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REVIEW

The innate immune roles of host factors TRIM5α and Cyclophilin A on HIV-1 replication

Yi-Qun Kuang[1,2] · Hong-Liang Liu[3] · Yong-Tang Zheng[4]

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Abstract During the long-term evolutionary history, the interaction between virus and host has driven the first-line barrier, innate immunity, to invading pathogens. Innate immune factor TRIM5α and host peptidyl-prolyl *cis–trans* isomerase Cyclophilin A are two key players in the interaction between HIV-1 and host. Interestingly, Cyclophilin A is retrotransposed into the critical host gene, *TRIM5*, locus via LINE-1 element in some primate species including New World monkeys and Old World monkeys. This review aims to comprehensively discuss the sensing and immune activation procedures of TRIM5α innate signaling pathway through Cyclophilin A. It will then present the production of TRIMCyp chimeric gene and the different fusion patterns in primates. Finally, it will summarize the distinct restriction activity of TRIMCyp from different primates and explain the current understanding on the innate immune mechanisms involved in the early phase of the viral life cycle during HIV-1 replication.

Keywords TRIM5α · Cyclophilin A · HIV-1 · Innate immune

Yi-Qun Kuang and Hong-Liang Liu have contributed equally to this work.

✉ Yong-Tang Zheng
zhengyt@mail.kiz.ac.cn

[1] Center for Translational Medicine, Huaihe Clinical Institute, Henan University, Kaifeng 475004, Henan, People's Republic of China

[2] Guangdong Institute of Public Health, Guangdong Center for Disease Control and Prevention, Guangzhou 510433, Guangdong, People's Republic of China

[3] Pharmaceutical College, Henan University, Kaifeng 475000, Henan, People's Republic of China

[4] Key Laboratory of Animal Models and Human Diseases Mechanisms of the Chinese Academy of Sciences & Yunnan Province, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming 650223, Yunnan, People's Republic of China

Introduction

Over the long evolutionary history, interaction between host and invading retroviruses has driven the development of some intrinsic barriers to pathogens. Retroviruses rely on host factors for many aspects of their replication cycle, including viral entry, uncoating, reverse transcription, nuclear import, proviral transcription, viral assembly and budding. Despite its limited genomic capacity, human immunodeficiency virus type 1 (HIV-1) hijacks host proteins to complete its replication life cycle. On the other hand, the host has evolved restriction factors, including APOBEC3G/F (apolipoprotein B mRNA-editing, enzyme-catalytic, polypeptide-like 3G/F) [1, 2], TRIM5α (tripartite motif protein 5α) [3], tetherin/BST-2/CD317 [4, 5], SAMHD1 (SAM domain and HD domain-containing protein 1) [6, 7] and Mx2 (myxovirus resistance 2) [8, 9] to counteract HIV-1 in different susceptible cells. These HIV-1 restriction factors are also called innate immune factors, which are stimulated by type I interferon (IFN). Moreover, the transcription level of certain IFN-interacting cytokine like IL32 has significant positive correlation with restriction factors such as Mx1 and APOBEC3G/F in untreated chronically HIV-1-infected patients [10]. In 1993, the host Cyclophilin A (CypA) was identified as an interacting protein that binds to the structure protein capsid (CA) of HIV-1 [11] and serves as a very important host factor during the HIV-1 infection and replication processes.

In 2004, TRIM5α, the longest splicing isoform of *TRIM5* gene, was identified as a key host restriction factor that inhibits the replication of a variety of retroviruses including HIV-1 in primate cells [3]. The host CypA is involved in modulating the restriction activity of TRIM5α, although it is not indispensable [12, 13]. Further work by others and us demonstrated that during the long-term host–virus interaction history, *TRIM5* and *CypA* genes formed fusion genes in diverse patterns in a number of New World and Old World primates [14–20]. The chimeric protein products of the *TRIM5–CypA* (TRIMCyp) fusion genes mediate the restriction to retroviruses replication involving a similar mechanism of TRIM5α in primates.

