked polyubiquitin chains are primarily involved in protein activation and in the regulation of signaling pathways. Moreover, unanchored polyubiquitin chains also recently emerged as important regulators of signal transduction and kinase activation (Pertel et al., 2011; Rajsbaum et al., 2014; Zeng et al., 2010).

In addition to their role as ubiquitin E3 ligases, TRIM proteins can also mediate the conjugation of ubiquitin-like molecules such as IFN-stimulated gene-15 (Zou and Zhang, 2006; Zou et al., 2007) and the small ubiquitin-like modifier SUMO (Liang et al., 2011; Chu and Yang, 2011). This further contributes to the biological flexibility of TRIM family members.

## TRIMs with Direct Antiviral Function

### TRIM5 $\alpha$ -Mediated Retroviral Restriction

TRIM5 $\alpha$  is one of the best-characterized TRIM factors with direct antiviral activity. TRIM5 $\alpha$  was originally identified by a cDNA library screen as the restriction factor responsible for the resistance of Old World monkeys to human immunodeficiency virus 1 (HIV-1) infection (Stremlau et al., 2004). Subsequent characterization of TRIM5 $\alpha$  proteins from other species unambiguously revealed that this factor has a general function in the control of retroviral infection and retroviral species tropism. For instance, rhesus macaque TRIM5 $\alpha$  strongly restricts HIV-1 but cannot prevent infection by the Simian immunodeficiency virus (SIV). Conversely, human TRIM5 $\alpha$  potentially restricts infection by xenotropic viruses such as N-tropic murine leukemia virus, but cannot inhibit HIV-1 or SIV infection (Perron et al., 2007; Hatzioannou et al., 2004; Keckesova et al., 2004). Interestingly, fine-mapping analysis demonstrated that a single point mutation within the PRY-SPRY domain is sufficient to lead to HIV-1 restriction by human TRIM5 $\alpha$  (Yap et al., 2005; Stremlau et al., 2005). This suggests that this domain is a major determinant of restriction specificity. Moreover, evolutionary genetic analysis revealed that the PRY-SPRY domain of TRIM5 $\alpha$  has been subjected to high levels of positive selection, providing compelling evidence of its coevolution with viruses (Sawyer et al., 2005).

The molecular mechanism of TRIM5 $\alpha$ -mediated restriction still remains to be fully elucidated. Nevertheless, it is clear

that TRIM5 $\alpha$  blocks retroviral infection at the very early stages of the virus life cycle: following fusion, but before reverse transcription (Stremlau et al., 2004; Wolf and Goff, 2008; Perron et al., 2004). Upon release into the cytoplasm of the target cell, TRIM5 $\alpha$  recognizes retroviral capsid via its C-terminal PRY-SPRY domain and forms a hexagonal lattice on top of it, which may induce premature uncoating of the virus and abortive infection (Ganser-Pornillos et al., 2011; Stremlau et al., 2006; Perron et al., 2007). TRIM5 $\alpha$  possesses E3 ubiquitin ligase activity and is autoubiquitinated and rapidly turned over by the proteasome (Diaz-Griffero et al., 2006; Rold and Aiken, 2008), indicating that the ubiquitin ligase activity of TRIM5 $\alpha$  may be important for virus restriction. However, ubiquitination of the retroviral capsid has not been observed, and proteasome inhibition or mutations within the RING domain cannot rescue viral infectivity (Grutter and Luban, 2012; Wu et al., 2006). This suggests that, rather than targeting the viral capsid for degradation, TRIM5 $\alpha$  may induce restriction in a proteasome-independent fashion upon exposure to sensitive viruses. Alternatively, as recently proposed, TRIM5 $\alpha$ -mediated restriction could induce proteasomal degradation of different components of the retroviral core. This effect could be blocked by the proteasome inhibition without rescuing viral infectivity (Kutluay et al., 2013).

Furthermore, TRIM5 $\alpha$  has also been shown to act as a PRR for the capsid lattice of many retroviruses to enhance innate immune signaling. TRIM5 $\alpha$ -mediated recognition of the capsid promotes the synthesis of unanchored K63-linked polyubiquitin chains that bind and activate transforming growth factor- $\beta$ -activated kinase 1 (TAK1), resulting in the induction of inflammatory cytokines (Pertel et al., 2011).

