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TRIMe7-CypA, an alternative splicing isoform of TRIMCyp in rhesus macaque, negatively modulates TRIM5α activity

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ABSTRACT

The existence of innate, host-specific restriction factors is a major obstacle to the development of nonhuman primate models for AIDS studies, and TRIM5α is one of the most important of these restriction factors. In recent years, a *TRIM5* chimeric gene that was retrotransposed by a cyclophilin A (CypA) cDNA was identified in certain macaque species. The TRIM5α-CypA fusion protein, TRIMCyp, which was expressed in these monkeys, had lost its restriction ability toward HIV-1. We previously found that TRIMe7-CypA, an alternative splicing isoform of the TRIMCyp transcripts, was expressed in pig-tailed and rhesus macaques but absent in long-tailed macaques. In this study, the anti-HIV-1 activity of TRIMe7-CypA in the rhesus macaque (RhTRIMe7-CypA) was investigated. The over-expression of RhTRIMe7-CypA in CrFK, HeLa and HEK293T cells did not restrict the infection or replication of an HIV-1-GFP reporter virus in these cells. As a positive control, rhesus (rh)TRIM5α strongly inhibited the reporter virus. Intriguingly, the anti-HIV-1 activity of RhTRIM5α was significantly reduced in a dose-dependent manner by the co-repression of RhTRIMe7-CypA. Our data indicate that although the RhTRIMe7-CypA isoform does not appear to restrict HIV-1, it may act as a negative modulator of TRIM family proteins, presumably by competitive inhibition.

1. Introduction

The challenge of developing animal models for HIV-1 is that the virus has a narrow host range and does not replicate in most tested animal species [1], except for chimpanzee and gibbon apes [2,3], and only rare animals develop AIDS-like symptoms typical of those experienced by humans [4,5]. Furthermore, chimpanzee and gibbon apes are endangered and costly to maintain, as well as with ethic concerns, limiting their use in HIV-1 research [6]. Therefore, macaques, including the pig-tailed macaque (*Macaca nemestrina*), the long-tailed macaque (*Macaca. fascicularis*) and the rhesus macaque (*Macaca mulatta*), represent primate models that might facilitate AIDS research.

It is now widely accepted that several host factors confer resistance to the cross-species spread of HIV-1; these factors include APOBEC3G and TRIM5α. APOBEC3G blocks HIV-1 replication in monkey cells by modifying minus strand viral cDNA during reverse transcription, resulting in its hypermutation or degradation [7–9]. TRIM5α targets incoming HIV-1 viral capsids (CA) and blocks retroviral replication in a species-specific manner [10,11]. Recently, human TRIM5α was shown to activate the NF-κB and AP-1 signaling pathways by interacting with the TAK1 complex [12]. Thus, TRIM5α is involved in the control of viral infection in multiple ways. Overcoming the APOBEC3G and TRIM5α barriers in monkeys using chimeric simian-tropic HIV-1 (stHIV-1) viruses appears to be a practical approach to allow cross-species transmission. StHIV-1 variants were constructed by replacing the HIV-1 CA and Vif regions with the corresponding regions from SIV [13,14].

However, in owl monkeys, cyclophilin A (CypA) cDNA has been transposed into the *TRIM5* locus, resulting in the expression of a TRIM5-CypA fusion protein (TRIMCyp) that restricts HIV-1 infection based on the retroviral CA-binding specificity of CypA [15,16]. Interestingly, the pig-tailed macaque also expresses a TRIMCyp protein that has lost its ability to restrict HIV-1 CA due to a point mutation near the CypA/CA-binding interface [17]. This finding means that the pig-tailed macaque may be more susceptible to stHIV-1 infection after converting the *vif* gene to the simian

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sequence to maintain the maximum number of HIV-1 properties [18,19]. However, the pig-tailed macaque is an endangered primate species, and other species of macaques that express TRIMCyp, such as the rhesus macaque and the long-tailed macaque, can also represent nonhuman primate models of HIV-1 infection. We previously investigated the distribution and expression status of TRIMCyp in four macaque species originating from China [20]. Interestingly, TRIMe7-CypA, a spliced isoform of the TRIMCyp transcript in which the CypA fragment is linked to exon 7 of the *TRIM5* gene, was abundant in the pig-tailed macaque (approximately 30%), present at a much lower levels in the rhesus macaque (approximately 10%) and absent entirely in the long-tailed macaque [20]. The homology of deduced amino acid sequences of the pig-tailed and rhesus TRIMe7-CypA were identical, except two residues at the RBCC domain. In the pig-tailed macaque, TRIMe7-CypA was previously reported to have lost anti-HIV-1 activity [21]. However, the function of this novel splicing isoform of TRIMCyp in the rhesus macaque is unclear.