Retroviruses, including HIV, can activate innate immune responses, but the host sensors for retroviruses are largely unknown. Recently, it has been shown that dendritic cells (DCs) activation required CypA interaction with newly synthesized HIV-1 CA protein during HIV-1 infection [21]. Upon recognition of CA, CypA acts as a cytosolic receptor that activates DCs, stimulates type I IFN production and induces HIV-1-specific $CD4^+$ and $CD8^+$ T cells [21]. Also, CypA activates nuclear factor-kappa B (NF-κB) signaling and downstream gene expression via interaction with p65/RelA [22]. Intriguingly, TRIM5α has emerged as a pattern recognition receptor (PRR) that recognizes HIV-1 CA, activates NF-κB and AP-1 (activator protein-1) and enhances the transcription of IFN-β via IRF3. Moreover, they show that TRIM5α is also involved in LPS-induced Toll-like receptor 4 (TLR-4) signaling pathway [23]. The TRIM5α and CypA (in TRIMCyp) are deemed to act as cytosolic sensors to recognize CA lattice and activate antiviral innate immune responses to combat HIV-1 infection [24]. In addition to the TRIM5α and CypA, the cyclic guanosine monophosphate–adenosine monophosphate (cGAMP) synthase (cGAS) was also identified as an innate immune sensor of HIV and other retroviruses [25].

Here, we will review the effects of CypA on HIV-1 replication and its contribution to the identification of TRIM5α and then explain how CypA modulates the recognition of HIV-1 CA, thus mediating the sensing by the innate immune pathway and restriction activity of TRIM5α. In addition, the review will present the most recent findings about the role of *TRIM5–CypA* fusion gene in primates and the mechanisms involved in the replication of HIV-1 in host cells.

CypA–CA interaction and the identification of TRIM5α

Increasing evidence has shown that host CypA is a pivotal modulator in HIV-1 replication and TRIM5α restriction activity. In 1993, CypA and CypB were discovered to interact with the HIV-1 structure precursor protein Gag by a yeast two-hybrid screening. Cyclosporin A (CsA), an immunosuppressant drug binds to CypA, efficiently disrupts the CypA–Gag interaction and, less efficiently, disrupts the CypB–Gag interaction [11]. Shortly after, two groups demonstrated that the Cyclophilin–Gag interaction is mediated by the CA unit of Gag protein [26, 27]. CypA from virion-producing cells is efficiently incorporated into the virions; the CypA–CA interaction is important for the HIV-1 life cycle and may be relevant to the pathology caused by this immunosuppressive virus [26, 27]. Although the CypA–CA interaction is important for the formation of infectious HIV-1 virions [26], it is not essential. It appears that the interaction is involved in the dynamic procedures of HIV-1 infection and mediating CA recognition by host restriction factors. It is known that CypA is incorporated into HIV-1 virions and locates inside the viral membrane with a CypA/CA ratio of about 1:10 [26–28]. Further gene-targeting assays of the host CypA in human cells formally demonstrated that CypA regulates the infectivity of HIV-1 virion via interactions with CA [29].

It has been long shown that the HIV-1 Gag precursor protein encodes determinants of species-specific lentiviral infection, related in part to host restriction factors. Interaction between CA and host CypA protects HIV-1 from restriction in human cells, but is essential for maximal restriction in simian cells. However, CypA antagonist CsA displays differential roles on simian immunodeficiency virus (SIV) replication in human and macaque T cells. In human T cells, CsA treatment enhanced SIV replication but abrogated SIV replication in macaque T cells. Concomitantly, further analyses indicated that CypA promotes SIV infection into macaque but not into human T cells. These results suggest a host cell species-specific effect of CsA on SIV replication, and the CypA appears to contribute to the determination of SIV tropism [30]. Actually, sequence variation between HIV-1 isolates leads to variation in sensitivity to restriction factors in human and simian cells. The sensitivity to restriction is controlled by some mutations like H87Q in the CypA-binding loop of CA [31]. As a matter of fact, it was known for a long time that the CA interaction with CypA is a determinant for the species-specific tropism of HIV-1 or SIV. The narrow host range of HIV-1 is due in part to dominant acting restriction factor 1 (Ref1) in humans and lentivirus susceptibility factor 1 (Lv1) in monkeys [31]. It later became clear that TRIM5α is the factor responsible for the previously described Lv1 and Ref1 antiretroviral activities [32–35]. The block to HIV-1 infection in nonhuman primate cells generally occurs at a postentry step, but prior to reverse transcription [36].

