



OPEN ACCESS

EDITED BY
Shailendra Saxena,
King George's Medical University, India

REVIEWED BY
Mohamed Mahdi,
University of Debrecen, Hungary
Fergan Imbert,
Rowan University, United States

*CORRESPONDENCE
Meixiu Jiang
✉ jiangmxs@163.com;
✉ jiangmxs@ncu.edu.cn

[†]These authors have contributed
equally to this work and share
first authorship

RECEIVED 08 November 2025
REVISED 13 March 2026
ACCEPTED 17 March 2026
PUBLISHED 07 April 2026

CITATION

Chen J, Chen S, Xu Y, Wang X and
Jiang M (2026) Updates on the role of
TRIM proteins in AIDS: molecular
mechanisms and potential for
interventions.
Front. Immunol. 17:1742036.
doi: 10.3389/fimmu.2026.1742036

COPYRIGHT

© 2026 Chen, Chen, Xu, Wang and Jiang.
This is an open-access article distributed
under the terms of the [Creative
Commons Attribution License \(CC BY\)](https://creativecommons.org/licenses/by/4.0/).
The use, distribution or reproduction in
other forums is permitted, provided the
original author(s) and the copyright
owner(s) are credited and that the
original publication in this journal is
cited, in accordance with accepted
academic practice. No use, distribution
or reproduction is permitted which does
not comply with these terms.

Updates on the role of TRIM proteins in AIDS: molecular mechanisms and potential for interventions

Jingxian Chen^{1†}, Siyu Chen^{1†}, Yu Xu²,
Xinling Wang³ and Meixiu Jiang^{3*}

¹The Huankui Academy, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi, China,
²School of Pharmacy, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi, China,

³Jiangxi Province Key Laboratory of Bioengineering Drugs, The National Engineering Research Center for Bioengineering Drugs and The Technologies, Institute of Translational Medicine, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi, China

AIDS (acquired immunodeficiency syndrome) is the final stage of infection with the human immunodeficiency virus (HIV) and adversely impacts the health of affected people globally, placing an added burden on healthcare systems. Nonetheless, advanced HIV infection is still not effectively curable, so the search for new drug targets remains an important research focus. Tripartite motif (TRIM) proteins constitute an extensive family of ubiquitin E3 ligases that regulate a wide range of cellular processes. Several recent studies have shown that many of TRIM proteins can take part in host defense to combat viral infection by diverse and distinct molecular mechanisms involving interaction with the NF- κ B (Nuclear Factor kappa-B) pathway, JAK(Janus Kinase)-STAT (Signal Transducer and Activator of Transcription) pathway, RLR/MDA5 (Melanoma Differentiation-Associated protein 5) pathway, as well as IRF (Interferon Regulatory Factor) pathway; it can even induce premature degradation of viral proteins. Thus, this review aims to offer an in-depth insight into the roles of TRIM proteins in the pathologic progression of advanced HIV infection, especially on HIV-1 invasion and long terminal transcription inhibition and nonhistone protein reversible ubiquitination, which may afford therapeutic targets for this challenging disease.

KEYWORDS

advanced HIV infection, clinical perspective, HIV, mechanisms, TRIM proteins

1 Introduction

AIDS (acquired immunodeficiency syndrome) typically follows a pattern starting with an acute infection that may resemble mononucleosis, followed by a latent asymptomatic period (WHO Clinical Stage 1), then progressing to WHO Clinical Stages 2 to 3. WHO Clinical stage 3 conditions include unexplained manifestations, including anemia (<8 g/dl), neutropenia ($<0.5 \times 10^9$ per liter) or chronic thrombocytopenia ($<50 \times 10^9$ per liter) (1). More than 40,000,000 deaths have been estimated to date since the first case was written in 1981. According to the latest surveillance data from China CDC, as of June 30, 2025 in China there were cumulatively reported living advanced HIV infection cases for a total of

1,387,471 and cumulative new deaths for a total of 506,664 (2, 3). Thus, advanced HIV infection is an epidemiologic, public health, medical, social and political problem to be solved.

Antiretroviral drugs are already in use for the treatment of HIV infection. Examples of antiviral medications that may be included are nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, integrase inhibitors, and entry/fusion inhibitors (4). These medications slow the advancement of acquired immune deficiency syndrome (AIDS), by inhibiting reproduction of the HIV organism in our figure. But advanced HIV infection currently has no cure, to be clear. Thus, searching and identification of novel drug targets is a necessity to obtain disease treatment outcomes, and finally in order to control this deadly disease (5–13).

TRIM proteins, a heterogeneous family of proteins, play seminal roles in several cellular processes such as innate immunity and cell differentiation, development among other cellular processes. Collectively, it is emerging that TRIM proteins can modulate immune responses (innate or adaptive) through their participation in signaling pathways like NF- κ B or interferon regulatory systems. In addition to their vital role in maintenance of cellular homeostasis, TRIM proteins are known to modulate host defense responses against a plethora of pathogens such as bacteria, viruses and parasites by regulating autophagy, ubiquitination and cytokine production circuits (14–18).

It has been recently reported that TRIMs have a significant role in the processes underlying antiviral responses. This review encapsulates their roles based on previous investigations, elucidating the underlying mechanisms in HIV infection and potentially providing TRIM proteins as an innovation tool for the therapeutic of advanced HIV infection.

2 TRIM family

2.1 Structure of TRIM family proteins

TRIM proteins have a highly conserved N-terminal RBCC domain made up of a RING finger domain, one or two B-box zinc finger domains and a coiled-coil domain which collectively define this family of proteins (19–23).

The typical location of the RING domain is 10–20 residues downstream from the initiating methionine. Initially, this domain was proposed to be responsible for DNA binding and recognition. The RING domain coordinates two zinc ions to form a RING finger motif, with structural similarities to classic zinc finger domains and this was established in research over the last decades. This configuration stabilizes the interaction in E2 enzymes to promote ubiquitination. It is interesting to note that the RING finger domain is a characteristic feature of a diverse range of E3 ubiquitin ligases (24).

The B-box is a zinc-binding motif found only in TRIM proteins, located C-terminal to the RING domain and able to chelate one or two zinc ions. Due to its structural similarity to the RING finger, the

B-box can also mediate substrate ubiquitination. Accordingly, B-box domains are divided into type 1 (B-box1) and type 2 (B-box2). It has been proposed that the B-box1 domain functions either as an independent E3 ligase or acts to increase the catalytic activity of RING-type E3 ligases. The TRIM homology domain is also dependent on the presence of a B-box2 domain, which in some contexts appears to be helpful but may not always be required. However, it has been suggested that this structure can alter context-dependent biochemical activity by potentially influencing RING function or combining with B-box1 thus having possible upstream effects upon substrate specialization and/or E3 ligase operating efficiency (25, 26).

The coiled-coil domain usually consists of two or three helical segments whose lengths are generally about 100–200 amino acid residues¹. It is well recognized that its mechanical properties are derived from a supercoiled organization of α -helices, held predominantly via hydrophobic interactions rendering its structure rope like. In TRIM proteins, this domain is responsible not only for homodimerization between similar subunits but also for heterodimeric associations with other proteins. This, in turn, determines not only their subcellular compartments towards which TRIM proteins are recruited but also the partnership patterns TRIM proteins form via these collaborations (25, 27).

While all TRIM proteins have this N-terminal motif conserved, there is notable diversity in their C-terminal domains that forms the basis for their classification into 11 distinct subgroups (C-I through C-XI), as well as an unclassified subgroup (UC) (Figure 1) (25, 28). Among these, the PRY/SPRY (B30. 2) domain which is particularly interesting as it acts on pathogen recognition and or surface molecule binding to regulate innate immune responses and host-pathogen interactions. Further functionally relevant C-terminal domains comprise COS (C-terminal Subgroup One Signature), FN3 (Fibronectin Type III), PHD (Plant Homeodomain) and MATH (Meprin and TRAF Homology) as well as TM (Transmembrane region) domains, either endowing each member of the TRIM family with distinct binding specificities or biological roles (Table 1) (29). This arrangement, consisting of well-conserved N-terminal motifs grafted with variable C-terminal extensions, permits TRIM proteins to mediate versatile biological functions, such as protein ubiquitination and signaling to transcription. Interestingly, a subset of TRIM proteins that are categorized into the UC group do not possess RING domain (which is responsible for E3 ligase activity), making this family particularly functionally diverse (30).

2.2 Function of TRIM family proteins

TRIM proteins possess dual functional capabilities as they are involved in both ubiquitination and SUMOylation processes. Through their RING domains, many TRIM members function as E3 ubiquitin ligases, catalyzing the attachment of ubiquitin chains to target proteins and regulating diverse cellular pathways including innate immunity, signal transduction, and protein degradation. Concurrently, specific TRIM proteins also participate in SUMOylation—either by acting as SUMO E3 ligases themselves or by serving as SUMO-modified substrates—thereby modulating

transcriptional repression, chromatin organization, and antiviral defense mechanisms. This functional duality allows TRIM proteins to integrate ubiquitin and SUMO signaling pathways, coordinating complex cellular responses through both degradative and non-degradative regulatory mechanisms.

2.2.1 Ubiquitination functions of TRIM proteins

TRIMs do possess a conserved RING domain acting as an E3 ubiquitin ligase, thus forming an important core component of the ubiquitous degradation machinery known as the ubiquitin-

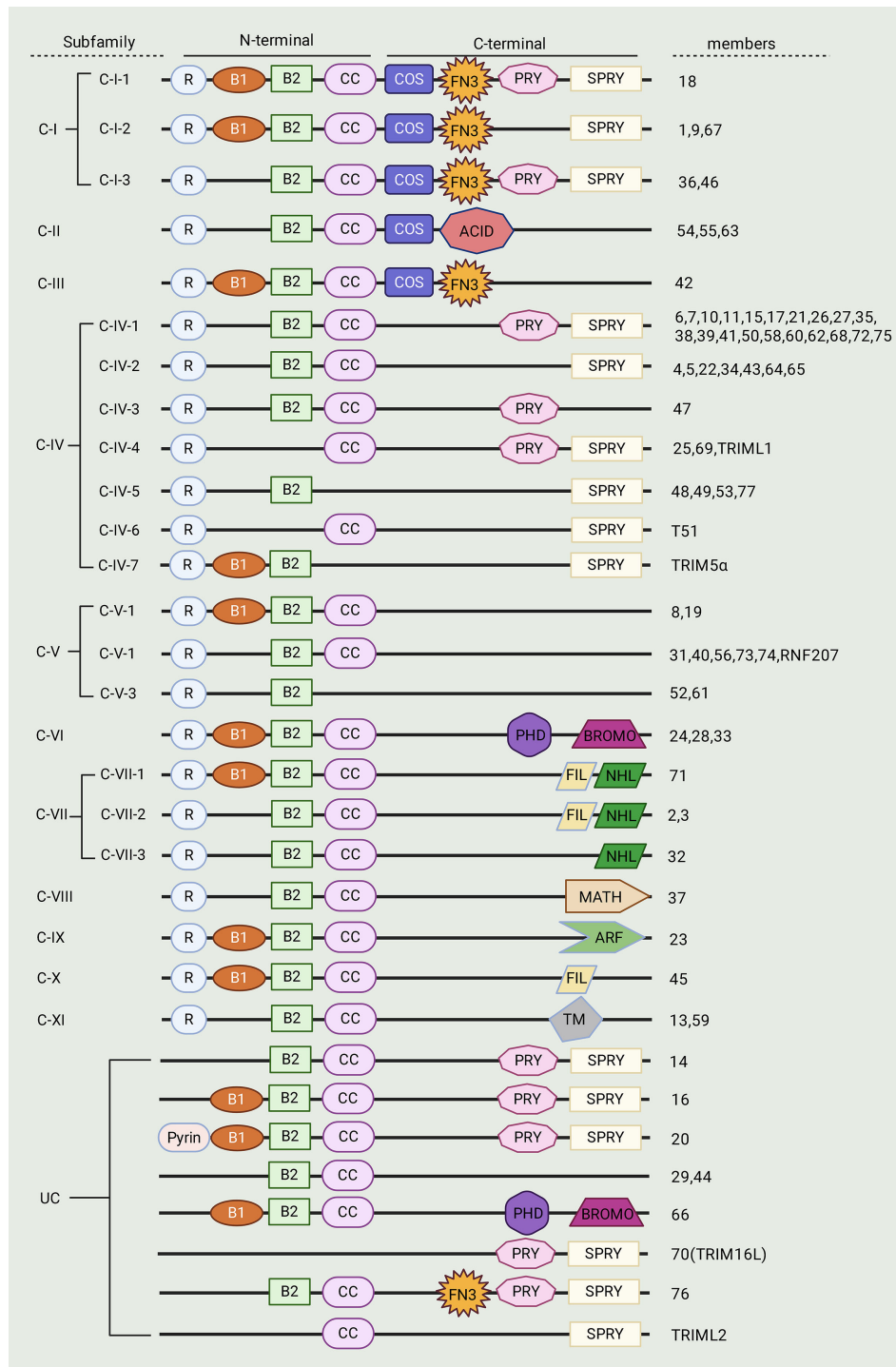


FIGURE 1
The classification of TRIM proteins based on structure. TRIM proteins are structurally categorized into 11 distinct subtypes and an unclassified subgroup (UC), which are defined by the composition of their variable C-terminal domains. A highly conserved RBCC motif, consisting of a RING finger domain, one or two B-box zinc finger domains, and a coiled-coil region, is characteristically found at the N-terminus. Key functional C-terminal domains include the PRY/SPRY (B30.2) domain, which mediates target recognition in immune regulation, as well as COS, FN3, PHD, MATH, and TM domains, each conferring specific binding and functional properties. This variability enables TRIM proteins to participate in diverse cellular processes such as ubiquitination, signaling, and transcriptional regulation. Meanwhile, the unclassified group lacks a RING-finger domain.

proteasome system (UPS), which includes ubiquitin (Ub) itself, ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and proteases with their substrates (31, 32).

