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Role of Trim5α in the Suppression of Cross-Species Transmission and its Defence Against Human Immunodeficiency Virus

Madhuri P. Puvvada and Snehal S. Patel*

Department of Pharmacology, Institute of Pharmacy, Nirma University, Ahmedabad, Gujarat, India

Abstract: Acquired Immunodeficiency Syndrome (AIDS) was discovered 30 years ago and was followed by the identification and characterization of its causative agent, Human Immunodeficiency Virus (HIV). Increasing spread of retroviral infections has impelled science to understand the evolution of retroviruses from primates to humans. In the course of evolution, host cells have developed intracellular proteins to counteract the transforming viral defence system. Such inhibitory endogenous intracellular proteins are known as restriction factors. Tripartite motif protein isoform 5 alpha (TRIM5α), Apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC), and Tetherin proteins are few important restriction factors that have been extensively studied. Several evidences have conveyed information regarding specific adaptations occurring in HIV-1 and its relatives to inhibit these host defenses; making the study more interesting. The characteristic potential of restriction factors to restrict the replication of retroviruses was enticing when studies were found that HIV-1 virus cannot infect nonhuman primate species. This review emphasizes on TRIM5α as a restriction factor and its significance in the evolution of retroviruses. It also accentuates the role of polymorphism within the regions of TRIM5α in both human and primate species that eventually affect the cross-species transmission of immunodeficiency viruses.

Keywords: Acquired immunodeficiency syndrome, human immunodeficiency virus, restriction factor, transmission, TRIM5α.

INTRODUCTION

Discovery of AIDS was followed by the identification and characterization of its causative agent, human immunodeficiency virus (HIV). Today even after immense research being done on this disease, there are 30 million people worldwide affected with AIDS. Every year 2.5 million people are newly infected and 1.7 million die due to AIDS. According to UNAIDS 2012 global AIDS report, 34 million people have been diagnosed with AIDS and 1.7 million deaths have been reported worldwide [1]. In the face of these daunting statistics, when we look back at the progress achieved in AIDS treatment, there are several effective drugs and ongoing attempts to establish a useful HIV-1 vaccine, but a deeper understanding of the innate defence mechanism by restriction factors in human cells will not only determine the underlying cause but also reveal the pattern of cross-species transmission. Several restriction factors have evolved with the advancement of retroviral infections. Soon after the identification of Friend-virus-susceptibility factor 1 (Fv1), TRIM5α was identified as a factor mediating HIV-1 resistance in rhesus macaque lung fibroblasts. It is a widely studied restriction factor that has provided significant evidence on the evolution of retroviruses from primates to humans [2-5]. The changes in the variable regions of TRIM5α have generated the potential to develop compounds that can bind to specific regions on human TRIM5α and retarget it to act against HIV-1 [2]. Retargeting TRIM5α would mark a crucial step in the development of novel therapeutic strategies for the treatment of AIDS.

*Address correspondence to this author at the Department of Pharmacology, Institute of Pharmacy, Nirma University, Ahmedabad, Gujarat, India;
Tel: +919099937466; Fax: +91 – 2717 – 241916;
E-mail: snehalpharma53@gmail.com

VIRUS-HOST INTERACTION

Viruses are obligate parasites as they depend on the host cells for their survival [6]. They are bits of genetic material covered in a protein sheath (capsid), capable of sequestering the protein synthesis machinery of the host for their own replication [7]. After utilizing this machinery they continue to amplify as part of the host cell DNA. Viruses have been classified into different families based on their characteristics. Retroviruses belong to the *Retroviridae* family [8]. The structure of retroviruses consists of a RNA genome embedded in a capsid which is surrounded by a lipid envelope studded with glycoprotein due to which they exist as a small particle called virion [9, 10]. The shape and location of the internal protein core are characteristic features of this family. The virion RNA is 7-12 kb in size, linear, single-stranded, non-segmented, and positively charged [9]. The distinguishing characteristic of this family is its replication pattern which include; reverse transcription of the virion RNA into a linear double-stranded DNA and further integration of this genome into the host cell genome [8, 11]. The integrated viral DNA (provirus) becomes an addition to the host chromosome and persists in latent stage until some unknown agents activate it to restart the replication [12, 13]. The latency of the virus is the biggest threat to diagnose the disease. Hence, the interplay between virus and host has generated the need to develop newer defense strategies [14]. Restriction factors are emerging to be better defense mechanisms against the sprouting replication of retroviruses [15-17].