In 2004, TRIM5α was identified as the predominant host factor that restricts the replication of HIV-1 postentry in rhesus macaque cells [3]. A genetic screening of rhesus

macaque fibroblast cDNA library revealed that TRIM5α, a splicing isoform product of *TRIM5* gene, confers HIV-1 resistance to otherwise permissive human cells. TRIM5 belongs to the large tripartite motif family of proteins (over 70 family members in human genome) that is defined by the tandem presence of RING (really interesting gene) finger, B-box and coiled-coil (RBCC) domains [37]. Among four alternative splicing TRIM5 isoforms, TRIM5α is the longest one that possesses a PRY/SPRY (SPla and the RYanodine Receptor) domain at the C-terminus. Shortly after the identification of TRIM5α in rhesus macaque, a couple of research groups demonstrated that TRIM5α orthologous from other mammals inhibits the replication of a broad range of retroviruses [33–35, 38, 39].

TRIM5α activates innate immune response to HIV-1 via sensing of CA lattice

Restriction mechanisms of TRIM5α besides direct action on HIV-1

TRIM5α is a cytoplasmic protein in host cells; the exact mechanism of its restriction remains unknown. Early studies indicate that TRIM5α has a direct effect on HIV-1 infection by blocking viral replication soon after the virion enters the target cell cytosol [3, 12, 35, 40]. The process is possibly that TRIM5α accelerates the uncoating of the incoming viral core, thus resulting in the aberrant viral uncoating or the rapid degradation of the viral RNA which impedes HIV-1 reverse transcription [3, 40]. CypA has been proposed to prevent restriction factor binding in human cells, thus optimizing HIV-1 infectivity, while potentiating restriction of HIV-1 in monkey cells. Early studies have shown that the host CypA is involved and modulates TRIM5α restriction postentry [12, 13]. However, Sokolskaja et al. [41] showed that CypA and TRIM5α independently regulate HIV-1 infectivity in human cells. In accordance with this, it was reported that the CypA–CA interaction occurs early after viral entry, but the CypA-enhanced restriction mostly acts on the stage after reverse transcription [42]. Disruption of CypA–CA interaction partially relieved the block to HIV-1 infection, and the CypA–CA binding was not absolutely required for TRIM5α antiviral activity [43]. It has also been shown that if the block to reverse transcription is bypassed, HIV-1 replication steps after reverse transcription are also blocked by TRIM5α [44]. In addition to the action in the host cell cytoplasm, biochemical experiments also showed that TRIM5α is shuttled in and out the cell nucleus [45], which implies that more intricate mechanisms might be involved. More recently, work has revealed versatile roles of TRIM5α on HIV-1 replication in host cells, which are not fully associated with viral restriction. TRIM5α affects various retroviral core components and indicates that proteasomes are required for TRIM5α-induced core disruption but not for TRIM5α-induced restriction of HIV-1 [46].