### Antiviral Functions of TRIM22

Another TRIM protein shown to play an important role in retroviral restriction is TRIM22. The human TRIM22 gene is located on chromosome 11, immediately adjacent but in opposite orientation to the TRIM5 gene (Tissot and Mechti, 1995). TRIM22 was originally identified as an antiviral factor based on its ability to inhibit HIV-1 transcription (Tissot and Mechti, 1995). However, a more recent report demonstrated that TRIM22 also inhibits HIV-1 particle production by interfering with intracellular trafficking of the Gag protein (Barr et al., 2008). Whether or not the observed phenotype depends on a direct effect of TRIM22 on the Gag protein still remains to be proven. Interestingly, evolutionary analysis across different species clearly revealed that TRIM22 evolved under strong positive selection. Similar to TRIM5 $\alpha$ , TRIM22 has been shown to interact with the HIV Gag protein, and since the majority of positive-selected amino acids are located within the PRY-SPRY domain, it is possible that this region is also important for TRIM22-Gag binding (Kelly et al., 2014; Hattlmann et al., 2012). Importantly, TRIM22 has also been shown to play a role in HIV-1 restriction *in vivo*. Indeed, elevated expression levels of TRIM22 in infected patients correlate with reduced viral load and higher CD4<sup>+</sup> T cell counts (Singh et al., 2011).

In addition to its critical role as a retroviral restriction factor, TRIM22 also restricts several other RNA viruses through different mechanisms. For instance, it has been reported that

TRIM22 inhibits encephalomyocarditis virus (EMCV) replication by promoting ubiquitination of the viral 3C protease (Eldin et al., 2009) and interacts with the influenza A nucleoprotein to induce its polyubiquitination and subsequent proteasome-dependent degradation (Di Pietro et al., 2013).

### TRIM19/PML

The TRIM19 gene, also known as PML, was originally identified in patients with acute promyelocytic leukemia, where it is fused to the retinoic acid receptor alpha gene as a result of a chromosomal translocation (de The et al., 1990; Pandolfi et al., 1991). As mentioned above, TRIM19 is the essential component of the PML-NBs that are highly dynamic macromolecular structures associated with a variety of cellular processes ranging from oncogenesis to antiviral defense. In this respect, PML has been implicated with the restriction of a large number of viruses, and several viral proteins have been shown to colocalize with PML-NBs (Bernardi and Pandolfi, 2007; Geoffroy and Chelbi-Alix, 2011). In addition, the implication of PML in antiviral defense is further supported by the fact that its expression is induced by IFN in many cell types, leading to an increase in both size and number of the NBs (Stadler et al., 1995; Lavau et al., 1995; Rajsbaum et al., 2008).

Analysis of PML<sup>-/-</sup> mice clearly revealed that, as compared to wild-type mice, they are more susceptible to lymphocytic choriomeningitis virus (LCMV) and vesicular stomatitis virus infection (Bonilla et al., 2002). In line with these findings, mouse embryonic fibroblasts derived from these mice exhibited enhanced viral replication upon infection with LCMV, EMCV, and rabies virus (Blondel et al., 2002; Djavani et al., 2001; El McHichi et al., 2010). Interestingly, PMLIV, but not other PML isoforms, could restrict EMCV infection by sequestering the viral polymerase into PML-NBs to impair virus replication (Maroui et al., 2011).

PML has also been shown to play a critical role in regulating HIV-1 latency. A recent study revealed that in latently infected T cell lines and primary CD4<sup>+</sup> T cells, the HIV provirus is associated with PML-NBs. Interestingly, this interaction negatively regulated viral transcription by recruiting the histone methyltransferase enzyme G9a to the HIV promoter. As a further support for a role of PML-NBs in latency, PML depletion and NB disruption resulted in transcriptional reactivation and release of G9a from the proviral DNA (Lusic et al., 2013).

### TRIM21 and Intracellular Antibody Immunity

TRIM21 is an IFN-stimulated protein that was first described as an autoantigen in autoimmune diseases such as systemic lupus erythematosus and Sjogren's syndrome (Moutsopoulos et al., 1985). However, more recently TRIM21 also emerged as a widely expressed cytosolic antibody receptor, which interacts with the antibody Fc region via its C-terminal PRY-SPRY domain (Keeble et al., 2008). Thanks to the high-affinity interaction with the antibody Fc region, TRIM21 was shown to directly neutralize infection by targeting antibody-opsonized viruses and bacteria for proteasomal degradation (Mallery et al., 2010; McEwan et al., 2013; Vaysburd et al., 2013; Watkinson et al., 2013).

Although the molecular mechanism has not been completely elucidated yet, TRIM21-mediated recognition of antibody-coated pathogens is also thought to activate innate immune-signaling pathways resulting in the upregulation of cytokine expression. Indeed, in addition to catalyzing the formation of K48-ubiquitin chains, once activated, TRIM21 may also synthesize unanchored K63-linked polyubiquitin chains via its RING domain and trigger the activation of TAK1-dependent signaling (McEwan et al., 2013). However, the role of TRIM21 in regulating type I IFN and inflammatory cytokine production still remains controversial. Indeed, two different knockout mice models have been independently developed, and TRIM21 gene disruption generated different effects on cytokine expression (Espinosa et al., 2009; Yoshimi et al., 2009). In one of the animal models, TRIM21 depletion did not result in altered cytokine production upon both virus infection and lipopolysaccharide (LPS) treatment (Yoshimi et al., 2009; Vaysburd et al., 2013). By contrast, TRIM21<sup>-/-</sup> mice generated by the second group developed systemic autoimmunity along with abnormal cytokine responses (Espinosa et al., 2009). The reasons accounting for these differences still remain unclear and could be due to the different gene-targeting strategies used by the two groups.