Ubiquitin, a 76-amino acid eukaryotic protein (~8.5 kDa), acts as a degradation signal when it is assembled into chains that are recognized by the proteasome. The process of ubiquitination is initiated when E1 activates ubiquitin and forms a thioester linkage between its catalytic cysteine and the C-terminal glycine of the ubiquitin to transfer it to an E2 conjugating enzyme. E2s, which also harbor active-site cysteines, work together with E3 ligases like TRIM proteins to provide substrate specificity and execute the attachment of ubiquitin to target proteins (33–36).

Polyubiquitination occurs through chains formed with the use of one of the seven lysine (K6, K11, K27, K29, K33, K48 or k63) in ubiquitin. Different types of linkages yield diverse functional outcomes: K48-linked chains generally mark substrates for degradation by the proteasome, whereas K63-linking is usually involved in non-degradative states such as signal transduction; K6-linked chains are linked with mitochondrial homeostasis, while all other linkages (K27, K11 and K29) can also act within a proteolytic mechanism. Two ubiquitin chain types between amino acid K48 and K63 are abundant in mammals. These polyubiquitin tags are recognized by the proteasome, which decomposes the tagged protein into short peptides and recycles ubiquitin. In

addition to homotypic chains, heterotypic ubiquitination enhances structural and functional diversity. K11/K48-branched ubiquitin chains, for instance, promote degradation efficiency (34, 37).

By binding substrate recognition modules located in their C-terminal regions and utilizing E3 ligase activity, TRIM proteins assemble specific ubiquitin chains and orchestrate numerous cellular processes from NF- κ B and interferon signaling to p53-mediated responses, apoptosis, and antiviral defense. Certain members of the TRIM family also function as scaffolds or modifiers of protein function without provoking degradation. The odyssey of TRIM proteins illustrates their functional pleiotropy, which helps explain their involvement in numerous human diseases (38–40).

2.2.2 SUMOylation functions of TRIM proteins

The RING domain of TRIM proteins is a cross-braced structural configuration formed by coordination with zinc ions. This exactly provides E2 with a structure that it can bind to. Relevant studies have shown that this complex structure promotes and catalyzes the reaction by stabilizing the E2~SUMO thioester bond to form a closed conformation. The molecular weight of the SUMO molecule is approximately 11 kDa. Its conformation has a typical $\beta\beta\beta\alpha\beta\alpha$ fold (41), and generally speaking, it is very similar to ubiquitin at the three-dimensional level. However, due to differences in surface electrostatic potential distribution and amino acid sequence composition, SUMO has unique functional properties. It obtains activity by hydrolyzing and removing the C-terminal peptide through ubiquitin-like protease 1 (ULP1) or sentrin-specific protease 1 (SEN1) (42). SUMOylation is a reversible post-translational modification. It is mediated by a hierarchical enzymatic cascade reaction, including the E1 activating enzyme (SAE1/SAE2), the E2 conjugating enzyme (Ubc9), and a series of E3 ligases (including members of the PIAS family and RanBP2). Their function is to jointly promote substrate specificity and conjugation efficiency. In essence, SUMOylation actually has two mechanisms. One is covalent modification, forming an iso peptide bond that is covalently linked to the lysine residue of the target protein. The other is to promote non-covalent interactions between SUMO-modified substrates and effector proteins that contain SUMO-interacting motifs (SIMs) (43). The SIM mentioned here generally consists of four hydrophobic residues. It can regulate substrate function and stability by binding to SUMOylated proteins (44). These will be discussed in detail later.

3 TRIMs in virus infection: the molecular mechanisms

TRIM proteins serve as important E3 ubiquitin ligases that globally regulate innate immunity via different mechanisms of ubiquitination. They tightly modulate important signaling pathways such as NF- κ B and interferon responses (JAK-STAT, RLR/MDA5, IRF pathways, PKR pathway) by promoting proteasomal degradation through K48-linked ubiquitination or

TABLE 1 Functions of C-terminal domains of TRIM proteins.

Domain name	Full name	Function	Domain name
PRY-SPRY	PRY/SPRY domain	Protein-protein interaction, recognition of viral proteins, involvement in innate immunity	PRY-SPRY
COS	C-terminal subgroup one signature	Interaction with the microtubule cytoskeleton	COS
FN3	Fibronectin type III	Serves as a molecular scaffold, mediating protein interactions	FN3
ACID	Acid-rich region	Acidic region rich in glutamate, involved in ubiquitin-mediated degradation	ACID
FIL	Filamin-type IG domain	Regulation of the immune system and RNA binding	FIL
NHL	NHL repeats	Binding to specific RNA sequences or structures	NHL
MATH	Meprin and TRAF homology	Mediation of protein-protein interactions, formation of oligomeric structures	MATH
ARF	ADP-ribosylation factor	Possesses GTPase activity, involved in autophagy regulation	ARF
TM	Transmembrane region	Localizes to the endoplasmic reticulum, suppresses inflammatory responses	TM
PHD-BROMO	PHD-Bromodomain	Recognition of histone modifications, regulation of transcription	PHD-BROMO

signal activation through chains K63. Moreover, TRIM proteins can directly bind and promote the degradation of viral components via ubiquitin-mediated processes, and they have established roles in triggering premature disassembly of viral capsids that also do not depend on ubiquitination. This intricately structured regulatory network empowers TRIM proteins to achieve optimum balance between antiviral defense and immune homeostasis indispensable for host protection.

3.1 By regulation of NF- κ B pathway

The NF- κ B signaling pathway is a master effector of immune and inflammatory responses, and cell survival, comprised of cytoplasmic NF- κ B hetero or homodimers bound to inhibitory I κ B proteins (45, 46). In response to cytokines, pathogen or stress signal, membrane receptors signal the I κ B kinase (IKK) complex including IKK α , IKK β and its regulatory subunit NEMO (NF- κ B Essential Modulator) (47). IKK phosphorylates I κ B, which then is K48-linked ubiquitinated and degraded by proteasome leading ultimately to the release of NF- κ B for translocation into nucleus to activate target genes such as pro-inflammatory cytokines, anti-apoptotic factors and immune regulators (48, 49). In addition to its role in transcriptional regulation, NF- κ B also directly inhibits viral replication through competition with viral transcription factors and induction of antiviral proteins that disrupt the assembly of viral replication complexes or mediate degradation of the entire viral

RNA (50–52). However, the HIV-1 long terminal repeat (LTR) has canonical NF- κ B binding motifs, and one of the effects of NF- κ B activation is enhanced viral transcription, especially in activated CD4⁺ T cells and macrophages. Inducible NF- κ B activity directly promotes HIV gene expression by binding to the LTR promoter, as shown in early studies (53–57). This should be attached to great importance.

Multiple TRIM proteins regulate the NF- κ B pathway via particular ubiquitination mechanisms (Figure 2). TRIM32 controls NF- κ B activity via K63-linked ubiquitination of its substrate and modulates the generation of proinflammatory cytokines and antiviral genes. Based on its antiviral mechanism, it is speculated that its role in viral infections is context-dependent—potentiating NF- κ B activation at early stage of HIV infection but eventually contributes to dampening it during later stages to minimize immunopathology (58, 59).

A second class of TRIM proteins modulates NF- κ B signaling via K48-linked ubiquitination. TRIM27 suppressed NF- κ B activation, leading to a reduction in the downstream type I interferon response that promotes viral replication. This function could be related to its E3 ubiquitin ligase activity by which it may enhance the ubiquitination and degradation of signal transducers in the NF- κ B cascade similar to ascribed role in mediating K48-linked ubiquitination and degradation of TBK1 in IRF3 pathway (60). These interactions help maintain immune tolerance to prevent autoimmune inflammation. This can facilitate the assembly of

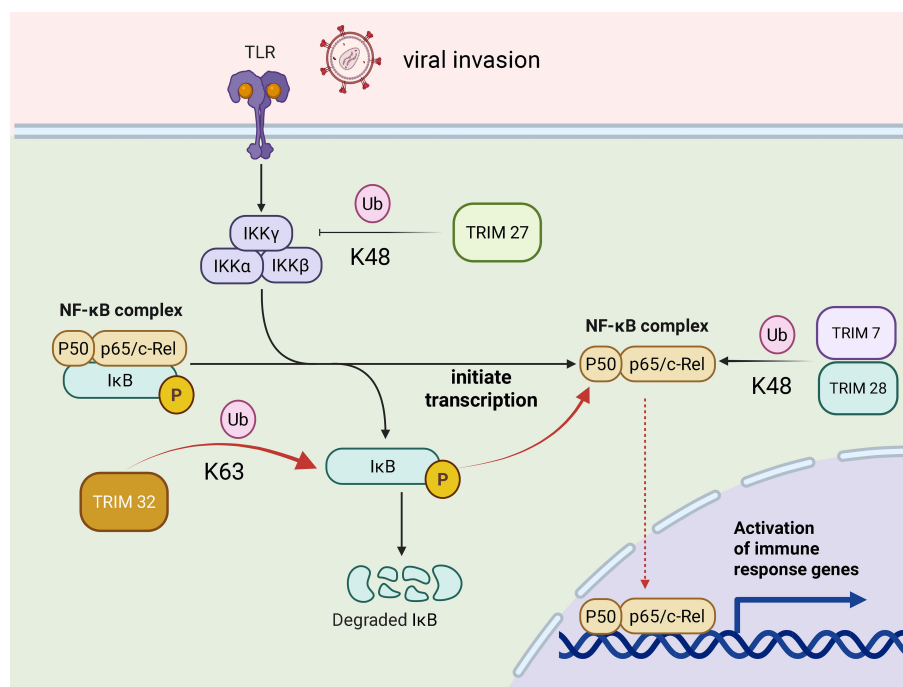


FIGURE 2

TRIM protein acts on the NF- κ B pathway. Under HIV infection conditions, the mechanism of interaction between TRIM proteins and the NF- κ B signaling pathway. Viral infection stimulates cell membrane receptors (TLR), resulting in the activation of the IKK complex. TRIM32 through distinct K63-linked ubiquitination mechanisms synergistically enhance NF- κ B-mediated transcription, driving robust inflammatory and antiviral responses. To further phosphorylate and activate the catalytic subunit IKK β , which then phosphorylates its canonical substrate, I κ B α , triggering its K48-linked ubiquitination and proteasomal degradation. Concurrently, TRIM32 also promotes NF- κ B signaling by directly mediating K63-linked ubiquitination of I κ B α , which does not lead to its degradation but instead induces its dissociation from NF- κ B, thereby facilitating the release and nuclear translocation of NF- κ B. TRIM27 suppressed NF- κ B activation, leading to a reduction in the downstream type I interferon response that promotes viral replication.

inhibitory complexes as well as induce ASF1 (Anti-Silencing Function 1) expression, and supports antiviral defense against influenza, HSV (Herpes Simplex Virus), and HIV.

3.2 Regulation of interferon signaling pathways

Interferons (IFNs) are a critical aspect of the innate immune response (61). Upon viral infection, host cells produce signaling proteins that have a central role in antiviral defense called IFNs, and these alert neighboring cells to activate their antiviral mechanisms. The major pathway that mediates IFN signaling is the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway that acts as a significant avenue for propagating an interferon signal (62). Interestingly, many TRIM proteins have been found to be key regulators of IFN-related signaling pathways. For example, while some members of the TRIM family regulate JAK-STAT signaling cascades via ubiquitination-independent mechanisms, others serve to attenuate the magnitude and persistency of interferon signatures through similar means (63). In addition to JAK-STAT, TRIM proteins are also involved in cytosolic sensing pathways, such as the RLR/MDA5 pathway: recognition of viral RNA that leads to production of IFN (64). Several TRIMs also regulate activation of IRF transcription factors in a positive or negative manner via direct interactions or ubiquitin-related regulation (65, 66).

3.2.1 Regulation of JAK-STAT pathway

Cytokine signal transduction occurs predominantly via the JAK-STAT signaling pathway that is widely recognized as a central mechanism (67, 68). It starts with the binding of interferon (IFN) to its cognate receptor and the subsequent activation of JAKs that are associated with receptors. Then activated JAKs phosphorylate Signal Transducers and Activators of Transcription (STAT) proteins, the phosphorylated STAT proteins dimerize and translocate to nucleus, where they function as transcription factors to promote expression of interferon-stimulated genes (ISGs). The antiviral effectors encoded by these ISGs, for example of Mx proteins or Oligoadenylate Synthetase (OAS), act by directly inhibiting viral replication via interference with viral protein synthesis or degradation of viral RNA (69, 70).