Despite the observations mentioned above, an increasing body of knowledge on TRIM members contributes to the finding of innate immune roles of TRIM5α. Among the TRIM family members, some other members such as TRIM1 and TRIM34 have also shown modest retroviral restriction activity [39, 47, 48]. In fact, the *TRIM5* locus has undergone expansions on more than one occasion in mammals. For example, there have been two independent paralogous expansions of *TRIM5* genes in cows and rodents [39, 47]. Cows have up to five *TRIM5* genes [39, 49], while rats have three and mice have up to eight [50]. Two of the mouse *TRIM5* genes were previously known as *TRIM12* and *TRIM30*. However, further phylogenetic analysis demonstrated that these two genes and their paralogs turn out to be the homologs of *TRIM5* gene [50]. Intriguingly, both mouse and primate (human and rhesus macaque) TRIM5α have been shown to negatively regulate TLR-mediated NF-κB activation by targeting TAB 2 (TAK1-binding protein 2) and TAB 3 (TAK1-binding protein 3) for degradation, though different effect levels were observed [51–53]. These observations suggested that TRIM5α might have additional roles in innate immunity besides direct recognition and degradation of retroviral CA [53].

TRIM5α activates innate immune to HIV-1 by acting as a PRR

More recently, studies have shown that, in addition to direct inhibition of the replication process of retroviruses, TRIM5α inhibits HIV-1 infection by acting as a PRR, which is inducing innate immune responses. The knockdown of TRIM5α in DCs prevents innate immune signaling downstream of LPS and other pathogen-associated molecular patterns [23]. TRIM5α, an E3 ubiquitin (Ub) ligase, exists as a dimer in the cytoplasm, and its restriction activity is very weak. TRIM5α multimerizes during HIV-1 invasion into the cytosol of the target cell, and its avidity for HIV-1 CA lattice increases accordingly [54]. Dissection of the mechanism by which TRIM5α activates innate immune signaling showed that HIV-1 CA binds to TRIM5α and activates its E3 Ub ligase activity, and then, TRIM5α recruits Ub-conjugating enzyme E2 heterodimer UBC13 (ubiquitin-conjugating enzyme 13)–UEV1A (ubiquitin-conjugating enzyme variant 1A) and other ubiquitination enzymes. This big ubiquitination enzyme complex catalyzes the synthesis of the Ub chains through the Lysine 63 (K63) residues of free Ub molecules (K63-linked Ub chains). After that complex formation, the Ub chain

promotes the phosphorylation of TAK1 (transforming growth factor β-activated kinase-1) of the protein kinase complex. The activated TAK1 triggers the transcription of AP-1 and NF-κB and thus up-regulating the expression of cytokines and chemokines, thus initiating host antiviral innate immune responses (Fig. 1) [23, 55, 56]. In addition, it is rational to speculate that the up-regulated expression of cytokines or chemokines within the cell might activate lysosome formation, and the secreted chemokines activate further cells such as neutrophils, macrophages and mast cells, as well as the complement cascade and the synthesis of acute-phase proteins, which all together compose the innate immune response. All these hypotheses call for much more experimental studies in the future work.

Pilot screening of TRIM proteins that are able to activate innate immune signaling pathways identified 16 TRIM proteins that induced NF-κB and/or AP-1 [57]. A recent systemic study of 75 human TRIM members suggests that about half of TRIM proteins possess the potential to enhance innate immune response [58]. Although the E3 Ub ligase activity mediated by the RING domain of TRIM5α is proved to be important for the innate signaling pathway activation [23, 59], two TRIM family members without RING domain, TRIM14 and TRIM66, have also demonstrated strong enhanced immune induction activity [58]. It appears that RING domain is not indispensable for innate immune activation, which calls for more investigations in the future.