### Additional TRIMs with Direct Antiviral Activity

In addition to the above-described family members, several other less-characterized TRIMs have been shown to possess antiviral activity. In a recent study, 55 TRIM proteins (36 human, 19 mice) were systematically analyzed for their ability to interfere with different stages of the retroviral life cycle (Uchil et al., 2008). Strikingly, approximately 20 of the proteins analyzed exhibited antiviral activity, thereby underlining the important role of this family of protein in retroviral restriction. Interestingly, most of the TRIMs inhibited the late stages of the viral life cycle, and only a minor fraction appeared to be important for viral replication. In addition, TRIM11 and TRIM30 emerged from this study as potential negative regulators of TRIM5 $\alpha$ -mediated restriction (Uchil et al., 2008).

In a similar overexpression study, 8 TRIMs (TRIM5/6/11/14/25/26/31/41) that significantly suppress hepatitis B virus transcription have been identified. Further characterization of TRIM41-mediated restriction suggested that both the E3 ubiquitin ligase activity and the C-terminal domain of TRIM41 are important for the observed antiviral effect (Zhang et al., 2013a).

TRIM56, previously identified as a restriction factor for bovine viral diarrhea virus (Wang et al., 2011), was recently shown to exert antiviral activity also against human pathogenic positive-strand RNA viruses such as yellow fever virus (YFV), dengue virus (DENV), and human coronavirus (HCoV) OC434 (Liu et al., 2014). Although the mechanism by which TRIM56 impairs viral replication has not been addressed, the authors demonstrated that restriction of YFV and DENV replication requires both the E3 ligase activity and an intact C-terminal domain, whereas the effect on the later steps of the HCoV life cycle only depends on the TRIM56 E3 ligase activity (Liu et al., 2014).

TRIM79 $\alpha$  also recently joined the group of TRIMs involved in flavivirus restriction. Interestingly, TRIM79 $\alpha$  is a rodent-specific factor that specifically inhibits tick-borne flaviviruses but not

the mosquito-borne West Nile virus (Taylor et al., 2011). Mechanistically, TRIM79 $\alpha$  interacts with the viral polymerase and induces its lysosomal degradation independently of the E3 ligase activity. Considering that small rodents constitute the main mammal reservoir for tick-borne encephalitis virus transmission (Bakhvalova et al., 2009), the TRIM79 $\alpha$ -mediated restriction of viral replication represents an example of virus–host coevolution that contributes to host-specific antiviral defense.

### TRIM Protein–Mediated Regulation of Immune Signaling Pathways

Recent studies in both human and mouse primary immune cells have shown that the expression of several TRIM genes is upregulated following viral infection, induction of TLR signaling, or type I IFN treatment, thereby highlighting their association with IFN-mediated immunity (Rajsbaum et al., 2008; Carthagena et al., 2009). Indeed, increasing evidence is accumulating that members of this family contribute to the regulation of antiviral signaling pathways in different ways (Uchil et al., 2013; Versteeg et al., 2013, 2014). As E3 ubiquitin ligases, TRIMs can either promote K48-linked ubiquitin-dependent degradation of important signaling molecules, or catalyze the formation of different types of polyubiquitin chains with activating functions.

TRIM25 represents one of the best-characterized examples of a TRIM factor that positively regulates the antiviral immune response. Upon viral RNA sensing, the C-terminal SPRY domain of TRIM25 directly interacts with the caspase recruitment domain of RIG-I and induces its K63-linked ubiquitination leading to activation of downstream signaling events (Gack et al., 2007). In support of the critical role of TRIM25 in the regulation of the antiviral response, the influenza A virus nonstructural protein 1 (NS1) was shown to directly interfere with TRIM25 activity to suppress RIG-I-dependent signaling (Gack et al., 2009). In addition, in an *in vitro* cell-free system, TRIM25 was able to promote RIG-I activation by synthesizing unanchored K63-linked polyubiquitin chains (Zeng et al., 2010). However, the functional contribution of covalent versus noncovalent ubiquitination in RIG-I activation *in vivo* still remains to be addressed.