A number of TRIM proteins modulate the JAK-STAT pathway through ubiquitination, often by mediating the proteasomal degradation of negatively acting JAK-STAT regulators via K48-linked ubiquitin chains (Figure 3). One example is TRIM8, which enhances JAK-STAT signaling in the host via binding to Suppressor of Cytokine Signaling 1 (SOCS1), an important negative regulator (70–73). TRIM8 facilitates K48-linked ubiquitination and subsequent proteasomal degradation of SOCS1, thus inhibiting SOCS1-mediated inhibition of IFN- γ signaling and facilitating the production of antiviral responses, and the resulting IFN- γ exerts direct antiviral effects that suggest a potential role for TRIM8 in

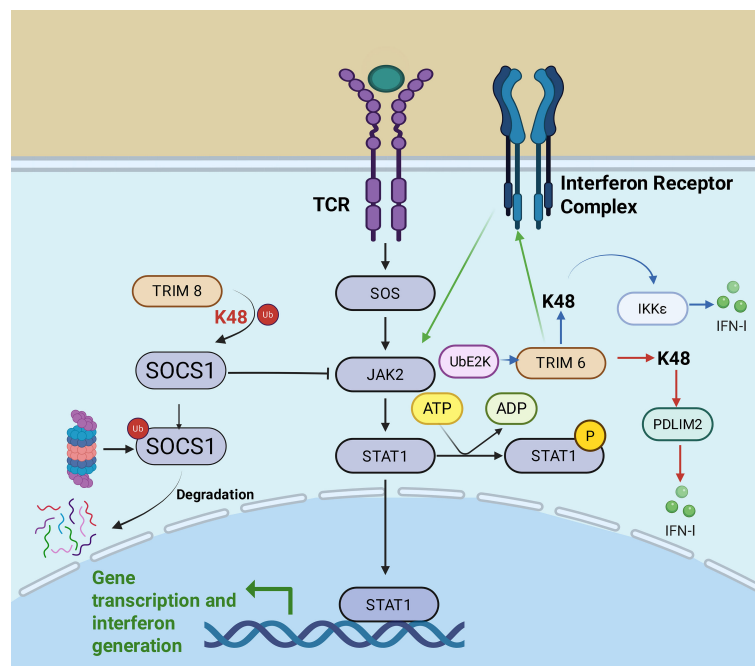


FIGURE 3

TRIM proteins exert the antiviral effects through modulation of the JAK-STAT signaling pathway. Following T cell receptor (TCR) activation, TRIM8 promotes K48-linked ubiquitination and subsequent degradation of SOCS1. As SOCS1 normally inhibits JAK2, its removal allows JAK2 to activate downstream STAT1, thereby promoting gene transcription and amplifying JAK-STAT signaling. TRIM6 enhances the JAK-STAT signaling pathway through a distinct mechanism involving the synthesis of unanchored K48-linked polyubiquitin chains in cooperation with the E2 enzyme UbE2K, which activates IKK ϵ kinase to promote type-I interferon signaling and establish an antiviral state. It also targets inhibitory host factors such as PDLIM2 for K48-linked ubiquitination to fine-tune the interferon response and prevent premature signal attenuation, while directly associating with the interferon receptor complex to facilitate signal transduction and promote robust STAT1/JAK2 activation, in addition to restricting viral replication via ubiquitination of viral proteins.

suppressing HIV replication and contributing to host defense against HIV infection. In addition, TRIM8 binds directly to the IFN receptor complex and promotes its signal transduction, resulting in strong activation of STAT1 and STAT2. It also serves to ubiquitinate viral proteins which may limit replication of HIV-1 (68).

Likewise, TRIM6 also utilizes K48-linked ubiquitination to target inhibitory host factors including LIM Domain Protein 2 (PDLIM2), regulating the IFN response and repressing unwanted early attenuation of signaling. Additional mechanisms of TRIM6 in potentiating the JAK-STAT pathway are also distinct from that described here. It co-assembles unanchored K48-linked polyubiquitin chains with the partner E2 enzyme, Ube2K (Ubiquitin-Conjugating Enzyme E2 K), to then activate its own associated IKK ϵ kinase, thereby enhancing IFN-I (Type I Interferon) signaling and triggering antiviral immunity, which may exert a potential anti-HIV effect through the action of interferons (74).

However, HIV-1 exerts divergent, context-dependent effects on the STAT pathway to evade immunity and maintain persistent infection. It can continuously activate STAT3 in dendritic cells and combine with STAT5 downregulation in CD8+ T cells and macrophages, which further impairs immune function. Meanwhile, STAT5 activation in CD4+ T cells enhance viral replication. Notably, HIV-1 inhibits IL-23-driven STAT3

activation in Th17 cells, which reduces IL-17 production. As a result, it disturbs the Th17/Treg balance and increases susceptibility to opportunistic infections. STAT5 additionally supports viral latency, particularly through the truncated STAT5 Δ isoform. This creates more challenges for the development of therapies targeting JAK-STAT pathway (75).

3.2.2 Regulation of RLR/MDA5 pathway

The pathway mediated by RIG-I-like receptors (RLRs), including key sensors such as RIG-I and MDA5, is one of the major routes for cytoplasmic detection of viral RNA (76). After binding to viral RNA, these receptors signal via the mitochondrial antiviral-signaling protein (MAVS) and exhibit a signaling cascade resulting in recruitment of transcription factors IRF3 and NF- κ B leading to production of type I interferons as well as proinflammatory cytokines that will lead to inhibition of viral replication and start of immune response against virus (77).

Three TRIM proteins inhibit the RLR/MDA5 pathway through ubiquitination (Figure 4). For example, TRIM65 amplifies MDA5-dependent antiviral signaling by mediating K63-linked ubiquitination of MDA5 to promote oligomerization and strengthen IFN production, and the resulting interferons exert broad-spectrum antiviral effects, which are speculated to include activity against HIV (78). Dynamically, TRIM22 may have

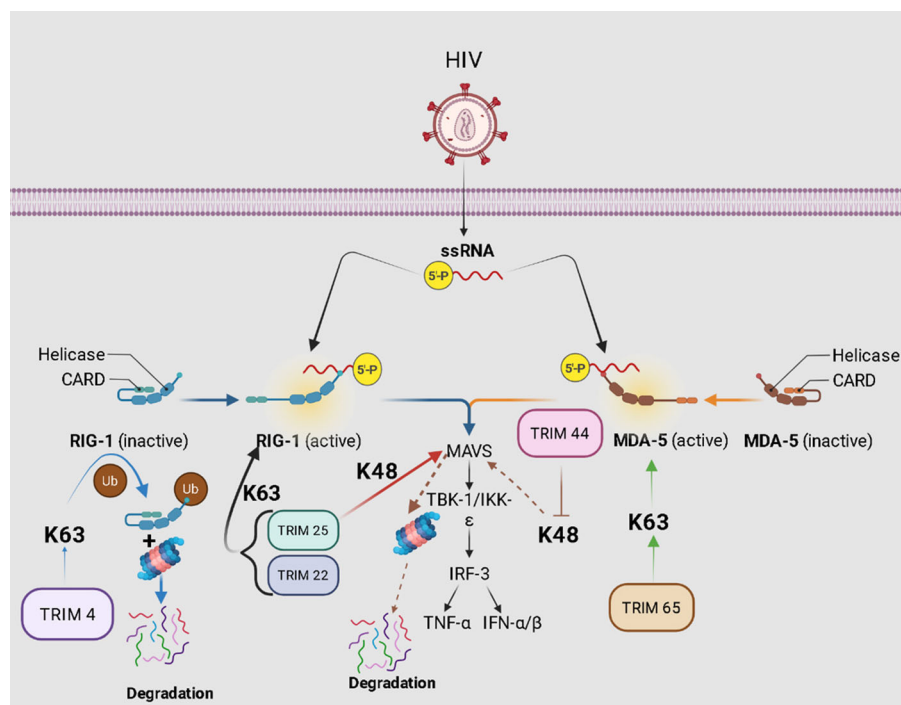


FIGURE 4

The role of TRIM proteins in the RLR/MDA5 pathway. During HIV replication, cytosolic sensors RIG-I or MDA5 recognize viral 5'-triphosphate single-stranded RNA (5'-ppp-ssRNA). This binding induces a conformational change in RIG-I/MDA5 that exposes the CARD domain, facilitating oligomerization via CARD-CARD interactions. TRIM65 specifically recognizes MDA5 and catalyzes K63-linked ubiquitination, which promotes MDA5 oligomerization and stabilizes its prion-like fibril assembly, thereby enhancing downstream signal transduction. Furthermore, TRIM22 and TRIM25 catalyze K63-linked ubiquitination of the adaptor protein MAVS, reinforcing its activation and promoting the assembly and function of the MAVS signalosome. Additionally, functioning as a deubiquitinating enzyme, TRIM44 enhances antiviral immunity by stabilizing VISA/MAVS through inhibition of K48-linked ubiquitination and proteasomal degradation—a mechanism mediated by its unique ZF-UBP domain, thereby reinforcing its regulatory role in innate immune responses. TRIM4 may enhance RIG-I activity through the conjugation of K63-linked ubiquitin chains, thereby promoting the production of type I interferons, and may also facilitate its interaction with adaptor proteins such as MAVS.

possibility to amplify RLR signaling by promoting K63-linked ubiquitination of the pathways' intermediaries like RIG-I whereas MAVS significantly potentiates interferon signal transduction thereby potentially preventing replication of HIV-1. Meanwhile, TRIM25 conjugates K63-linked polyubiquitin chains on RIG-I and promotes the K48-linked ubiquitination and proteasomal degradation of MAVS, revealing that TRIM25 plays a crucial dual role in the RLR signaling pathway, and this interaction may potentially contribute to combating HIV (38, 79–82). Additionally, TRIM44 boosts antiviral signaling by binding to and stabilizing VISA (Virus-Induced Signaling Adaptor), an essential adaptor protein in the RIG-I-like receptor pathways by antagonizing K48-linked ubiquitination leading to proteasomal decay—a feature of this module is provided through its N-terminal zinc-finger ubiquitin protease domain (ZF-UBP) that gives TRIM44 a functional advantage over classical RING domain is central for most catalytic activity. By acting as a ubiquitin stabilizer, TRIM44 reduces VISA protein degradation via this action, thus further enhancing its modulatory function in innate immune responses and potentially contributing to an anti-HIV effect. TRIM44 engages in the positive regulation of VISA to prevent its excessive turnover, resulting in a boost in the outputs from IFN- β (Interferon Beta) and TNF-(Tumor Necrosis Factor Alpha), thus enhancing antiviral innate immunity (83–85). Whereas TRIM4 acts as a counterpart that inhibits the pathway, eliciting K63-linked ubiquitination of RIG-I and targeting it to proteasomal degradation to prevent excessive immune activation, and may similarly protect against immune overactivation in the context of HIV infection (86, 87).

3.2.3 Regulation of IRF pathway

A key pathway of antiviral innate immunity involves the induction of type I interferons (IFN-I) through the IRF signaling cascade. After viral infection, Pattern Recognition Receptors (PRR), like RIG-I or TLR (Toll-Like Receptor) recognize the virus components and activate downstream signaling pathways who included kinase like TBK1 (TANK-Binding Kinase 1) or IKK neighbors. These kinases phosphorylate the transcriptional factors IRF, mainly IRF3 and IRF7, which then dimerize and translocate into nuclei. In the nucleus, interferon regulatory factors (IRF) bind to interferon-stimulated response elements (ISREs) to activate IFN-I and other antiviral genes (88).

And there are of TRIM proteins that regulate the IRF pathway in a ubiquitin-dependent manner. Along similar lines, TRIM25 transcriptionally uplifts the IRF signaling cascade by stimulating K63-linked ubiquitination to activate downstream signaling pathways that include kinases like TBK1, thereby inhibiting RNA viruses such as HIV-1. (38). In addition, many other examples have been reported, which will not be listed here individually.

3.2.4 Regulation of PKR pathway

Many members of the TRIM family can interact with double-stranded RNA-dependent protein kinase (PKR) to jointly resist viral infection.

HPAIV infects human lung epithelial cells. Krischuns et al. showed that during HPAIV infection, TRIM28 acts through the PKR-p38-MSK1 pathway, thereby triggering high levels of IFN- β , IL-6, and IL-8. These immune factors increase the body's response level to pathogens, thus achieving an antiviral effect, which we speculate also includes activity against HIV (89). For TRIM25, it has two completely different roles; it can both inhibit viral infection and promote it. In most cases, it promotes type I interferon signaling by adding ubiquitin to RIG-I, which helps RIG-I bind better to MAVS, thereby promoting the body's recognition of the virus and the downstream immune response. However, when TRIM25 is overexpressed, it prevents bcIKK ϵ from activating antiviral genes, such as PKR, which in turn promotes replication of HIV-1 (90). TRIM21 also inhibits viruses. Relevant animal experiments show that in largemouth bass, overexpressing TRIM21 (MsTRIM21) increases the levels of IRF3, IRF7, Mx1, ISG15, PKR, and TNF- α . These immune factors can act as signals to enhance the reactivity of the immune system, strengthening the body's immune and inflammatory responses against HIV-1 (91). In addition to functioning independently as a dsRNA kinase, PKR also directly interacts with NLRs and AIM2 to assist in the formation of inflammasomes, such as NLRP1, NLRP3, NLRC4, and AIM2 (92). These inflammasomes will all participate in downstream immune responses, raising the overall level of inflammation in the body, and may thus play a role in combating HIV.

Overall, many proteins of the TRIM family can effectively activate the immune system and increase the level of inflammatory response by regulating PKR and its related upstream and downstream pathways, thereby achieving an antiviral effect.

4 Treatment strategies of TRIM family proteins in HIV infection

The TRIM protein family comprises a potentially unexplored set of therapeutic HIV/HIV infection target. Of more than 70 TRIM members, TRIM5 α , TRIM22, TRIM28 and TRIM37 have emerged as leading candidates on the basis of compelling preclinical evidence.

4.1 Targeting TRIM5 α : mechanistic understanding and therapeutic approaches

Evidence is accumulating that rhTRIM5 α 's restriction of HIV-1 can be modified by both capsid recognition and ubiquitin functions — importantly, its intracellular antiviral activity appears to be regulated at multiple points through the SUMO (small ubiquitin-like modifier) system (93, 94). However, the often-overlooked huTRIM5 α has also shown new progress in recent years (95).