Investigations of our and other groups revealed that approximately 10% of TRIMCyp-genotype rhesus and 20–95% long-tailed macaques were heterozygotes [22,23], which means that HIV-1-restrictive TRIM5α and -nonrestrictive TRIMCyp can coexist in a single individual. The potential functional interaction between these two TRIM proteins is an interesting but insufficiently understood topic of research. In this study, we investigated the role of rhesus macaque (Rh)TRIMe7-CypA in anti-HIV-1 activity.

2. Materials and methods

2.1. Construction of expression plasmids

RNA was extracted from the blood of pig-tailed macaque, rhesus macaque and long-tailed macaque, and cDNA was synthesized as previously described [20]. Rhesus macaque (Rh)TRIM5α, RhTRIMe7-CypA and pig-tailed (Pt)TRIMCyp were cloned into pcDNA3.1 at the Eco RI and Xho I sites and fused to an N-terminal HA tag using PCR with the following primers: RhTRIM5α forward, 5′-CCGGAATTCATGTACCCATATGACGTTCCAGACTACGCGGCTTCTGGAATCCTGCTTAAT-3′; RhTRIM5α reverse, 5′-CCGCTCGAGTCAAGAGCTTGGTGAGCACAGAGT-3′; PtTRIMCyp forward, 5′-CCGGAATTCGCCACCATGTACCCATATGACGTTCCAGACTACGCGGCTTC-3′; PtTRIMCyp reverse, 5′-CCGCTCGAGTTATTCGAGTTGTCCACAGTCAGC-3′; RhTRIMe7-CypA forward, 5′-CCGGAATTCGCCACCATGTACCCATATGACGTTCCAGACTACGCGGCT-3′ and RhTRIMe7-CypA reverse, 5′-CCGCTCGAGTTACCAAATCCTTTCTCT-3′.

2.2. Infections of a GFP-expressing HIV-1 reporter virus

A green fluorescent protein (GFP)-expressing HIV-1 reporter virus (HIV-GFP) was constructed by packaging pFUGW with psPAX2 and pMD2.G (all from Addgene, Massachusetts, USA). HEK293T cells were co-transfected with 9 μg of pFUGW, 6 μg of psPAX2 and 3 μg of pMD2.0G. The virus stock was collected 48 h post transfection. To infect HEK293T, HeLa and CrFK cells with HIV-GFP, the cells were seeded in 48-well plates and incubated with this pseudotyped virus for 24 h post transfection. The cells were washed and then analyzed using flow cytometry with a FACSAria flow cytometer (Becton, Dickinson and Company, New Jersey, USA) 48 h post infection.

2.3. Transfection and Western blotting

Cells were transfected using Lipofectamine 2000 (Life Technologies, California, USA) following the manufacturer's instructions. Cells and culture supernatants were harvested 48 h post-transfection, washed once in PBS and lysed in RIPA lysis buffer containing a cocktail of protease inhibitors (Roche, Basel, Switzerland). The lysates were centrifuged at 12,000*g* for 10 min at 4 °C to remove cell debris, and the supernatant was then centrifuged at 20,000*g* for 2 h at 4 °C to precipitate the viral particles. Whole-cell lysates were separated by SDS–PAGE, transferred to PVDF membranes (Millipore, Massachusetts, USA) and then probed with the indicated antibodies.

3. Results and discussion

3.1. TRIMe7-CypA did not restrict HIV-1 infection in vitro

In a previous study analyzing the polymorphisms of TRIM5α and TRIMCyp in four species of macaques, the expression of RhTRIMe7-CypA (a rarely reported, alternatively spliced isoform of the TRIMCyp transcript) was discovered in pig-tailed and rhesus macaques (Fig. 1A). Several variant splicing isoforms of TRIM5α and TRIMCyp have been reported, some of which are unable to restrict viruses [21,24,25]. The RhTRIMe7-CypA isoform was first reported in the pig-tailed macaque in 2007 [21]. An arginine-rich domain at the C terminus of this protein is generated as the result of a frame shift, creating a positively charged domain that is presumed to bind to the retroviral CA domain through electrostatic attraction [20]. It was found that TRIM5α variants lacking the SPRY domain lost activity against HIV-1 [24,26,27]. However, it was also reported that some proteins of the TRIM family, such as TRIM19, lack the SPRY motif but retain their antiviral function [28]. To investigate the functions of RhTRIMe7-CypA, this isoform of TRIMCyp was first examined for its ability to restrict HIV-1 infection.