Similar to nonself viral RNA, double-stranded DNA in the cytoplasm is also recognized by cytosolic sensors that bind the DNA directly and trigger the activation of the innate immune response (Goubau et al., 2013). DEAD-box polypeptide 41 (DDX41) is one of those sensors (Zhang et al., 2011), and TRIM21 was recently identified as a negative regulator of its activity (Zhang et al., 2013b). TRIM21 was shown to bind the DEADc domain of DDX41 through the C-terminal SPRY-PRY domain. This interaction resulted in K48-linked ubiquitination of DDX41 and subsequent degradation through the proteasome. Consistently, TRIM21-deficient mice exhibited lower viral titers than wild-type mice upon HSV-1 challenge (Zhang et al., 2013b).

In addition to regulating PRR activation, several TRIMs have also been shown to modulate the activity of downstream adapter proteins. For instance, TRIM14 was recently reported to localize at the mitochondrial membrane and to associate with mitochondrial antiviral signaling protein (MAVS) upon viral infection to enhance the type I IFN responses.

Interestingly, TRIM14 does not contain an N-terminal RING domain; therefore, rather than acting as an E3 ligase, it is thought to be an essential scaffolding protein implicated in the recruitment of nuclear factor- $\kappa$ B essential modulator (NEMO) to the MAVS signaling complex (Zhou et al., 2014). Furthermore, two different family members, TRIM32 and TRIM56 have been shown to mediate K63-linked ubiquitination of the DDX41 adapter protein stimulator of interferon genes (STING) and to promote downstream IFN induction (Tsuchida et al., 2010; Zhang et al., 2012).

The nuclear factor- $\kappa$ B (NF- $\kappa$ B) is a critical transcription factor involved in the regulation of inflammatory cytokines expression in response to numerous stimuli (Hayden and Ghosh, 2012). Abnormal activation of the NF- $\kappa$ B pathway has been linked to many pathological conditions such as autoimmune diseases and various kind of cancer. Therefore, it has to be tightly regulated (Iwai, 2012; Vallabhapurapu and Karin, 2009). In this respect, TRIM30 $\alpha$ , the murine ortholog of TRIM5 $\alpha$ , has been shown to interact with the TAK1 kinase complex and to induce its lysosomal degradation leading to the inhibition of TLR-dependent NF- $\kappa$ B activation (Shi et al., 2008). In addition, a different study recently identified that the brain-specific TRIM9 protein acts as a new negative regulator of NF- $\kappa$ B activity (Shi et al., 2014). Mechanistically, TRIM9 interacts with the beta-transducin repeat-containing protein ( $\beta$ -TrCP), which is involved in the degradation of the inhibitor of NF- $\kappa$ B alpha (I $\kappa$ B $\alpha$ ) protein, a critical step implicated in the activation of NF- $\kappa$ B signaling. This interaction resulted in the inhibition of I $\kappa$ B $\alpha$  degradation and subsequent NF- $\kappa$ B activation (Shi et al., 2014).

Interestingly, a TRIM protein regulating the signaling pathway triggered by IFN has also been identified, and perhaps more family members acting at this level of innate immune response will be revealed by future studies. In a recent study, the IFN-inducible TRIM6 protein emerged as a key regulator in the induction of IKK $\epsilon$ -dependent IFN-stimulated genes (ISGs) (Rajsbaum et al., 2014). TRIM6 was shown to directly interact with IKK $\epsilon$  through its C-terminal PRY-SPRY domain and to activate downstream signaling events by promoting the formation of unanchored K48-linked polyubiquitin chains that bind to and activate IKK $\epsilon$  (Rajsbaum et al., 2014). Importantly, this study revealed the important role of K48-linked polyubiquitin chains in kinase activation, and provided the first evidence that unanchored polyubiquitin chains are indeed synthesized *in vivo*.

### Summary

The studies discussed in this article clearly indicate that TRIM proteins exert a crucial role in both viral restriction and immune regulation. However, only a few family members have been individually studied, and our knowledge of the specific mechanisms of action is still limited. The broad range of TRIMs' biological roles may be achieved; thanks to their diversity, splicing variants, tissue expression profiles, and ability to form highly dynamic protein complexes in different cellular compartments. Therefore, it is important that future studies focus on better understanding of TRIMs' transcriptional and posttranslational regulation as well as on unraveling their functions in physiologically relevant cell types and disease

models. Knowledge gained in this field may open new horizons to develop novel strategies to treat or prevent infectious diseases and immune disorders.

**See also: Cytokines and Their Receptors: Interferon  $\alpha/\beta$ . Immunity to Viral Infections: Immunity to HIV; Innate Cytokine Responses and Their Functions during Viral Infections; Sensors of Viral Infection. Molecular Aspects of Innate Immunity: Cytoplasmic Viral RNA Sensors: RIG-I-Like Receptors. Signal Transduction: Jak-STAT Signaling Pathways; Ubiquitin Signaling to NF- $\kappa$ B.**

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