Small ubiquitin-like modifier (SUMO) proteins conjugation of viral proteins can be essential for viral replication. Recently, in the effort to further elucidate the relationship between SUMO conjugation and early events of the murine leukemia virus (MLV) replication, Arriagada et al. [60] identified that human TRIM5α contains three small ubiquitin-like modifier 1 (SUMO-1)-interacting motifs (SIMs) in the B30.2/SPRY domain, and the SIM-mutated TRIM5α was unable to block the N-tropic MLV (N-MLV). The restriction activity to HIV-1 is required by TRIM5α SIMs binding to the SUMO-conjugated CA [60]. Interestingly, the SIM-mutated rhesus TRIM5α also failed to restrict HIV-1 and translocate into the nucleus [61, 62]. However, there was no interaction between SIM and HIV-1 CA, and the interaction between B30.2/SPRY domain and the SUMO-1 was observed [61, 62]. Furthermore, the SUMO-1 knockdown attenuated the TRIM5α-activated NF-κB signaling [62], which suggests that the domains of TRIM5α are probably involved in the triggering of innate immune responses to incoming retroviruses except for the RING domain. Work by Nepveu-Traversy et al. [63] showed that the sumoylated lysine mutant (lysine to arginine, K10R) decreased the TRIM5α-induced generation of free K63-linked ubiquitin chains. Naturally, it decreases TRIM5α-mediated activation of both NF-κB and AP-1. The K10R mutant also generated numerous ubiquitylated TRIM5α proteins in the cells. Taken together, the RING domain, in synergy with the B30.2/SPRY domain, is involved in modulating the TRIM5α-induced innate immune response through the SUMO-1 pathways. This modulatory mechanism is associated with the nuclear shuttle of TRIM5α [61].

TRIM5–CypA and HIV-1 restriction

Formation of TRIM5–CypA and TRIMCyp's restriction activity to retroviruses

Members of the TRIM big family share a conserved tandem arrangement of three functional domains, an N-terminal RING domain, followed by one or two B-boxes and a coiled coil at the C-terminus, which constitutes the tripartite motif for which the family is named. However, the C-termini of TRIM proteins vary and include at least nine evolutionarily distinct, unrelated protein domains. Intriguing work in the Luban and Stoye laboratories showed that in Owl monkey (*Aotus trivirgatus*), a New World monkey species, *CypA* cDNA is retrotransposed into the *TRIM5* locus [14, 15]. The retrotransposed CypA copy is only present in four species of *Aotus* genus among New World monkeys; the other 15 genera do not possess the *TRIM5–CypA* fusion pattern [64]. In contrast, the *TRIM5–CypA* fusion phenomenon occurs in some Old World monkeys, including northern pigtailed macaque (*M. leonina*), Sunda pigtailed macaque (*M. nemestrina*), Indian rhesus macaque (*M. mulatta*), cynomolgus macaque (*M. fascicularis*) and assam macaque (*M. assamensis*) [16–20, 65]. The LINE-1 element mediates retrotransposition of *CypA* cDNA into *TRIM5* locus in distinct fusion patterns and genotype among New and Old World primates. In the *Aotus* genus of New World monkeys, the TRIMCyp exists in the pattern of homozygosity at the *TRIM5* locus; there was no *TRIMCyp/TRIM5* heterozygote observed [14, 64, 66]. The TRIMCyp identified in the rhesus macaques of the Old World monkey is encoded by a single, but common, allele (*Mamu7*) of the rhesus *TRIM5* gene, among at least six further alleles that encode full-length TRIM5 proteins with no homology to CypA [66]. However, in Old World monkeys, the cynomolgus macaques and Indian rhesus macaques contain heterozygous *TRIM5/TRIMCyp* existing at different portions in the populations; the homozygous *TRIMCyp* exists as well [16, 19, 67]. In Sunda pigtailed macaque, all screened macaque individuals were homozygous for the CypA insertion. In contrast, the CypA-containing allele was present in 17 % (17/101) of rhesus macaques [67]. Further studies demonstrated that the generation of the *TRIM5–CypA* is caused by the G-to-T mutation at the 3′ splice site in