A pseudotyped HIV-1 (termed HIV-GFP) that expresses GFP and is enveloped by the vesicular stomatitis virus (VSV) G glycoprotein was generated. The restriction of transiently expressed RhTRIMe7-CypA toward HIV-GFP was tested in three cell lines, including CrFK, HeLa and HEK293T. Recombinant RhTRIM5α and PtTRIMCyp were also expressed separately in these cell lines to serve as positive and negative controls of TRIM5 restriction of HIV-1, respectively. The three TRIM proteins, which were tagged with hemagglutinin (HA), were expressed at similar levels in all three cell lines (Fig. 1B, D and F). However, the numbers of cells expressing the recombinant proteins (the FITC-positive population) in transfected HEK293T and HeLa cells were much higher (approximately 80–90%) than that in CrFK cells (approximately 50%) when analyzed using flow cytometry.

Twenty-four hours post transfection, the cells were infected with the HIV-GFP virus, and infected cells (GFP-positive) were counted using flow cytometry 24 h later. The results demonstrated that RhTRIMe7-CypA lost its ability to restrict HIV-1 when compared with RhTRIM5α, which is the primate TRIM protein in macaques that restricts HIV-1 infection (Fig. 1C, E and G). The inhibitory activity of RhTRIM5α in CrFK cells was lower than that in HEK293T and HeLa cells, possibly due to the lower transfection efficiency of CrFK cells or the different cellular environment, which is important for the efficacy of the TRIM5α restriction of HIV-1 [29].

3.2. TRIMe7-CypA did not inhibit HIV-1 production

Macaque TRIM5α restricts HIV-1 infection by multiple mechanisms. Rapid degradation of HIV-1 Gag proteins is one of the most effective activities and depends on the RBCC domain [30]. Although TRIMe7-CypA does not have the SPRY domain, it retains the RBCC domain, implying that TRIMe7-CypA may mediate HIV-1 Gag degradation during viral replication. To investigate the effect of RhTRIMe7-CypA on HIV-1 replication, HEK293T cells were transfected with an HIV-1 Gag-Pol-expressing plasmid (psPAX2) and a