4.1.1 The SUMOylation of rhTRIM5 α

Many studies demonstrated that the regulation of rhTRIM5 α is SUMO-dependent. First, Lys10 was identified as an SUMOylation

site and showed that rhTRIM5 α can be conjugated to SUMO1 and SUMO2 in cells and *in vitro*. The modification of the SUMO pathway has an impact on the efficiency of restriction: inhibition of SUMO conjugation reduces HIV-1 restriction whilst overexpression of either SUMO1 or Ubc9 increases antiviral activity. Lys10 mutation-induced loss of antiviral activity suggests that SUMOylation of rhTRIM5 α is a regulatory event rather than necessary catalytic event. Interestingly, Lys10 mutation does not obliterate the antiviral activity (96–98). Under physiological conditions, rhTRIM5 α is SUMOylated at Lys84 in a RanBP2-dependent manner (Recent research). As depleting the SUMO E3 ligase RanBP2 decreases rhTRIM5 α SUMOylation and its ability to restrict HIV-1, it appears that SUMO modification *in vivo* is functionally relevant (99).

4.1.2 SUMO-interacting motifs of rhTRIM5 α

RhTRIM5 α contains PIPIRs that are SUMO-interacting motifs beyond covalent modification. When partial capsid binding is retained, further disruption of these motifs dramatically decreases HIV-1 restriction, highlighting the importance for non-covalent SUMOylation dependent interactions (96). This observation is consistent with broader multiple summary studies of TRIM family proteins indicating that many function more like SUMO-dependent signaling scaffolds than conventional SUMO E3 ligases. Enhanced SIM domain binding can lead to the 'integration' of ubiquitin and SUMO signaling pathways, as well as stabilization of higher-order signaling complexes through the recruitment of SUMOylated partners (96).

Overall, the SUMO pathway, when combined with rhTRIM5 α function, acts as a modulating layer that enhances rhTRIM5 α activity but is not the primary effector of HIV-1 restriction; thus, this work identifies new opportunities for therapeutic manipulation of cellular antiviral defenses.

4.1.3 Inducing premature viral degradation of rhTRIM5 α

Induction of Premature Viral Degradation, intended early disassembling of the viral envelope limiting successful replication at the cellular level, is a host viral defense mechanism. Notably, important proteins like TRIM family members bind directly to viral capsids soon after virus entry and promote uncoating while exposing viral components to cellular degradation pathways. This leads to proteasomal or autophagic destruction, thereby stopping the viral life cycle before reverse transcription and gene expression. It is an important innate intracellular defense mechanism against diverse viruses (100, 101).

rhTRIM5 α inhibits viral infection by triggering premature uncoating of the viral capsid followed by degradation (98). RhTRIM5 α substantially binds to the HIV capsid through its C-terminal PRY/SPRY domain, resulting in rapid uncoating and autophagic clearance of viral particles. After binding to the capsid, rhTRIM5 α also induces formation of K63-linked polyubiquitin chains and activation of the TAK1–NF- κ B pathway, thus coupling direct viral restriction with innate

immune signaling. It should be noted that this study was conducted based on Old World monkeys (97, 102). Deletion of this domain greatly impairs antiviral function. This mechanism is efficient against both HIV-1 and HIV-2, considering that the siRNA (Small Interfering RNA)-mediated knockdown of rhTRIM5 α is responsible for restoring viral infectivity (40, 46, 103–105).

Notably, TRIM34, which has ~57% amino acid identity to rhTRIM5 α , also facilitates capsid recognition and restriction in a cooperative manner. Both proteins colocalize with newly arrived viral capsids and display mutant-specific targeting. RhTRIM5 α restricts the P90A HIV-1 capsid mutant, whereas TRIM34 inhibits the N74D counterpart. The TRIM34-dependent restriction of N74D is dependent on rhTRIM5 α but occurs independently for P90A. These dual functional capacities provide necessary coaction for pluripotent antiviral activity against HIV and SIV in primary T cells as well as more conveniently in monocyticTHP-1 cells (106).

4.1.4 Recent studies of huTRIM5 α

It has been suggested that the differing patterns of retrovirus restriction by rhTRIM5 α versus huTRIM5 α observed in cell lines is due to variation in the SPRY v1 sequence between the two orthologues, in line with the long-standing belief that HIV-1 restriction by rhTRIM5 α is species-specific (107, 108). The apparent decreased ability of huTRIM5 α to restrict HIV-1 in cell lines has been associated to low affinity for the viral core and instability of the protein (109).

Compared with the proteasome-dependent mechanism observed in proteins such as rhTRIM5 α , the selective autophagy mediated by huTRIM5 α appears to play a more important role. HuTRIM5 α can function as a platform for autophagy by forming a TRIM5 α –ATG16L1–ATG5–HIV capsid complex. This complex subsequently induces the formation of an autophagosome, leading to the encapsulation of the HIV capsid. The autophagosome then fuses with the lysosome, resulting in viral degradation. In addition, huTRIM5 α contains an LIR (LC3-Interacting Region) motif, which enables it to bind LC3 and p62 and thereby directly recruit the autophagic machinery (95).

Notably, the anti-HIV activity of huTRIM5 α is highly dependent on cell type. Studies have shown that in epidermal Langerhans cells (LCs), HIV is captured by the Langerin receptor, which subsequently specifically recruits huTRIM5 α to initiate autophagy. Langerhans cells (LCs) belong to the subset of dendritic cells (DCs) that line the mucosal epithelia of vagina and foreskin and have the ability to sense and induce immunity to invading pathogens. HuTRIM5 α potently restricts HIV-1 infection of LCs but not of subepithelial DC-SIGN+ DCs. HIV-1 binding to DC-SIGN+ DCs leads to disassociation of huTRIM5 α from DC-SIGN, which abrogates huTRIM5 α restriction. These findings also provide new directions for potential therapeutic strategies (95, 110).

4.2 TRIM28: epigenetic regulation of viral latency

TRIM28 (KAP1) is a target of interest, as it promotes viral latency by epigenetically silencing the integrated provirus. Small

molecule inhibitors targeting TRIM28-mediated repression are investigating as potential latency reversing agents in “shock and kill” treatment strategies. TRIM28 (KAP1) SUMOylation, required for transcriptional repression, might go beyond its ubiquitin-related activities (95, 111, 112).

4.2.1 SUMO-dependent regulation of TRIM28

Recruitment of chromatin repressors that require intramolecular auto-SUMOylation of the proximal bromodomain is mediated by the PHD domain of TRIM28's SUMO E3 ligase activity (111, 113). Although SUMOylated TRIM28 by itself directly represses transcription, it also facilitates the TRIM28-SETDB1 complex formation which is associated with heterochromatin establishment and H3K9me3 chromatin modification (114, 115). H3K9me3 enrichment promotes the binding of heterochromatin protein 1 (HP1), conferring stability to transcriptional silencing (116).

TRIM28 has specifically been identified bound at the proviral LTR in HIV-1 latency models, where it contributes to maintaining a repressive chromatin conformation characterized by high levels of H3K9me3 (117). TRIM28 depletion results in a partial reactivation of viral transcription and reduced H3K9me3 levels at the LTR, implicating its role in latency maintenance. Post-translational modifications of TRIM28, including SUMOylation have been proposed to play an important role in the stability and repressive capacity of TRIM28-containing chromatin complexes at viral promoters (111, 113, 118, 119).

Notably, TRIM28 acts as a negative regulator, prevent excessive inflammation and consequently promoting viral replication by inhibiting IRF3 activity and successive IFN-I production through K48-linked ubiquitination and degradation of IRF3 (120).

4.2.2 Conclusion

These results suggest two therapeutic avenues that require further investigation. For example, inhibition of the SUMOylation pathway relieves TRIM28-mediated repression as shown here thus reactivating latent HIV whereby infected cells can then be cleared. Improvement of TRIM28 SUMOylation is another strategy that would enhance transcriptional silencing and also lead to more long-term suppression of HIV replication. From a risk-benefit perspective, the former approach may pose an unacceptably high risk considering the limited immune surveillance to which central nervous system is subjected and further limitations brought on by the blood-brain barrier. The latter strategy, however, may have greater translational value and thus warrant more research.

4.3 The perspective of microtubule dynamics of TRIM69

Studies have shown that TRIM69 suppresses the early stages of HIV replication in myeloid cells by regulating microtubule dynamics. Experimental evidence demonstrates that TRIM69 can directly bind to microtubules and promote the accumulation of stabilized microtubules, thereby altering cytoskeletal organization. This change interferes with the intracellular trafficking of the virus

after entry into the cell. Although TRIM69 does not affect HIV-1 entry, it significantly reduces the efficiency of reverse transcription, thereby inhibiting the establishment of viral infection. Meanwhile, evolutionary analyses in primates and humans further indicate that the antiviral function of TRIM69 is highly conserved. This represents a highly meaningful new perspective, as it examines antiviral mechanisms from the standpoint of microtubule structure for the first time, thereby helping to broaden potential therapeutic strategies (121).

4.4 The role of other TRIMs

In contrast, PML (Promyelocytic Leukemia Protein)—a major organizer of nuclear PML bodies—displays a powerful antiviral effect through repression of viral transcription (122). Notably, TRIM19 (PML), a prototypic TRIM protein with established SUMO E3 ligase activity (123). There is close proximity between silent HIV-1 provirus and PML NBs, whereas transcriptional activation induced by TNF- α or TPA led to a significant displacement of PML NBs. PML occupancy at the HIV LTR in resting conditions and its dynamic release after induction. It contributes to viral latency (122, 124). On the other hand, it was reported that human TRIM37 which has a TRAF (TNF Receptor-Associated Factor) domain in its C-terminal domain was showed to have anti-HIV-1 activity (125). TRIM22 has diverse antiviral effects through the regulation of NF- κ B and direct binding with viral RNA. It acts as a suppressor of basal HIV-1 LTR-driven transcription by preventing Sp1 binding to the HIV-1 promoter (126). TRIM11 is a new HIV-1 capsid binding protein, which restricts HIV-1 reverse transcription by accelerating viral uncoating. Overexpression of TRIM11 accelerates HIV-1 uncoating and reduces viral reverse transcription (127).

4.5 Potential roles of TRIMs in advanced HIV infection-associated complications

Advanced HIV infection is often accompanied by a range of complications. In this context, we also attempt to explore the potential of TRIM proteins in supporting the treatment of these complications, rather than limiting the discussion solely to the treatment of HIV infection itself.

4.5.1 TRIM28 in neuroinflammation and HIV-associated neurocognitive disorder

Persistence of HIV in macrophage-lineage cells and microglia of the central nervous system causes sustained neuroinflammation associated with HIV-associated neurocognitive disorders (HAND) (128).

TRIM28 has been shown to regulate endogenous retroelement silencing and interferon-stimulated gene expression through chromatin-dependent mechanisms. TRIM28 execute structure H3K9me3-enriched heterochromatin that might modulated proviral transcription and inflammatory gene expression programs in CNS reservoirs which is regulated in SUMO-dependent manner. Recent studies in HIV neuropathogenesis speculate on the involvement of chromatin regulators, including

TRIM28, as linking HIV persistence to neuroinflammatory states (118, 129, 130).

4.5.2 TRIM antiviral activity and cancer

TRIM family proteins play a critical role in antiviral immunity. However, the long-term regulation of this antiviral activity may disrupt cellular homeostasis, affecting tumor suppressor pathways such as p53, and consequently altering tumor susceptibility (131). TRIM family members participate in the regulation of multiple oncogenic signaling pathways through their E3 ubiquitin ligase activity, including JAK/STAT, PI3K/AKT, TGF- β , NF- κ B, Wnt/ β -catenin, and p53 pathways, thereby influencing the proliferation, migration, and invasion of tumor cells (132, 133). In the early stages of tumorigenesis, TRIM proteins promote or inhibit malignant transformation by regulating ROS homeostasis (134), glucose metabolic reprogramming (135), and protein folding homeostasis (134). For example, TRIM22 induces autophagic cell death by destabilizing NRF2 and activating the AMPK/mTOR pathway (135). During tumor progression, TRIM proteins also promote tumor invasion and metastasis by regulating the epithelial-mesenchymal transition (EMT) process and maintaining cancer stem cell properties (136). Furthermore, the TRIM family plays significant roles in chemotherapy, targeted therapy, and radiotherapy resistance. For instance, TRIM7 mediates doxorubicin resistance in osteosarcoma by degrading BRMS1 (137), while TRIM23 regulates cisplatin resistance in lung cancer cells through the NF- κ B/GLUT1 axis (138). In summary, when developing TRIM-based therapeutic strategies for HIV, the potential carcinogenic risks must be carefully considered.

4.5.3 TRIMs in advanced HIV infection-associated opportunistic infections

As is well known, in the advanced stage, HIV causes immune system deficiency. This greatly increases susceptibility to various infectious complications and damage caused by inflammatory responses. We attempt to explore the help that TRIMs might bring in this context.

Relevant studies have found that TRIMs can play a role in tuberculosis by regulating the process of autophagy, such as TRIM16, 14, 22, 27, and 32. This inhibits bacterial proliferation. It is worth mentioning that TRIM14 and 25 prevent excessive immune responses by regulating inflammation in this process (139). This helps avoid unnecessary damage. In herpesvirus infections, experiments have proven that TRIM43 works by tagging and degrading a protein called Pericentrin. This protein can slow the replication of several herpesviruses (140). Fungal infections like candidiasis are also very common complications. Research has also pointed out the important role of TRIM26 in inhibiting excessive immune responses in these cases. It can control the production of CXCL1/CXCL2 and prevent kidney failure induced by acute nephritis (141). Human cytomegalovirus is also a common complication. Studies have pointed out that TRIM19 can limit its infection through sumoylation. In herpesvirus infections, experiments have proven that TRIM43 works by tagging and degrading a protein called Pericentrin. This protein can slow the replication of several herpesviruses (142).

However, some TRIM proteins can also promote the occurrence and development of AIDS-related complications, which requires great care when using these TRIMs to inhibit viral replication. For example, studies have pointed out that TRIM29 achieves degradation through K48 ubiquitination of the STING protein. Stimulator of interferon genes (STING) leads to the production of IFN-I and the spontaneous generation of anti-tumor CD8+ T cell responses, which are key factors in fighting HSV. This mechanism of TRIM29 undoubtedly weakens the immune response, thus giving HSV an opportunity and worsening the infection (143). Similar to this is TRIM21. In human papillomavirus (HPV) infection, TRIM21 tags and degrades the DNA sensor IFI16, blocking pyroptosis, thereby allowing the virus to evade immune system surveillance (144).