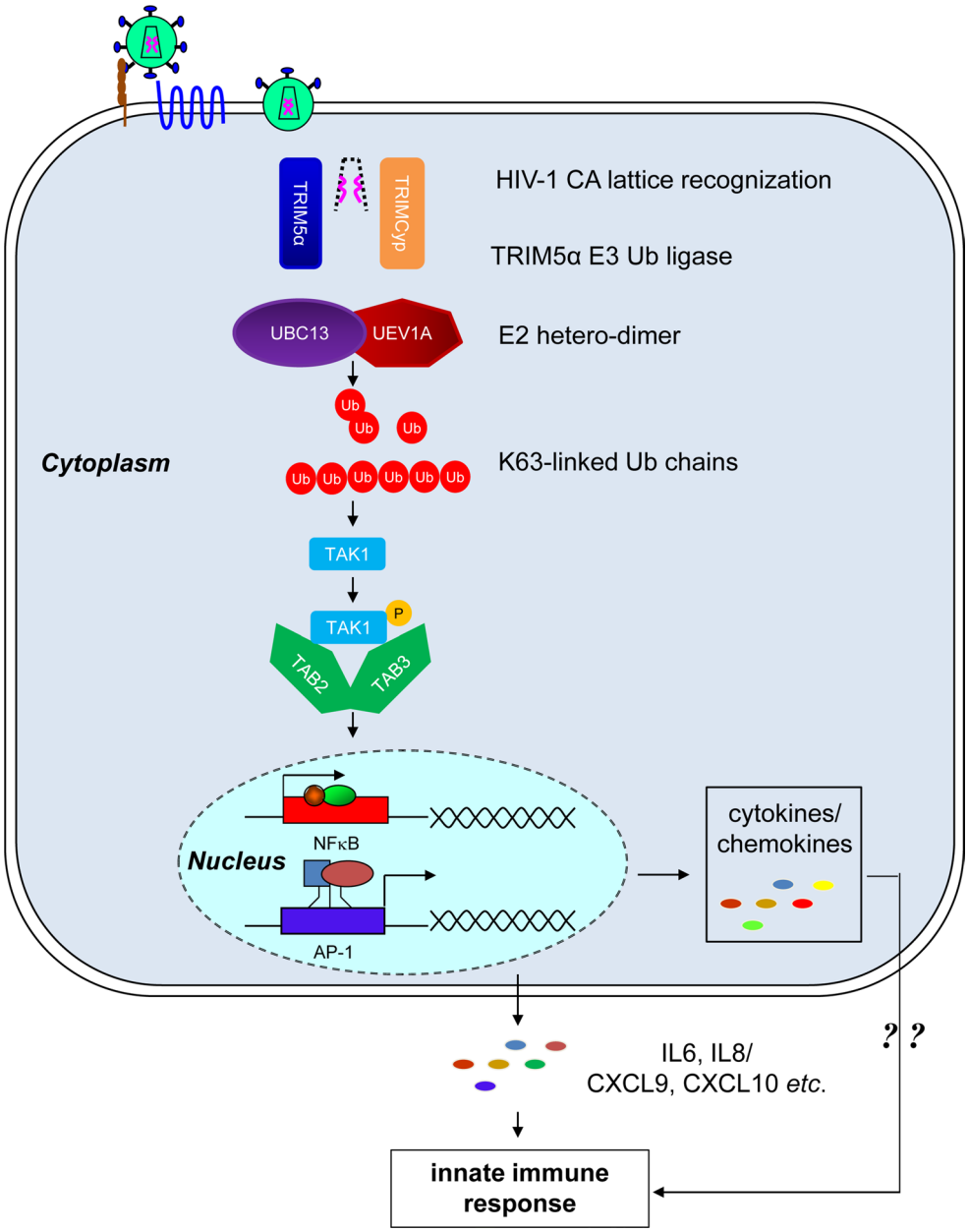

Fig. 1 The innate immune activation by TRIM5α or TRIMCyp during HIV-1 infection. In the target cell, the invasive HIV-1 CA lattice in the cytosol is recognized and bound by TRIM5α via the SPRY domain or TRIMCyp via the CypA domain. TRIM5α multimerizes and forms a hexagonal lattice on top of the CA. TRIM5α binding to CA triggers its E3 Ub ligase activity and subsequently promotes the formation of the E2 Ub-conjugating enzyme complex UBC13–UEV1A. Then, the UBC13–UEV1A heterodimer catalyzes the synthesis of free K63-linked Ub chain complex (indicated with Ub in *red circle*), which in turn activates the phosphorylation (indicated as a letter P in *orange circle*) of the TAK1 and in complex with TAB 2 and TAB 3. The TAK1–TAB 2–TAB 3 complex results in the induction and expression of downstream NF-κB-responsive and AP-1-responsive inflammatory genes, thereby leading to the cytokines or chemokines expression-mediated innate immune response to HIV-1 in the infected cell. The secretory cytokines (IL6 and IL8) and chemokines (CXCL9 and CXCL10) directly act as the innate immune factors outside the cell. The cytokines and chemokines inside host cells might involve other components, such as the formation of the lysosome, to act as a part of the role of innate immune system, which remains unknown. *SPRY* SPla and the RYanodine Receptor, *Ub* ubiquitin, *UBC13* ubiquitin-conjugating enzyme 13, *UEV1A* ubiquitin-conjugating enzyme variant 1A, *K63* Lysine 63, *TAK1* transforming growth factor β-activated kinase-1, *TAB 2* TAK1-binding protein 2, *TAB 3* TAK1-binding protein 3, *NF-κB* nuclear factor-kappa B, *AP-1* activator protein-1 (color figure online)

TRIM5 intron 6 [19, 67], and this might be associated with the loss of exon 7 in transcripts [68].

The cynomolgus macaque TRIMCyp is unable to inhibit HIV-1 and SIVmac239 [17, 18]. Nevertheless, the TRIMCyp in Indonesian cynomolgus macaques could restrict HIV-1, SIV_{AGM}Tan (SIV from African green monkey tantalus species) and FIV (feline immunodeficiency virus), but failed to restrict HIV-2 [69]. Further work showed that the single mutation, E143K, results in the loss of restriction to HIV-2 and a significant decrease in restriction activity to SIV_{AGM}Tan by TRIMCyp in cynomolgus macaques [70]. Dietrich et al. [71] analyzed the prevalence of TRIMCyp in cynomolgus macaque samples from four different regions, i.e., Indonesia, Indochina, Philippines