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PATTERN OF CROSS-SPECIES TRANSMISSION

With the transmission of Simian Immunodeficiency Virus (SIV) from Chimpanzees (SIVcpz) and Sooty Mangabeys (SIVsm) to humans; the virus has magnanimously developed itself being competent to several external threats. Excogitating the transmission pattern to the discovery of AIDS will uncover the extent of competency developed by the virus to resist against the anti-retroviral therapy and the diminution of restriction caused by restriction factors over the years.

As shown in Fig. (**1**), HIV-1 and HIV-2 had their emergence from SIVcpz and SIVsm, respectively [18-20]. The question that arises is: What led to the emergence of Simian precursors of HIV and how this led to the occurrence of AIDS epidemic? Retracing the evolution from SIV to HIV; researchers have concluded several theories that could be used to trace the emergence of AIDS and find a possible solution to combat it. To resolve the mystery of origin of SIV in chimpanzees; fecal and urine samples were collected from different field sights and were evaluated for the presence of virus specific antibodies. After scrutinizing antibody positive specimens; molecular characterization was performed by RNA extraction and RT-PCR amplification of the virus specific samples. The results obtained from the experiment provided an in-depth scenario of prevalence of SIV and confirmed Chimpanzees as reservoirs of SIV (called as SIVcpz) [21]. The geographic distributions of SIVcpz and SIVgor infections in Sub-Saharan African regions have been meticulously described in previous studies [18-21]. These studies described minor prevalence of SIVcpz in Central and Eastern regions of Africa and absence of infection in the Western and Nigeria-Cameroonian chimpanzees. On the contrary, major prevalence of SIVsm was observed in these regions. The inference from these studies have suggested, rare occurrence of SIV in chimpanzees was due to migration of Western African apes that were members of P.t. verus subspecies (members of Chimpanzees found in Western Africa) to Eastern regions and their inability to get infected by SIV [21].

It is quiet speculating that chimpanzees being predators of monkeys; considered as natural reservoirs of SIV have acquired the virus during the process. Thereafter, the spread of the virus was rapid as humans came into contact with the mucous of Chimpanzees while hunting. But, the interesting