Overall, TRIM has both promoting and inhibiting effects on complications caused by AIDS. When using TRIM for antiviral therapy, we must pay attention to these aspects to prevent the effect of promoting complications from bringing negative impacts.

4.6 Prospects for the application of TRIM-targeted drugs in HIV

Two therapeutic strategies aim to exploit the antiviral activities of TRIM proteins: gene therapy and pharmacological modulation, with unique benefits and challenges.

4.6.1 Pharmacological targeting of TRIM proteins

Unlike the aforementioned strategy, pharmacological modulation of TRIM proteins is complementary to that, and could be pursued pretty much straight away. To this end, small molecules or biologics that elevate TRIM protein expression or E3 ligase activity may potentially potentiate interferon signaling and enhance viral restriction (145) (Table 2). Pharmacological approaches have advantages over gene therapy with respect to their ease of administration, dose titration and reversibility. Nevertheless, they face challenges including low bioavailability, fast clearance and off-target effects caused by the structural homologues of TRIM family members. Moreover, the pharmacologically off-target binding in viral sanctuaries stills a challenge.

4.6.2 Gene therapy-based strategies

Considering the limitations of exogenous TRIM proteins expressed via plasmids, which are inefficient in providing enduring immunization to cells over extended periods of time with continuous high viral levels, gene therapy modalities have been applied that could provide an enduring endogenous expression (146). It is realized mainly by a non-viral or viral vector delivery system. Lentiviral vectors and LNPs have facilitated the development of TRIM-based gene therapy by allowing transduction of hematopoietic stem cells (HSC) and primary T-cells at high efficiencies (147). One possible solution could involve TRIM5 α -engineered HSCs that generate HIV-resistant immune cell types, thereby enabling a functional cure. This strategy, however, is fraught with obstacles. A drawback of using these exogenous TRIM proteins is their potential to be recognized as foreign, leading to immune responses against the administered TRIM proteins themselves or

TABLE 2 Therapeutic targeting of TRIM proteins in HIV/advanced HIV infection.

Drug/compound	Mechanism of action	Targeted TRIM protein	Development status
cryptotanshinone	Cryptotanshinone upregulates TRIM28 expression by inhibiting HIF-1 α , as HIF-1 α physically interacts with TRIM28 and its activation counteracts the induction of TRIM28	TRIM28 (KAP1)	Discovery Phase
Non-immunosuppressive cyclosporine	It binds directly to cyclophilin A (CypA), preventing CypA from binding to the HIV-1 capsid and thereby allowing TRIM5 α to recognize and restrict the virus	TRIM5 α	Discovery Phase
Decitabine	It involves demethylation of its promoter region of TRIM37	TRIM37	Discovery Phase (In tumor models)

towards vector components that can hinder long-term expression and elicit inflammatory responses. Additionally, targeting the viral reservoirs is inefficient and off-target effects or insertional mutagenesis can incur safety issues. On the other hand, the high cost and complex manufacturing processes of gene therapies will likely limit their access, especially in resource-limited regions where HIV is endemic (148).

TRIM gene function has been modulated *in vitro*, using CRISPR/Cas9-mediated genome editing. In a proof-of-concept experiment, this was demonstrated by CRISPR/Cas9-mediated disruption of TRIM5 α in MDBK cells that yielded an approximately 12-fold increase in the transduction efficiency of an HIV-1-based lentiviral vector (149). Importantly, this was not an

intention to provide HIV resistance as alluded from the application but rather utilizing an improvement in viral vector production titers when applied to non-human cell lines. Introduction TRIM5 α is a broad-spectrum retroviral restriction factor found in human cells, and loss of TRIM5 α may undermine intrinsic antiviral defense. Knockout-based strategies are therefore not directly translatable into human therapy. Rather, these data mechanically validate TRIM5 α as a prime restriction node and provide further support for the rationale of overexpressing TRIM5 α or its orthologs in human cells as an increasingly feasible anti-HIV approach (150).

While genetic editing technologies have continued to evolve, parallel efforts such as nanoparticle-based platforms for targeted

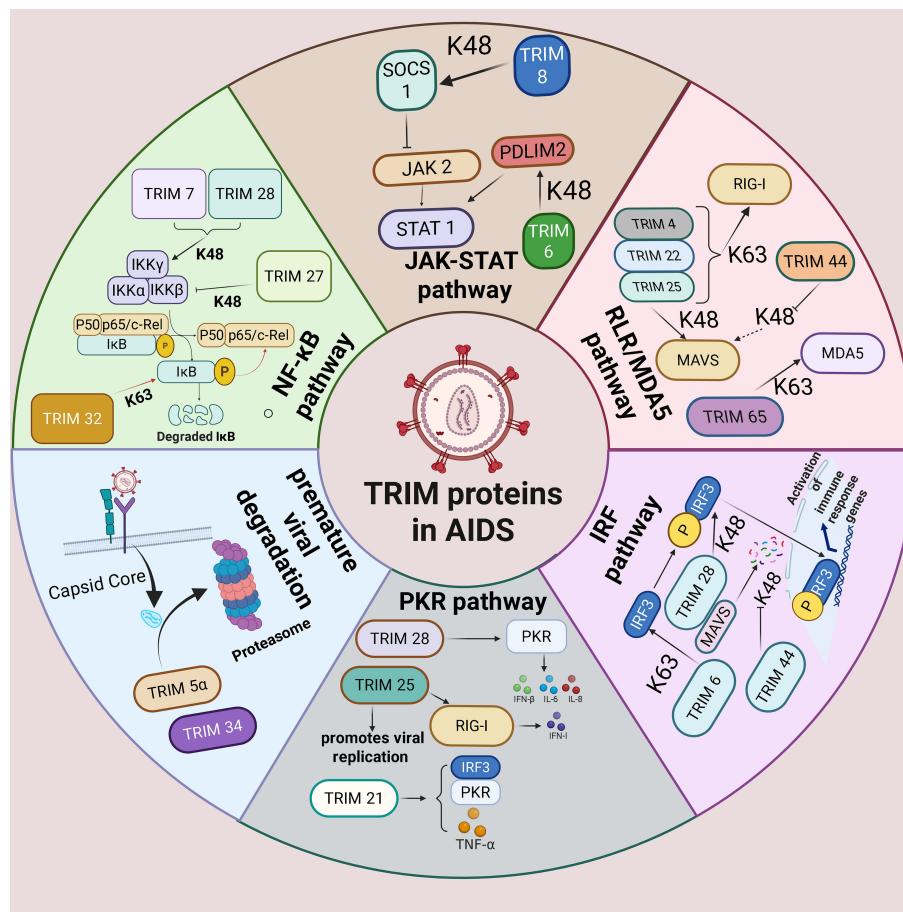


FIGURE 5 The overall graphical diagram to summarize the roles and mechanisms of TRIM proteins in AIDS. TRIM proteins mainly exert the antiviral effects via the NF- κ B pathway, the JAK-STAT pathway, the RLR/MDA5 pathway, the IRF pathway, the PKR pathway, and direct viral degradation.

delivery of antiviral effectors have also been explored. A study of SIV vaccines found that encapsulation of TLR ligands within PLGA nanoparticles provoked stronger and more lasting antibody responses in rhesus macaques, compared to alum adjuvants, and provided greater protection against vaginal challenge in animals expressing restrictive TRIM5 α alleles (151). Yet, poor endosomal escape and variable encapsulation and targeting render PLGA nanoparticles substantial translational barriers to mRNA/protein delivery. Currently, lipid nanoparticles (LNPs) represent a more advanced platform than any other for TRIM-encoding mRNA delivery but findings from the adjuvant studies must be extrapolated with caution to therapeutic settings.

Recent mechanistic studies have broadened the therapeutic potential of TRIM-mediated restriction. TRIM34 has been shown to mediate a broad-spectrum lentiviral restriction in a TRIM5 α -dependent manner: it shows negligible activity alone but strongly restricts the HIV-1 capsid when co-expressed with TRIM5 α , suggesting functional cooperation through heterodimerization or shared downstream effectors (152). This synergy enables combinatorial targeting of functionally related TRIM paralogs. Moreover, inhibition of CSNK2—or knockdown of its downstream TRIM effectors—enhances autophagic flux and restricts diverse viruses, including HIV-1 (153). These discoveries expand the list of therapeutic targets associated with TRIM, although their relative relevance *in vivo*, tissue specificity and long-term safety will need to be systematically studied.

4.6.3 Translational risks and future directions

The translational development of TRIM-targeting agents faces several common obstacles: many TRIMs, including TRIM29, exert context-dependent activities in viral restriction and oncogenesis requiring high specification to afford detrimental off-target events (154). Overzealous chronic engagement or overexpression may also invoke autoimmunity or hyperinflammation, especially in therapies having a long duration. Efficient delivery to viral reservoirs without systemic exposure is a key translational bottleneck (155), exacerbated in high burden HIV regions by economic and infrastructural shortfalls (156).

Nevertheless, future work should focus on developing tissue-specific delivery systems or highly specific small-molecule modulators with good pharmacokinetic properties, as well as biomarker development to track TRIM activity *in vivo*. Combination approaches which include TRIM-optimizing agents alongside current antiretrovirals could have synergistic potentials and limit risk of resistance emergence. Although to our knowledge no TRIM-targeting agent is yet in clinical trials for HIV, advances in protein delivery, and gene-delivery vehicles have been developed and used clinically which would be applicable within the next couple decades. Further study of TRIM biology and therapeutic targeting is a promising avenue to understand how intrinsic immunity might be recruited for long-term virologic control.

5 Conclusion

In summary, the present review has discussed the roles of TRIM family members in advanced HIV infection pathogenesis. Most of them mediate their antiviral functions in innate immunity and immune regulation through antagonizing specific mechanisms, including the NF- κ B pathway, the JAK-STAT pathway, RLR/MDA5 pathway, IRF pathway, the SUMOylation and inducing premature viral degradation (Figure 5). We also briefly highlight several emerging mechanistic directions, which may provide readers with a different perspective. Additionally, we discussed the pharmacological properties of TRIM target proteins and how targeting these proteins can represent novel therapeutic strategies which could encompass antiviral and immune modulation to addressing one of patients' major challenges: viral reservoirs.

However, there are significant barriers to the translational use of these discoveries. As such, the functional pleiotropy of TRIM proteins, as well as the possibility for off-target effects and context-dependent functions of certain family members highlight a need for highly specific intervention strategies. Future exploration in this area starts with systematic CRISPR-Cas9 screens to determine what TRIM proteins are non-redundant for restriction of HIV in primary human cells, and whether we can develop specific small-molecule agonists or antagonists targeting signaling pathways upstream or downstream of key TRIM players (TRIM5 α and TRIM22 exemplified here), determining their effectiveness/side effects in advanced models including humanized mice infected with HIV.

Nonetheless, as summarized here, the evidence concludes that harnessing TRIM proteins' antiviral arsenal presents remarkable potential for a new class of therapeutics. If this line of research continues to be pursued and focused on, it could help achieve a functional cure for advanced HIV infection.

Author contributions

JC: Investigation, Conceptualization, Software, Writing – original draft, Visualization. SC: Writing – original draft, Resources, Investigation. YX: Investigation, Writing – original draft. XW: Writing – original draft, Resources. MJ: Funding acquisition, Conceptualization, Writing – review & editing, Supervision.

Funding

The author(s) declared that financial support was received for this work and/or its publication. This study was supported

by Natural Science Foundation of Jiangxi Province (20252BAC240143 to MJ), Jiangxi province Science and Technology Program of the Health Commission (202311127 to MJ), the Jiangxi Province Key Laboratory of bioengineering drugs (2024SSY07061).