and Mauritius. The TRIMCyp is present at a higher frequency in Indonesian than in Indochinese cynomolgus macaques and is also present in macaques from the Philippines. Interestingly, the different *TRIM5–CypA* fusion frequency is also different in two rhesus macaques: Indian rhesus macaque and Chinese rhesus macaque (reference [55] and our unpublished data). TRIMCyp is absent in Mauritian cynomolgus macaques. The restriction specificity of TRIMCyp derived from three animals of Indonesian origin is different as well. One allele, like the prototypic TRIMCyp alleles described for rhesus macaques and Sunda pigtailed macaques, restricts HIV-2 and FIV but not HIV-1 replication. The other alleles of Indonesian TRIMCyp restrict HIV-1 and FIV, but they do not restrict HIV-2 replication. Taken together, these data suggest that the high diversity of TRIMCyp in Asian macaques may contribute to the diverse retroviral restrictions during their evolution.

TRIMCyp restriction mechanisms to HIV-1

Although the RING and B-box2 domains affect TRIMCyp half life and anti-HIV-1 activity, they are not absolutely necessary for TRIMCyp antiviral activity [69]. This may attribute to that CypA itself has the ability to promote CA shedding and restrict HIV-1 in making TRIMCyp antiviral activity; thus, it is less dependent on the proceeds from the cofactor by the RBCC [72]. Early studies have shown that TRIMCyp in mammalian cells, mainly in the form of trimer, the CA binding mediated by coiled coil and CypA and B-box2-mediated effector function are required for TRIMCyp restriction of HIV-1 [73, 74]. However, in recent years, the TRIMCyp dimer, hexamer and other very complex polymers were also found in addition to the trimeric form, and the hexamer seems to be the main polymer form of TRIMCyp that exists in the mammalian cells. The hexamer TRIMCyp structure is a benefit to the recognition of mature retroviral CA component units of the hexamer CA particles (Capsomer), but the TRIMCyp polymerization is not associated with the specific viral CA recognition [75]. CypA displays different roles in restriction by Old World monkey TRIM5α and owl monkey TRIMCyp. In Old World monkeys, CypA isomerization of a proline residue in the TRIM5α sensitivity determinant of the HIV-1 CA sensitizes it to restriction by Old World monkey TRIM5α. Owl monkey TRIMCyp recruits its tripartite motif to HIV-1 CA via the CypA domain and inhibits HIV-1 replication [76].