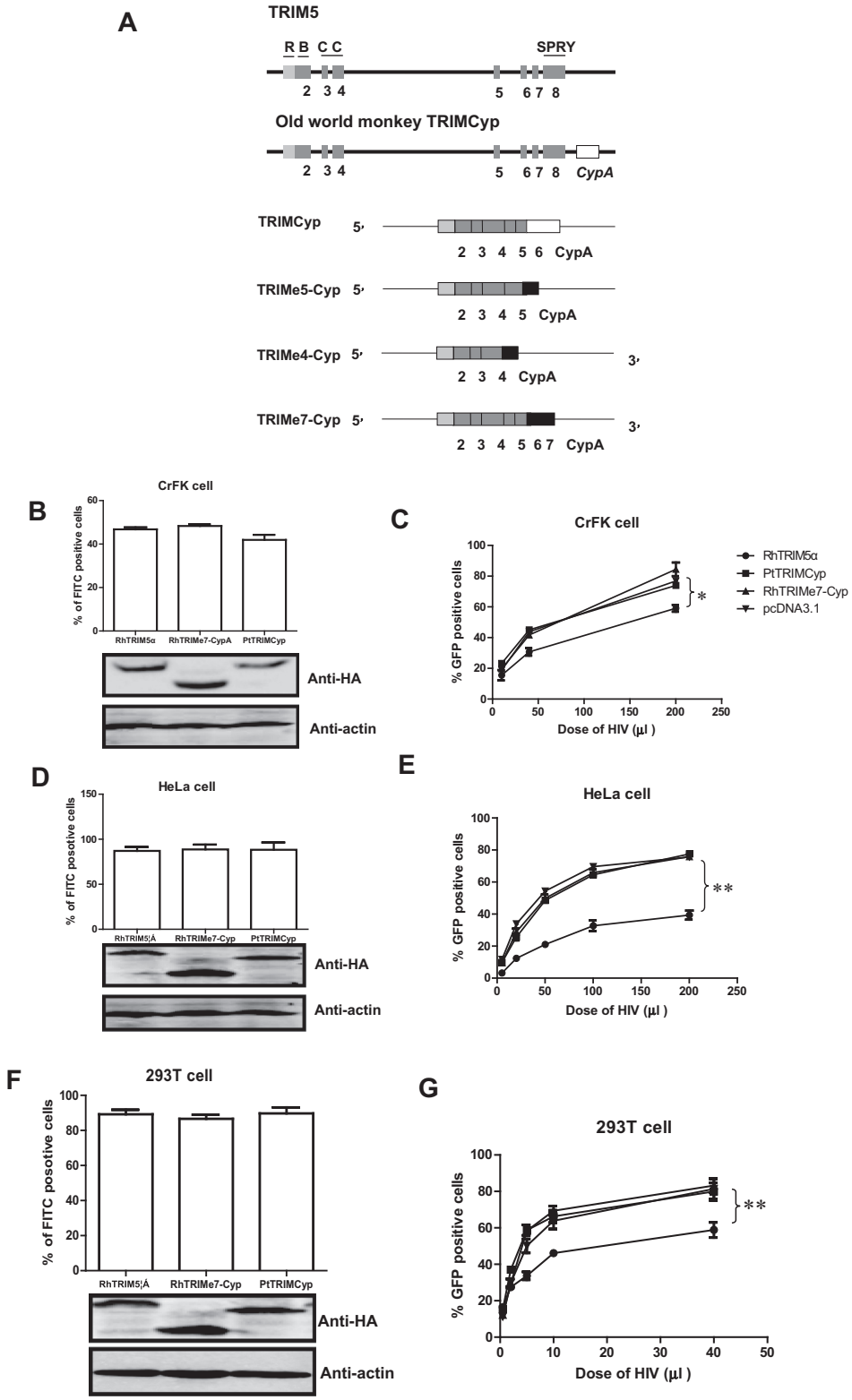

Fig. 1. TRIMe7-CypA did not inhibit HIV-1 infection of target cells. (A) The CypA pseudogene fragment was fused to TRIM5 mRNA at various sites from exon 4 to exon 7, forming a series of splicing isoforms that were termed TRIMe4-CypA, TRIMe5-CypA, TRIMCyp and TRIMe7-CypA, respectively. The boxes in black indicate a reading frame shift from the original sequence. To examine whether the macaque isoform TRIMe7-CypA retained its ability to restrict HIV-1 infection, CrFK, HeLa and HEK293T cells were transfected with plasmids expressing HA-tagged RhTRIM5α, PtTRIMCyp or RhTRIMe7-CypA. The transfection efficacies were examined using flow cytometry and a FITC-labeled anti-HA antibody, and the expression levels of these recombinant proteins were analyzed in three cell lines using western blotting 48 h post transfection (B, D and F). In another set of experiments, the HIV-GFP reporter virus was prepared as described in the Section 2. CrFK (C), HeLa (E) and HEK293T (G) cells were transfected with 2 μg of RhTRIM5α, PtTRIMCyp or RhTRIMe7-CypA expression plasmid DNA. These cells were infected with increasing doses of HIV-GFP virus 24 h post transfection and collected for flow cytometry analysis at the indicated times. All experiments were performed three times, and the Western blotting images presented in the figure are from a representative experiment. Statistic differences of flow cytometry results were analyzed between cells transfected with positive control plasmid expressing RhTRIM5α and the empty vector pcDNA3.1. There were no differences between cells transfected with the RhTRIMe7-CypA expression plasmid and pcDNA3.1 or pPtTRIMCyp.* $P<0.05$; ** $P<0.01$.

plasmid expressing RhTRIMe7-CypA, RhTRIM5α or PtTRIMCyp. RhTRIM5α and PtTRIMCyp alone were used as positive and negative controls for the restriction of HIV-1, respectively. The cells and culture supernatants were harvested 48 h later and analyzed using western blotting. The results revealed that the expression of RhTRIM5α, but not that of PtTRIMCyp or RhTRIMe7-CypA, dramatically inhibited the production of HIV-1 Gag protein (p55) and also the cleaved mature CA (p24) (Fig. 2), indicating that although RhTRIMe7-CypA contains an intact RBCC domain, it also requires a complete CYPA/SPRY domain to bind and degrade HIV-1 Gag. Recently, it has been shown that human TRIM5α induces a signaling cascade that activates the innate immunity and that the RBCC domain is essential for this activity [12]. Whether RhTRIMe7-CypA stimulates this signaling pathway requires further investigation.