Acknowledgments

Figures were created with BioRender.com.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

- World Health Organization. *WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children*. Geneva: World Health Organization (2007).
- De Cock KM, Jaffe HW, Curran JW. Reflections on 40 years of AIDS. *Adv Clin Immunology Med Microbiology COVID-19 Big Data*. (2021) 27(6):1555–67. doi: 10.3201/eid2706.210284
- 2025 年6月全国艾滋病性病疫情. *中国艾滋病性病*. (2025) 31:927. doi: 10.13419/j.cnki.aids.2025.09.01
- Arts EJ, Hazuda DJ. HIV-1 antiretroviral drug therapy. *Cold Spring Harbor Perspect Med*. (2012) 2:a007161. doi: 10.1101/cshperspect.a007161
- Phanuphak N, Gulick RM. HIV treatment and prevention 2019: current standards of care. *Curr Opin HIV AIDS*. (2020) 15:4–12. doi: 10.1097/coh.0000000000000588
- Kumar L, Verma S, Prasad DN, Bhardwaj A, Vaidya B, Jain AK, et al. Nanotechnology: a magic bullet for HIV AIDS treatment. *Artif Cells Nanomed Biotechnol*. (2015) 43:71–86. doi: 10.3109/21691401.2014.883400
- Wachter RM, Luce JM, Lo B, Raffin TA. Life-sustaining treatment for patients with AIDS. *Chest*. (1989) 95:647–52. doi: 10.1016/0168-8510(90)90318-8
- Wang J, Zou W. Practices, challenges, and opportunities: HIV/AIDS treatment with traditional Chinese medicine in China. *Front Med*. (2011) 5:123–6. doi: 10.1007/s11684-011-0124-z
- Ef WJ, Wen Z. Recent advances of HIV/AIDS treatment with traditional Chinese medicine in China. *J Traditional Chin Med*. (2010) 30:305–8. doi: 10.1016/s0254-6272(10)60062-3
- Bourinbaiar AS, Root-Bernstein RS, Abulafia-Lapid R, Rytik PG, Kanev AN, Jirathitikal V, et al. Therapeutic AIDS vaccines. *Curr Pharm Des*. (2006) 12:2017–30. doi: 10.1586/14760584.4.3.289
- Weidle PJ, Mastro TD, Grant AD, Nkengasong J, Macharia D. HIV/AIDS treatment and HIV vaccines for Africa. *Lancet*. (2002) 359:2261–7. doi: 10.1016/s0140-6736(02)09297-8
- Chen B. Molecular mechanism of HIV-1 entry. *Trends Microbiol*. (2019) 27:878–91. doi: 10.1016/j.tim.2019.06.002
- Nomaguchi M, Doi N, Koma T, Adachi A. HIV-1 mutates to adapt in fluxing environments. *Microbes Infection*. (2018) 20:610–4. doi: 10.1016/j.micinf.2017.08.003
- Sharp PM, Hahn BH. Origins of HIV and the AIDS pandemic. *Cold Spring Harbor Perspect Med*. (2011) 1:a006841. doi: 10.1101/cshperspect.a006841
- Dambaya B, Nkenfou CN, Mekue L, Têto G, Ngoufack N, Ambada G, et al. TRIM5 α 136Q, CCR5 promoter 59029G and CCR264I alleles impact the progression of HIV in children and adolescents. *Appl Clin Genet*. (2019) 12:203–11. doi: 10.2147/tacg.s205335
- Khan R, Khan A, Ali A, Idrees M. The interplay between viruses and TRIM family proteins. *Rev Med Virol*. (2019) 29:e2028. doi: 10.1002/rmv.2028
- Wu F, Ourmanov I, Riddick N, Matsuda K, Whitted S, Plishka RJ, et al. TRIM5 α restriction affects clinical outcome and disease progression in simian

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

- immunodeficiency virus-infected rhesus macaques. *J Virol*. (2015) 89:2233–40. doi: 10.1128/jvi.02978-14
- Vicenzi E, Poli G. The interferon-stimulated gene TRIM22: A double-edged sword in HIV-1 infection. *Cytokine Growth Factor Rev*. (2018) 40:40–7. doi: 10.1016/j.cytogfr.2018.02.001
- Van Gent M, Sparrer KM, Gack MU. TRIM proteins and their roles in antiviral host defenses. *Annu Rev Virol*. (2018) 5:385–405. doi: 10.1146/annurev-virology-092917-043323
- Jiang MX, Hong X, Liao BB, Shi SZ, Lai XF, Zheng HY, et al. Expression profiling of TRIM protein family in THP1-derived macrophages following TLR stimulation. *Sci Rep*. (2017) 7:42781. doi: 10.1038/srep42781
- An Y, Ni Y, Xu Z, Shi S, He J, Liu Y, et al. TRIM59 expression is regulated by Sp1 and Nr1 in LPS-activated macrophages through JNK signaling pathway. *Cell Signalling*. (2020) 67:109522. doi: 10.1016/j.cellsig.2019.109522
- Zeng X, Deng X, Ni Y, Bi H, Jiang M, Wang D, et al. LPS inhibits TRIM65 expression in macrophages and C57BL/6j mouse by activating the ERK1/2 signaling pathway. *Exp Ther Med*. (2023) 25:188. doi: 10.3892/etm.2023.11887
- Chen Y, Han X, Liu T, Ni Y, Deng X, Wei W, et al. TRIM59 deficiency aggravates HFD-induced obesity in mice associated with increased adipose tissue inflammation, lipid accumulation, and apoptosis. *Cell Signalling*. (2025) 134:111954. doi: 10.1016/j.cellsig.2025.111954
- Jiang M, Wang D, Su N, Lou W, Chen Y, Yang H, et al. TRIM65 knockout inhibits the development of HCC by polarization tumor-associated macrophages towards M1 phenotype via JAK1/STAT1 signaling pathway. *Int Immunopharmacol*. (2024) 128:111494. doi: 10.1016/j.intimp.2024.111494
- Torok M, Etkins LD. Two B or not two B? Overview of the rapidly expanding B-box family of proteins. *Differentiation*. (2001) 67:63–71. doi: 10.1046/j.1432-0436.2001.067003063.x
- Massiah MA, Simmons BN, Short KM, Cox TC. Solution structure of the RBCC/TRIM B-box1 domain of human MID1: B-box with a RING. *J Mol Biol*. (2006) 358:532–45. doi: 10.2210/pdb2ffw/pdb
- Chen R, Tie Y, Lu J, Li L, Zeng Z, Chen M, et al. Tripartite motif family proteins in inflammatory bowel disease: Mechanisms and potential for interventions. *Cell Proliferation*. (2022) 55:e13222. doi: 10.1111/cpr.13222
- Sanchez JG, Okreglicka K, Chandrasekaran V, Welker JM, Sundquist WI, Pornillos O, et al. The tripartite motif coiled-coil is an elongated antiparallel hairpin dimer. *Proc Natl Acad Sci*. (2014) 111:2494–9. doi: 10.1073/pnas.1318962111
- Liu S, Bi H, Jiang M, Chen Y, Jiang M. An update on the role of TRIM/NLRP3 signaling pathway in atherosclerosis. *Biomedicine Pharmacotherapy*. (2023) 160:114321. doi: 10.1016/j.biopha.2023.114321
- Cao X, Chen Y, Chen Y, Jiang M. The role of tripartite motif family proteins in chronic liver diseases: molecular mechanisms and therapeutic potential. *Biomolecules*. (2024) 14:1038. doi: 10.3390/biom14081038

31. Short KM, Cox TC. Subclassification of the RBCC/TRIM superfamily reveals a novel motif necessary for microtubule binding. *J Biol Chem.* (2006) 281:8970–80. doi: 10.1074/jbc.m512755200
32. Meroni G, Desagher S. Cellular function of TRIM E3 ubiquitin ligases in health and disease. In: *Cells*. Basel: MDPIAG (2022). p. 250. doi: 10.3390/cells11020250
33. Ikeda K, Inoue S. TRIM proteins as RING finger E3 ubiquitin ligases. In: *Trim/Rbcc proteins*. New York: Springer (2013). p. 27–37. doi: 10.1007/978-1-4614-5398-7_3
34. Yamauchi K, Wada K, Tanji K, Tanaka M, Kamitani T. Ubiquitination of E3 ubiquitin ligase TRIM5 α and its potential role. *FEBS J.* (2008) 275:1540–55. doi: 10.1111/j.1742-4658.2008.06313.x
35. Qin Y, Li Q, Liang W, Yan R, Tong L, Jia M, et al. TRIM28 SUMOylates and stabilizes NLRP3 to facilitate inflammasome activation. *Nat Commun.* (2021) 12:4794. doi: 10.1038/s41467-021-25033-4
36. Fiorentini F, Esposito D, Rittinger K. Does it take two to tango? RING domain self-association and activity in TRIM E3 ubiquitin ligases. *Biochem Soc Trans.* (2020) 48:2615–24. doi: 10.1042/bst20200383
37. Qu J, Liu GH, Wu K, Han P, Wang P, Li J, et al. Nitric oxide destabilizes Pias3 and regulates sumoylation. *PLoS One.* (2007) 2:e1085. doi: 10.1371/journal.pone.0001085
38. Gack MU, Shin YC, Joo CH, Urano T, Liang C, Sun L, et al. TRIM25 RING-finger E3 ubiquitin ligase is essential for RIG-I-mediated antiviral activity. *Nature.* (2007) 446:916–20. doi: 10.1038/nature05732
39. Yap MW, Stoye JP. TRIM proteins and the innate immune response to viruses. In: *TRIM/RBCC Proteins*. New York: Springer (2013). p. 93–104. doi: 10.1007/978-1-4614-5398-7_7
40. Nakayama EE, Shioda T. Impact of TRIM5 α *in vivo*. *AIDS.* (2015) 29:1733–43. doi: 10.1097/qad.0000000000000812
41. Wang Y, Dasso M. SUMOylation and deSUMOylation at a glance. *J Cell Sci.* (2009) 122:4249. doi: 10.1242/jcs.050542
42. Nayak A, Müller S. SUMO-specific proteases/isopeptidases: SENPs and beyond. *Genome Biol.* (2014) 15:422. doi: 10.1186/s13059-014-0422-2
43. Minty A, Dumont X, Kaghad M, Caput D. Covalent modification of p73 α by SUMO-1: two-hybrid screening with p73 identifies novel SUMO-1-interacting proteins and a SUMO-1 interaction motif. *J Biol Chem.* (2000) 275:36316–23. doi: 10.1074/jbc.m004293200
44. Lascorz J, Codina-Fabra J, Reverter D, Torres-Rosell J. SUMO-SIM interactions: From structure to biological functions. In: *Seminars in Cell & Developmental Biology*. Amsterdam: Elsevier (2022).
45. Hayden MS, West AP, Ghosh S. SnapShot: NF- κ B signaling pathways. *Cell.* (2006) 127:1286.e1–1286.e2. doi: 10.1016/j.cell.2006.12.005
46. Lukic Z, Campbell EM. The cell biology of TRIM5 α . *Curr HIV/AIDS Rep.* (2012) 9:73–80. doi: 10.1007/s11904-011-0102-8
47. Giraldo MI, Hage A, van Tol S, Rajsbaum R. TRIM proteins in host defense and viral pathogenesis. *Curr Clin Microbiol Rep.* (2020) 7:101–14. doi: 10.1007/s40588-020-00150-8
48. Zha J, Han KJ, Xu LG, He W, Zhou Q, Chen D, et al. The Ret finger protein inhibits signaling mediated by the noncanonical and canonical I κ B kinase family members. *J Immunol.* (2006) 176:1072–80. doi: 10.4049/jimmunol.176.2.1072
49. Han T, Guo M, Gan M, Yu B, Tian X, Wang JB, et al. TRIM59 regulates autophagy through modulating both the transcription and the ubiquitination of BECN1. *Autophagy.* (2018) 14:2035–48. doi: 10.1080/15548627.2018.1491493
50. Zein L, Dietrich M, Balta D, Bader V, Scheuer C, Zellner S, et al. Linear ubiquitination at damaged lysosomes induces local NF κ B activation and controls cell survival. *Autophagy.* (2025) 21:1075–95. doi: 10.1080/15548627.2024.2443945
51. Deshaies RJ, Joazeiro CA. Ring domain E3 ubiquitin ligases. *Annu Rev Biochem.* (2009) 78:399–434. doi: 10.1146/annurev.biochem.78.101807.093809
52. Zhao J, He S, Minassian A, Li J, Feng P. Recent advances on viral manipulation of NF- κ B signaling pathway. *Curr Opin Virol.* (2015) 15:103–11. doi: 10.1016/j.coviro.2015.08.013
53. Nabel G, Baltimore D. An inducible transcription factor activates expression of human immunodeficiency virus in T cells. *Nature.* (1987) 326:711–3. doi: 10.1038/326711a0
54. Chen L-F, Greene WC. Shaping the nuclear action of NF- κ B. *Nat Rev Mol Cell Biol.* (2004) 5:392–401. doi: 10.1038/nrm1368
55. Chan JK, Greene WC. Dynamic roles for NF- κ B in HTLV-I and HIV-1 retroviral pathogenesis. *Immunol Rev.* (2012) 246:286–310. doi: 10.1111/j.1600-065X.2012.01094.x
56. Bruder JT, Heidecker G, Tan TH, Weske JC, Derse D, Rapp UR, et al. Oncogene activation of HIV-LTR-driven expression via the NF- κ B binding sites. *Nucleic Acids Res.* (1993) 21:5229–34. doi: 10.1093/nar/21.22.5229
57. Gnanakandan S, Srikanth P. Nuclear factor kappa B p65: A possible biomarker for persistent inflammation in HIV-1 infection? *Cureus.* (2024) 16:e71308. doi: 10.7759/cureus.71308
58. Zhang J, Hu MM, Wang YY, Shu HB. Trim32 protein modulates type I interferon induction and cellular antiviral response by targeting MITA/STING protein for K63-linked ubiquitination. *J Biol Chem.* (2012) 287:28646–55. doi: 10.1074/jbc.m112.362608
59. Ruelas DS, Chan JK, Oh E, Heidersbach AJ, Hebbeler AM, Chavez L, et al. MicroRNA-155 reinforces HIV latency. *J Biol Chem.* (2015) 290:13736–48. doi: 10.1074/jbc.m115.641837
60. Cai J, Chen HY, Peng SJ, Meng JL, Wang Y, Zhou Y, et al. USP7-TRIM27 axis negatively modulates antiviral type I IFN signaling. *FASEB J.* (2018) 32:5238–49. doi: 10.1096/fj.201700473rr
61. Ivashkiv LB, Donlin LT. Regulation of type I interferon responses. *Nat Rev Immunol.* (2014) 14:36–49. doi: 10.1038/nri3581
62. Briscoe J, Guschin D, Rogers NC, Watling D, Müller M, Horn F, et al. JAKs, STATs and signal transduction in response to the interferons and other cytokines. *Philos Trans R Soc London Ser B Biol Sci.* (1996) 351:167–71. doi: 10.1098/rstb.1996.0013
63. Versteeg GA, Rajsbaum R, Sánchez-Aparicio MT, Maestre AM, Valdiviezo J, Shi M, et al. The E3-ligase TRIM family of proteins regulates signaling pathways triggered by innate immune pattern-recognition receptors. *Immunity.* (2013) 38:384–98. doi: 10.1016/j.immuni.2012.11.013
64. Kawai T, Akira S. Toll-like receptor and RIG-1-like receptor signaling. *Ann N Y Acad Sci.* (2008) 1143:1–20. doi: 10.1196/annals.1443.020
65. Jefferies C, Wynne C, Higgs R. Antiviral TRIMs: Friend or foe in autoimmune and autoinflammatory disease? *Nat Rev Immunol.* (2011) 11:617–25. doi: 10.1038/nri3043
66. Qu J, Liu GH, Wu K, Han P, Wang P, Li J, et al. IRF1 promotes the innate immune response to viral infection by enhancing the activation of IRF3. *J Virol.* (2020) 94:10.1128/jvi.01231–20. doi: 10.1128/jvi.01231-20
67. Darnell JE, Kerr LM, Stark GR. Jak-STAT pathways and transcriptional activation in response to IFNs and other extracellular signaling proteins. *Science.* (1994) 264:1415–21. doi: 10.1126/science.8197455
68. Stark GR, Darnell JE. The JAK-STAT pathway at twenty. *Immunity.* (2012) 36:503–14. doi: 10.1016/j.immuni.2012.03.013
69. Rajsbaum R, García-Sastre A, Versteeg GA. Trimmunity: The roles of the TRIM E3-ubiquitin ligase family in innate antiviral immunity. *J Mol Biol.* (2014) 426:1265–84. doi: 10.1016/j.jmb.2013.12.005
70. Toniato E, Chen XP, Losman J, Flati V, Donahue L, Rothman P, et al. TRIM8/GERP RING finger protein interacts with SOCS-1. *J Biol Chem.* (2002) 277:37315–22. doi: 10.1074/jbc.m205900200
71. Durham GA, Williams JLL, Nasim MT, Palmer TM. Targeting SOCS proteins to control JAK-STAT signalling in disease. *Trends Pharmacol Sci.* (2019) 40:298–308. doi: 10.1016/j.tips.2019.03.001
72. Cooney RN. Suppressors of cytokine signaling (SOCS): Inhibitors of the JAK/STAT pathway. *Shock.* (2002) 17:83–90. doi: 10.1097/00024382-200202000-00001
73. Yoshikawa H, Matsubara K, Qian GS, Jackson P, Groopman JD, Manning JE, et al. SOCS-1, a negative regulator of the JAK/STAT pathway, is silenced by methylation in human hepatocellular carcinoma and shows growth-suppression activity. *Nat Genet.* (2001) 28:29–35. doi: 10.1038/ng0501-29
74. Rajsbaum R, Versteeg GA, Schmid S, Maestre AM, Belicha-Villanueva A, Martínez-Romero C, et al. Unanchored K48-linked polyubiquitin synthesized by the E3-ubiquitin ligase TRIM6 stimulates the interferon-IKK ϵ kinase-mediated antiviral response. *Immunity.* (2014) 40:880–95. doi: 10.1016/j.immuni.2014.04.018
75. Tolomeo M, Cascio A. The STAT signaling pathway in HIV-1 infection: Roles and dysregulation. *Int J Mol Sci.* (2025) 26(7):3184. doi: 10.3390/ijms26189123
76. Yoneyama M, Kikuchi M, Natsukawa T, Shinobu N, Imaizumi T, Miyagishi M, et al. The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. *Nat Immunol.* (2004) 5:730–7. doi: 10.1038/ni1087
77. Seth RB, Sun L, Ea CK, Chen ZJ. Identification and characterization of MAVS, a mitochondrial antiviral signaling protein that activates NF- κ B and IRF3. *Cell.* (2005) 122:669–82. doi: 10.1016/j.cell.2005.08.012
78. Lang X, Tang T, Jin T, Ding C, Zhou R, Jiang W, et al. TRIM65-catalyzed ubiquitination is essential for MDA5-mediated antiviral innate immunity. *J Exp Med.* (2017) 214:459–73. doi: 10.1084/jem.20160592
79. Okamoto M, Kouwaki T, Fukushima Y, Oshiumi H. Regulation of RIG-I activation by K63-linked polyubiquitination. *Front Immunol.* (2018) 8:1942. doi: 10.3389/fimmu.2017.01942
80. Yang E, Huang S, Jami-Alahmadi Y, McInerney GM. Elucidation of TRIM25 ubiquitination targets involved in diverse cellular and antiviral processes. *PLoS Pathog.* (2022) 18:e1010743. doi: 10.1371/journal.ppat.1010743
81. Jin CX, Feng TZ, Ji X, Liu YS, Qin HN, Teng YB, et al. E3 ligase TRIM22 promotes melanoma proliferation by regulating cell cycle progression through K63-linked ubiquitination of p21. *Sci Rep.* (2025) 15:22311. doi: 10.1038/s41598-025-06348-4
82. Castanier C, Zemirli N, Portier A, Garcin D, Bidère N, Vazquez A, et al. MAVS ubiquitination by the E3 ligase TRIM25 and degradation by the proteasome is involved in type I interferon production after activation of the antiviral RIG-I-like receptors. *BMC Biol.* (2012) 10:44. doi: 10.1186/1741-7007-10-44