Host antiviral proteins and pathogenic viruses countervail each other with the long-term evolution history. Selection pressure from pathogenic infection has driven rapid evolution of *TRIM5* genes in primates, leading to the antiviral specificities we see today. Remarkably, the New World owl monkey encoded TRIMCyp restricts infection by a subset of lentiviruses that recruit CypA to their CAs, including HIV-1 and FIV. The hypothesis has been established that owl monkey TRIMCyp fusion protein may limit the HIV-1 infection by the following mechanisms: Firstly, after HIV-1 entering into the target cells, the CypA domain of TRIMCyp immediately binds to the HIV-1 CA [13, 14, 64, 77], accelerating the uncoating of HIV-1 core and CA degradation to prevent HIV-1 RNA from reverse transcription [74, 78]. In this process, the coiled-coil domain and CypA domain are crucial for the interaction between TRIMCyp and HIV-1 CA-NC (capsid–nucleocapsid) complex. The TRIMCyp trimer that contains the two domains is more effective in combination with the CA protein [43]. Secondly, although the proteasome inhibitor can restore HIV-1 reverse transcription and promote the formation of an active PIC (pre-integration complex), the PIC nuclear import is blocked via an unknown way by TRIMCyp, thus limiting further viral replication [79]. The antiviral specificity of the rhesus TRIMCyp is distinct, restricting infection of HIV-2 and FIV but not HIV-1. Restriction by rhesus TRIMCyp is before reverse transcription and inhibited by blocking CypA binding, with CsA or by mutation of the CA–CypA-binding site [66]. These observations suggest a mechanism of restriction that is conserved between TRIMCyp proteins. The detailed working mechanism of Old World monkey TRIMCyp needs more studies in the future.

Like the innate immune activity of TRIM5α, the owl monkey TRIMCyp fusion protein was also proved to be able to catalyze free K63-linked Ub chain synthesis in vitro. After the recognition and binding to HIV-1 CA via CypA domain, the amount of free Ub chains will increase substantially, newly synthesized Ub chains promote TAK1 phosphorylation [23, 55, 80]. It implies that the owl monkey TRIMCyp also could act as a PPR and interact with retroviral CA proteins, thus eliciting the antiviral functions of host innate immune system. However, the exact mechanism of TRIMCyp in the PPRs signaling pathway is not clear and remains to be elucidated.

Conclusions

The identification of TRIM5α is tightly associated with the interaction between CypA and CA in infected cells. The cytoplasmic E3 Ub ligase TRIM5α exists as a dimer in the cytosol; it recognizes HIV-1 CA lattice and triggers the innate immune response to incoming virion by activating the TAK1. Besides, the formation of *TRIM5–CypA* fusion gene in primate genomes especially calls for more appreciations. The host protein CypA could also sense the CA proteins in DCs, thus helping the innate immune activity of TRIMCyp fusion protein. The species-specific sensing and activation of innate immune response by TRIM5α and CypA were observed in T cells, macrophages and DCs. Further investigation into the function and the mechanism of TRIM5α as an innate immune sensor for retrovirus CA might shed light on developing more effective interventions against HIV-1 infection. Although a robust prophylactic vaccine based on adaptive immune memory response is irreplaceable to prevent AIDS progression, finding ways to artificially employ TRIM5α to induce more highly protective responses in the context of candidate HIV vaccines might prove to be a helpful strategy, and the TRIMCyp has been proposed to as candidate gene in gene therapy approaches as well [81, 82].

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Conflict of interest All contributing authors declare no conflict of interest.

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