3.3. TRIMe7-CypA limited the anti-HIV-1 activity of rhesus TRIM5α

TRIM5 isoforms lacking the SPRY domain were able to silence the antiviral activity of TRIM5α by forming heteromultimers that impaired the recognition of targeted viruses [24,26,27]. Although RhTRIMe7-CypA did not inhibit HIV-1 replication (Figs. 2 and 3), it is necessary to investigate whether this isoform of TRIMCyp acts as a dominant-negative competitor of RhTRIM5α. HeLa cells were co-transfected with RhTRIM5α and increasing doses of RhTRIMe7-CypA. Twenty-four hours post transfection, these cells were infected with the HIV-GFP virus. The infected GFP-positive cells were counted 24 h later using flow cytometry. Fig. 3 demonstrates that RhTRIM5α inhibition of the pseudotyped HIV-GFP infection of HeLa cells was significantly decreased following RhTRIMe7-CypA over-expression and that further increases in the expression level of RhTRIMe7-CypA enhanced this inhibition. In addition, western blotting analysis revealed that TRIMe7-CypA over-expression did not alter the level of RhTRIM5α protein that was co-expressed in the cells, suggesting that RhTRIM5α antiviral activity is negatively modulated by RhTRIMe7-CypA through competitive inhibition.

Taken together, these findings demonstrate that TRIMe7-CypA (a rarely reported, alternatively spliced transcript of the TRIMCyp chimeric gene) is expressed in pig-tailed and rhesus macaques but silent in long-tailed macaques. This study demonstrates that TRIMe7-CypA cannot restrict HIV-1 in vitro. Instead, this protein acts as a negative regulator of the anti-HIV-1 activity of RhTRIM5α, presumably by competitive inhibition.

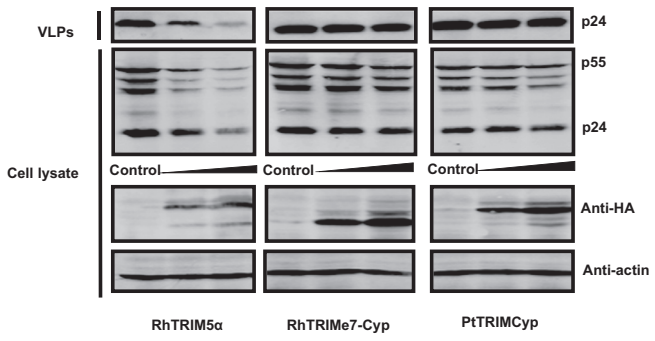

Fig. 2. TRIMe7-CypA did not inhibit HIV-1 production. HEK293T cells were co-transfected with an HIV-1 Gag-Pol expression plasmid (20 ng) and increasing doses (0, 0.7 and 1.4 μg) of plasmids expressing RhTRIM5α (left), RhTRIMe7-CypA (middle) or PtTRIMCyp (right). Cells were lysed 48 h post transfection, and the expression levels of viral Gag (p55) and the cleaved mature capsid protein (p24) in viral-like particles (VLP) that were secreted into the medium or remained in the cells (cell lysate) were examined by Western blotting using a p24 monoclonal antibody. All experiments were performed three times, and a representative result is shown.

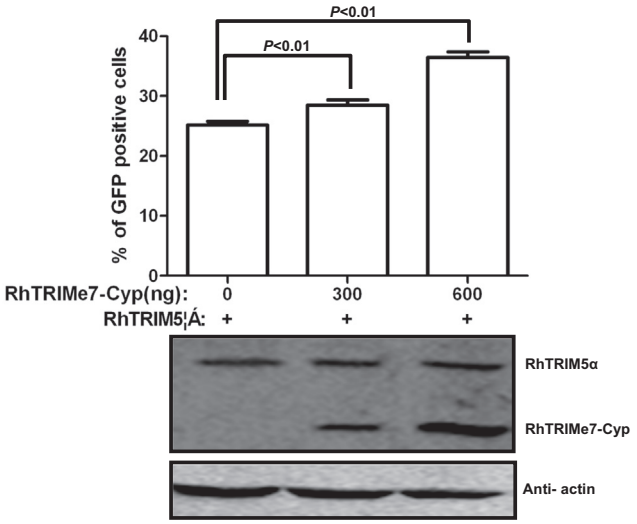

Fig. 3. TRIMe7-CypA limited the antiviral activity of rhesus TRIM5α. HeLa cells were co-transfected with RhTRIM5α (600 ng) and increasing doses (0, 300 and 600 ng) of the RhTRIMe7-CypA expression plasmid. The HIV-GFP reporter virus was added 24 h post transfection, and cells infected with HIV-GFP were examined by flow cytometry 24 h post infection (upper panel). In addition, the expression levels of RhTRIM5α and RhTRIMe7-CypA were examined in the transfected cells by western blotting 48 h post infection (lower panel). All of the experiments were performed three times, and a representative image of Western blotting is shown.

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