83. Yang B, Wang J, Wang Y, Zhou H, Wu X, Tian Z, et al. Novel function of Trim44 promotes an antiviral response by stabilizing VISA. *J Immunol.* (2013) 190:3613–9. doi: 10.4049/jimmunol.1202507
84. Urano T, Usui T, Takeda S, Ikeda K, Okada A, Ishida Y, et al. TRIM44 interacts with and stabilizes terf, a TRIM ubiquitin E3 ligase. *Biochem Biophys Res Commun.* (2009) 383:263–8. doi: 10.1016/j.bbrc.2009.04.010
85. Weng G-X, Ling T, Hou W, Li SN, Chen T, Zhang Z, et al. Mitochondrial DUT-M potentiates RLR-mediated antiviral signaling by enhancing VISA and TRAF2 association. *Mol Immunol.* (2021) 132:117–25. doi: 10.1016/j.molimm.2021.01.023
86. Yan J, Li Q, Mao AP, Hu MM, Shu HB. TRIM4 modulates type I interferon induction and cellular antiviral response by targeting RIG-I for K63-linked ubiquitination. *J Mol Cell Biol.* (2014) 6:154–63. doi: 10.1093/jmcb/mju005
87. Sun X, Xian H, Tian S, Sun T, Qin Y, Zhang S, et al. A hierarchical mechanism of RIG-I ubiquitination provides sensitivity, robustness and synergy in antiviral immune responses. *Sci Rep.* (2016) 6:29263. doi: 10.1038/srep29263
88. Honda K, Taniguchi T. IRFs: Master regulators of signalling by Toll-like receptors and cytosolic pattern-recognition receptors. *Nat Rev Immunol.* (2006) 6:644–58. doi: 10.1038/nri1900
89. Krischuns T, Günl F, Henschel L, Binder M, Willemsen J, Schloer S, et al. Phosphorylation of TRIM28 enhances the expression of IFN- β and proinflammatory cytokines during HPAIV infection of human lung epithelial cells. *Front Immunol.* (2018) 9:2229. doi: 10.3389/fimmu.2018.02229
90. Yang C, Shu J, Miao Y, Liu X, Zheng T, Hou R, et al. TRIM25 negatively regulates IKK ϵ -mediated interferon signaling in black carp. *Fish Shellfish Immunol.* (2023) 142:109095. doi: 10.1016/j.fsi.2023.109095
91. Peng Z, Zhang C, Yin B, He Y, Li W, Wang J, et al. TRIM21 of *Micropterus salmoides* exerts antiviral roles against largemouth bass ulcer syndrome virus. *Fish Shellfish Immunol.* (2023) 142:109176. doi: 10.1016/j.fsi.2023.109176
92. Cui J, Chen Y, Wang HY, Wang RF. Mechanisms and pathways of innate immune activation and regulation in health and cancer. *Hum Vaccines Immunotherapeutics.* (2014) 10:3270–85. doi: 10.4161/21645515.2014.979640
93. Ghimire D, Rai M, Gaur R. Novel host restriction factors implicated in HIV-1 replication. *J Gen Virol.* (2018) 99:435–46. doi: 10.1099/jgv.0.001026
94. Lukic Z, Goff SP, Campbell EM, Arriagada G. Role of SUMO-1 and SUMO interacting motifs in rhesus TRIM5 α -mediated restriction. *Retrovirology.* (2013) 10:10. doi: 10.1186/1742-4690-10-10
95. Cloherty APM, Rader AG, Compeer B, Ribeiro CMS. Human TRIM5 α : Autophagy connects cell-intrinsic HIV-1 restriction and innate immune sensor functioning. *Viruses.* (2021) 13(2):320. doi: 10.3390/v13020320
96. Dutriex J, Portillo DM, Arhel NJ, Hazan U, Nisole S. TRIM5 α is a SUMO substrate. *Retrovirology.* (2015) 12:28. doi: 10.1186/s12977-015-0155-7
97. Stremlau M, Owens CM, Perron MJ, Kiessling M, Autissier P, Sodroski J, et al. The cytoplasmic body component TRIM5 α restricts HIV-1 infection in Old World monkeys. *Nature.* (2004) 427:848–53. doi: 10.1038/nature02343
98. Pertel T, Hausmann S, Morger D, Züger S, Guerra J, Lascano J, et al. TRIM5 is an innate immune sensor for the retrovirus capsid lattice. *Nature.* (2011) 472:361–5. doi: 10.1038/nature09976
99. Maarifi G, Fernandez J, Portillo DM, Boulay A, Dutriex J, Oddo S, et al. RanBP2 regulates the anti-retroviral activity of TRIM5 α by SUMOylation at a predicted phosphorylated SUMOylation motif. *Commun Biol.* (2018) 1:193. doi: 10.1038/s42003-018-0198-0
100. Lilienbaum A. Relationship between the proteasomal system and autophagy. *Int J Biochem Mol Biol.* (2013) 4:1.
101. Ganser-Pornillos BK, Pornillos O. Restriction of HIV-1 and other retroviruses by TRIM5. *Nat Rev Microbiol.* (2019) 17:546–56. doi: 10.1038/s41579-019-0225-2
102. Imam S, Kömürlü S, Mattick J, Selyutina A, Talley S, Eddins A, et al. K63-linked ubiquitin is required for restriction of HIV-1 reverse transcription and capsid destabilization by rhesus TRIM5 α . *J Virol.* (2019) 93(20):e00558–19. doi: 10.1128/jvi.00558-19
103. Li X, Yeung DF, Fiegen AM, Sodroski J. Determinants of the higher order association of the restriction factor TRIM5 α and other tripartite motif (TRIM) proteins. *J Biol Chem.* (2011) 286:27959–70. doi: 10.1074/jbc.m111.260406
104. Javanbakht H, Yuan W, Yeung DF, Song B, Diaz-Griffero F, Li Y, et al. Characterization of TRIM5 α trimerization and its contribution to human immunodeficiency virus capsid binding. *Virology.* (2006) 353:234–46. doi: 10.1016/j.virology.2006.05.017
105. Jimenez-Moyano E, Ruiz A, Kløverpris HN, Rodriguez-Plata MT, Peña R, Blondeau C, et al. Nonhuman TRIM5 variants enhance recognition of HIV-1-infected cells by CD8+ T cells. *J Virol.* (2016) 90:8552–62. doi: 10.1128/jvi.00819-16
106. Twentyman J, Khalifeh A, Felton AL, Emerman M, Ohainle M. Primate TRIM34 is a broadly-acting, TRIM5-dependent lentiviral restriction factor. *Retrovirology.* (2023) 20:15. doi: 10.1186/s12977-023-00629-4
107. Ohkura S, Yap MW, Sheldon T, Stoye JP. All three variable regions of the TRIM5 α B30. 2 domain can contribute to the specificity of retrovirus restriction. *J Virol.* (2006) 80:8554–65. doi: 10.1128/jvi.00688-06
108. Pham Q, Bouchard A, Grütter MG, Berthoux L. Generation of human TRIM5 α mutants with high HIV-1 restriction activity. *Gene Ther.* (2010) 17:859–71. doi: 10.1038/gt.2010.40
109. Richardson MW, Guo L, Xin F, Yang X, Riley JL. Stabilized human TRIM5 α protects human T cells from HIV-1 infection. *Mol Ther.* (2014) 22:1084–95. doi: 10.1093/oso/9780190098230.003.0005
110. Ribeiro CM, Sarrami-Forooshani R, Setiawan LC, Zijlstra-Willems EM, van Hamme JL, Tigchelaar W, et al. Receptor usage dictates HIV-1 restriction by human TRIM5 α in dendritic cell subsets. *Nature.* (2016) 540:448–52. doi: 10.1038/nature20567
111. Ivanov AV, Peng H, Yurchenko V, Yap KL, Negorev DG, Schultz DC, et al. PHD domain-mediated E3 ligase activity directs intramolecular sumoylation of an adjacent bromodomain required for gene silencing. *Mol Cell.* (2007) 28:823–37. doi: 10.1016/j.molcel.2007.11.012
112. Xin R, Garigliany MM, Li J. KAP1 in antiviral immunity: dual roles in viral silencing and immune regulation. *Front Cell Infect Microbiol.* (2025) 15:1618103. doi: 10.3389/fcimb.2025.1618103
113. Parker KA. Determining the mechanisms in which lncRNA BORG drives cellular plasticity in breast cancer metastasis. In: *Case Western Reserve University.* Cleveland, OH: Case Western Reserve University (2024).
114. Schultz DC, Ayyanathan K, Negorev D, Maul GG, Rauscher FJ. SETDB1: a novel KAP-1-associated histone H3, lysine 9-specific methyltransferase that contributes to HP1-mediated silencing of euchromatic genes by KRAB zinc-finger proteins. *Genes Dev.* (2002) 16:919–32. doi: 10.1101/gad.973302
115. Sripathy SP, Stevens J, Schultz DC. The KAP1 corepressor functions to coordinate the assembly of de novo HP1-demarcated microenvironments of heterochromatin required for KRAB zinc finger protein-mediated transcriptional repression. *Mol Cell Biol.* (2006) 26:8623–38. doi: 10.1128/mcb.00487-06
116. Maison C, Almouzni G. HP1 and the dynamics of heterochromatin maintenance. *Nat Rev Mol Cell Biol.* (2004) 5:296–305. doi: 10.1038/nrm1355
117. Ma X, Yang T, Luo Y, Wu L, Jiang Y, Song Z, et al. TRIM28 promotes HIV-1 latency by SUMOylating CDK9 and inhibiting P-TEFb. *Elife.* (2019) 8:e42426. doi: 10.7554/elifesciences.42426
118. Imbert F, Langford D. Comprehensive SUMO proteomic analyses identify HIV latency-associated proteins in microglia. *Cells.* (2025) 14:235. doi: 10.3390/cells14030235
119. Yuan J, Wang H, Sun X, Huan C. The emerging roles of ubiquitin-like modifications in regulating HIV replication and host defense. *Front Cell Infect Microbiol.* (2025) 15:1593445. doi: 10.3389/fcimb.2025.1593445
120. Chen Y-Y, Ran XH, Ni RZ, Mu D. TRIM28 negatively regulates the RLR signaling pathway by targeting MAVS for degradation via K48-linked polyubiquitination. *J Biol Chem.* (2023) 299(5):104660. doi: 10.1016/j.jbc.2023.104660
121. Song Y, Nguyen XN, Kumar A, da Silva C, Picard L, Etienne L, et al. Trim69 is a microtubule regulator that acts as a pantropic viral inhibitor. *Proc Natl Acad Sci USA.* (2022) 119:e2211467119. doi: 10.1073/pnas.2211467119
122. Marini B, Giacca M, Lusica M. 126 PML nuclear bodies determine the repressive environment and restrict viral gene expression in primary human lymphocytes. *JAIDS J Acquired Immune Deficiency Syndromes.* (2011) 56:51. doi: 10.1097/01.qai.0000397314.01966.b8
123. Geoffroy M-C, Chelbi-Alix MK. Role of promyelocytic leukemia protein in host antiviral defense. *J Interferon Cytokine Res.* (2011) 31:145–58. doi: 10.1089/jir.2010.0111
124. Masroori N, Merindol N, Berthoux L. The interferon-induced antiviral protein PML (TRIM19) promotes the restriction and transcriptional silencing of lentiviruses in a context-specific, isoform-specific fashion. *Retrovirology.* (2016) 13:19. doi: 10.1186/s12977-016-0253-1
125. Tabah AA, Tardif K, Mansky LM. Anti-HIV-1 activity of trim 37. *J Gen Virol.* (2014) 95:960–7. doi: 10.1099/vir.0.057653-0
126. Turrini F, Marelli S, Kajaste-Rudnitski A, Lusica M, Van Lint C, Das AT, et al. HIV-1 transcriptional silencing caused by TRIM22 inhibition of Sp1 binding to the viral promoter. *Retrovirology.* (2015) 12:104. doi: 10.1186/s12977-015-0230-0
127. Yuan T, Yao W, Tokunaga K, Yang R, Sun B. An HIV-1 capsid binding protein TRIM11 accelerates viral uncoating. *Retrovirology.* (2016) 13:72. doi: 10.1186/s12977-016-0306-5
128. Saylor D, Dickens AM, Sacktor N, Haughey N, Slusher B, Pletnikov M, et al. HIV-associated neurocognitive disorder—pathogenesis and prospects for treatment. *Nat Rev Neurol.* (2016) 12:234–48. doi: 10.1038/nrneuro.2016.27
129. Imbert F, Leavitt G, Langford D. SUMOylation and viral infections of the brain. *Pathogens.* (2022) 11:818. doi: 10.3390/pathogens11070818
130. Imbert FE. Productive and latent HIV infection of the central nervous system: Virus and host wrestle for control of the SUMOylation system. In: *Temple University.* Philadelphia, PA: Temple University (2025).

131. Everett RD, Chelbi-Alix MK. PML and PML nuclear bodies: implications in antiviral defence. *Biochimie*. (2007) 89:819–30. doi: 10.1016/j.biochi.2007.01.004
132. Hatakeyama S. TRIM proteins and cancer. *Nat Rev Cancer*. (2011) 11:792–804. doi: 10.1038/nrc3139
133. Muller PA, Vousden KH. Mutant p53 in cancer: new functions and therapeutic opportunities. *Cancer Cell*. (2014) 25:304–17. doi: 10.1016/j.ccr.2014.01.021
134. Chen L, Brewer MD, Guo L, Wang R, Jiang P, Yang X, et al. Enhanced degradation of misfolded proteins promotes tumorigenesis. *Cell Rep*. (2017) 18:3143–54. doi: 10.1016/j.celrep.2017.03.010
135. Liu W, Zhao Y, Wang G, Feng S, Ge X, Ye W, et al. TRIM22 inhibits osteosarcoma progression through destabilizing NRF2 and thus activation of ROS/AMPK/mTOR/autophagy signaling. *Redox Biol*. (2022) 53:102344. doi: 10.1016/j.redox.2022.102344
136. Dongre A, Weinberg RA. New insights into the mechanisms of epithelial–mesenchymal transition and implications for cancer. *Nat Rev Mol Cell Biol*. (2019) 20:69–84. doi: 10.1038/s41580-018-0080-4
137. Zhou C, Zhang Z, Zhu X, Qian G, Zhou Y, Sun Y, et al. N6-methyladenosine modification of the TRIM7 positively regulates tumorigenesis and chemoresistance in osteosarcoma through ubiquitination of BRMS1. *EBioMedicine*. (2020) 59:102955. doi: 10.2139/ssrn.3562445
138. Zhang Y, Du H, Li Y, Yuan Y, Chen B, Sun S, et al. Elevated TRIM23 expression predicts cisplatin resistance in lung adenocarcinoma. *Cancer Sci*. (2020) 111:637–46. doi: 10.1111/cas.14226
139. Di Rienzo M, Zuchegna C, Perri V, Piacentini M, Falasca L, Romagnoli A, et al. The role of TRIM proteins in the pathogenesis of mycobacterium tuberculosis. *Biol Direct*. (2025) 21(1):1. doi: 10.1186/s13062-025-00707-x
140. Full F, van Gent M, Sparrer KMJ, Chiang C, Zurenski MA, Scherer M, et al. Centrosomal protein TRIM43 restricts herpesvirus infection by regulating nuclear lamina integrity. *Nat Microbiol*. (2019) 4:164–76. doi: 10.1038/s41564-018-0285-5
141. Zhao G, Li Y, Chen T, Liu F, Zheng Y, Liu B, et al. TRIM26 alleviates fatal immunopathology by regulating inflammatory neutrophil infiltration during *Candida* infection. *PLoS Pathog*. (2024) 20:e1011902. doi: 10.1371/journal.ppat.1011902
142. Schilling E-M, Scherer M, Reuter N, Schweininger J, Muller YA, Stamminger T, et al. The human cytomegalovirus IE1 protein antagonizes PML nuclear body-mediated intrinsic immunity via the inhibition of PML de novo SUMOylation. *J Virol*. (2017) 91(16):e02049–16. doi: 10.1128/jvi.02049-16
143. Xing J, Zhang A, Zhang H, Wang J, Li XC, Zeng MS, et al. TRIM29 promotes DNA virus infections by inhibiting innate immune response. *Nat Commun*. (2017) 8:945. doi: 10.1038/s41467-017-00101-w
144. Song Y, Wu X, Xu Y, Zhu J, Li J, Zou Z, et al. HPV E7 inhibits cell pyroptosis by promoting TRIM21-mediated degradation and ubiquitination of the IFI16 inflammasome. *Int J Biol Sci*. (2020) 16:2924. doi: 10.7150/ijbs.50074
145. Hage A, Janes M, Best SM. A no-brainer! The therapeutic potential of TRIM proteins in viral and central nervous system diseases. *Viruses*. (2025) 17:562. doi: 10.3390/v17040562
146. Luís MA, Goes MAD, Santos FM, Mesquita J, Tavares-Ratado P, Tomaz CT, et al. Plasmid gene therapy for monogenic disorders: challenges and perspectives. *Pharmaceutics*. (2025) 17:104. doi: 10.3390/pharmaceutics17010104
147. Chan E, Towers GJ, Qasim W. Gene therapy strategies to exploit TRIM derived restriction factors against HIV-1. *Viruses*. (2014) 6:243–63. doi: 10.3390/v6010243
148. Brown R, Deeks SG, Eyal N. *Maximising the global health impact of future HIV cure-related interventions through advance planning*. Amsterdam: Elsevier (2018) p. 182–5. doi: 10.1016/s2055-6640(20)30266-1
149. Wo L, Qi S, Guo Y, Sun C, Yin X. TRIM5 α /Cyclophilin A-modified MDBK cells for lentiviral-based gene editing. *Viruses*. (2025) 17:876. doi: 10.3390/v17070876
150. Glazkova D, Urusov FA, Bogoslovskaya EV, Shipulin GA. Retrovirus restriction factor TRIM5 α : The mechanism of action and prospects for use in gene therapy of HIV infection. *Mol Biol*. (2020) 54:623–32. doi: 10.1134/s0026893320050039
151. Kasturi SP, Kozlowski PA, Nakaya HI, Burger MC, Russo P, Pham M, et al. Adjuvanting a simian immunodeficiency virus vaccine with toll-like receptor ligands encapsulated in nanoparticles induces persistent antibody responses and enhanced protection in TRIM5 α restrictive macaques. *J Virol*. (2017) 91(12):e01844–16. doi: 10.1128/jvi.01844-16
152. Ohainle M, Kim K, Komurlu Keceli S, Felton A, Campbell E, Luban J, et al. TRIM34 restricts HIV-1 and SIV capsids in a TRIM5 α -dependent manner. *PLoS Pathog*. (2020) 16:e1008507. doi: 10.1371/journal.ppat.1008507
153. Hoenigsperger H, Koepke L, Acharya D, Hunszinger V, Freisem D, Grenzner A, et al. CSNK2 suppresses autophagy by activating FLN-NHL-containing TRIM proteins. *Autophagy*. (2024) 20:994–1014. doi: 10.1080/15548627.2023.2281128
154. Xu W, Chen B, Ke D, Chen X. TRIM29 mediates lung squamous cell carcinoma cell metastasis by regulating autophagic degradation of E-cadherin. *Aging (Albany NY)*. (2020) 12:13488. doi: 10.18632/aging.103451
155. Mao Q, Li L, Wen H. Beyond monotherapy: Combination therapies for HIV-1 cure through joint application of neutralizing antibodies, genome editing, and reservoir management. *Infect Med*. (2025) 4(4):100215. doi: 10.1016/j.imj.2025.100215
156. Kulohoma BW, Wesonga CA. HIV response financing challenges in Sub-Saharan Africa: barriers to achieving the 95–95–95 UNAIDS targets. *Front Public Health*. (2025) 13:1658229. doi: 10.3389/fpubh.2025.1658229

Glossary

ADVANCED HIV INFECTION	Acquired Immunodeficiency Syndrome	NEMO	NF- κ B Essential Modulator (IKK γ)
ARC	AIDS-Related Complex	NNRTIs	NHL repeats (named after Ncl-1, HT2A, and Lin-41)
ARF	ADP-Ribosylation Factor	NRTIs	Non-Nucleoside Reverse Transcriptase Inhibitors
ASF1	Anti-Silencing Function 1	OAS	Nucleoside Reverse Transcriptase Inhibitors
CARD	Caspase Activation and Recruitment Domain	PDLIM2	Oligoadenylate Synthetase
COS	C-terminal Subgroup One Signature	PHD	PDZ and LIM Domain Protein 2
CRISPR-Cas9	Clustered Regularly Interspaced Short Palindromic Repeats - CRISPRAssociated Protein 9	PML	Plant Homeodomain
ECSIT	Evolutionarily Conserved Signaling Intermediate in Toll pathways	PRY/SPRY	Promyelocytic Leukemia Protein
FN3	Fibronectin Type III	RBCC	Domain found in TRIM proteins (also known as B30.2)
HAND	HIV-Associated Neurocognitive Disorders	RIG-I	RING-B-box-Coiled-Coil
HIF-1 α	Hypoxia-Inducible Factor 1 Alpha	RLR	Retinoic acid-Inducible Gene I
HIV	Human Immunodeficiency Virus	siRNA	RIG-I-like Receptor
HSCs	Hematopoietic Stem Cells	SIV	Small Interfering RNA
HSV	Herpes Simplex Virus	SOCS1	Simian Immunodeficiency Virus
IFN(s)	Interferon(s)	STAT	Suppressor of Cytokine Signaling 1
IFN-I/IFN- β	Type I Interferon/Interferon Beta	TBK1	Signal Transducer and Activator of Transcription
IKK	I κ B Kinase	TCR	TANK-Binding Kinase 1
IRF	Interferon Regulatory Factor	TLR	T Cell Receptor
ISGs	Interferon-Stimulated Genes	TNF- α	Toll-Like Receptor
ISREs	Interferon-Stimulated Response Elements	TM	Tumor Necrosis Factor Alpha
JAK	Janus Kinase	TRAF	Transmembrane Region
KAP1	KRAB-associated Protein 1 (synonym for TRIM28)	TRIM	TNF Receptor-Associated Factor
LNPs	Lipid Nanoparticles	Ub	Tripartite Motif
MAVS	Mitochondrial Antiviral-Signaling Protein (also known as VISA)	UbE2K	Ubiquitin
MATH	Meprip and TRAF Homology	UPS	Ubiquitin-Conjugating Enzyme E2 K
MDA5	Melanoma Differentiation-Associated protein 5	VISA	Ubiquitin-Proteasome System
		ZF-UBP	Virus-Induced Signaling Adaptor (synonym for MAVS)
			Zinc-Finger Ubiquitin Protease domain.