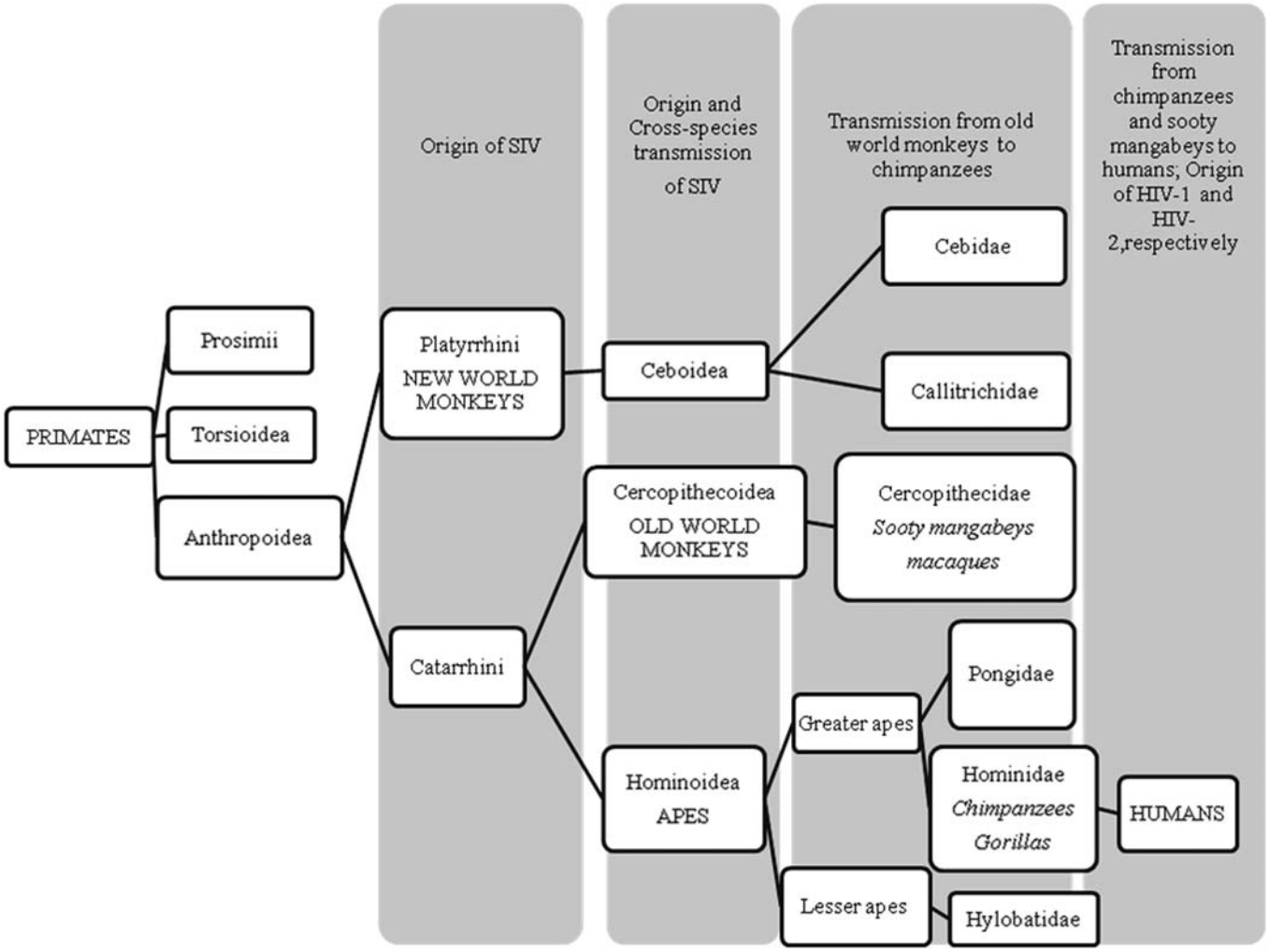

Fig. (1). Cross-species transmission of SIV from old world monkeys to human HIV. SIV: Simian immunodeficiency Virus, HIV: Human immunodeficiency virus [18-21].

fact is that these viruses are non-pathogenic in their natural host and exert their pathogenic nature when transmitted to a foreign host like humans. Phylogenetic analyses of full-length pro-viral sequences have revealed that SIVcpz has been generated by recombination of two lineages of SIVs that infect monkeys. The 5'half of the genome, *nef* gene and the 3'LTR of the SIVcpz is related to the SIVrcm from red-capped monkeys whereas, the *vpu*, *tat*, *rev* and *env* genes are related to SIVs infecting several Cercopithecus species [21]. Hence, it can be inferred that SIV in the process of cross-species transmission has undergone several host-specific changes to inure itself to the new environment [22, 23]. Based on the prevalence of transmission of SIVcpz to HIV in humans; Fig. (**2**) represents the subgroups of HIV and their occurrence in different parts of the world.

RESTRICTION FACTORS

Retroviruses are obligate intracellular parasites that have extremely evolved with their increasing occupancy in the host cells for millions of years consequently utilizing several host factors; needed for their survival. On the contrary, to compete with these mechanisms, host cells have evolved with their intracellular proteins to restrict the rapid replication of viruses. Such intracellular inhibitory cellular factors are referred to as restriction factors [24, 25]. These factors serve as activators of the defence system in the host cell, but their expression remains complicated. Restriction factors inhibit the reverse transcription of the newly synthesized DNA to the nucleus by conferring on the retroviral capsid [26]. They act as natural watch-guards by keeping an eye on the replication of viruses and inhibiting rapid replication and spread of the disease.

Tissue tropism of retroviruses largely depends on the factors and the conditions provided by the host cells for their optimal completion of the viral life cycle. The inhibition of replication in a given cell type could be attributed to the inhibition of viral entry into the host cell. It might be caused due to the absence of specific cell surface receptors or species-species differences in receptor molecules that make them unable to support infection. When the virus is inside the cell, it requires several conditions to carry out its life cycle. Therefore at the level of gene expression, replication of retroviruses may be halted due to improper transcriptional machinery that can mediate synthesis of retroviral mRNAs. These intriguing concepts lead to the development of various restriction factors [27]. Both dormant and expressive restriction factors were found in humans. Fv1, TRIM5α, RNA silencing and zinc-finger antiviral proteins are few to list [28].

TRIM5α AS A RESTRICTION FACTOR

Fv1 was the first restriction factor identified in 1996 by positional cloning strategy. It was found as a mouse locus, having potential resistance towards Friend Murine Leukemia virus and Murine Leukemia Virus (MLV) [29-32]. Soon after the identification of Fv1, TRIM5α gene was identified as a factor mediating HIV-1 resistance in rhesus macaque lung fibroblasts by cDNA library screening technique [33]. There are several cellular factors that block retroviruses in

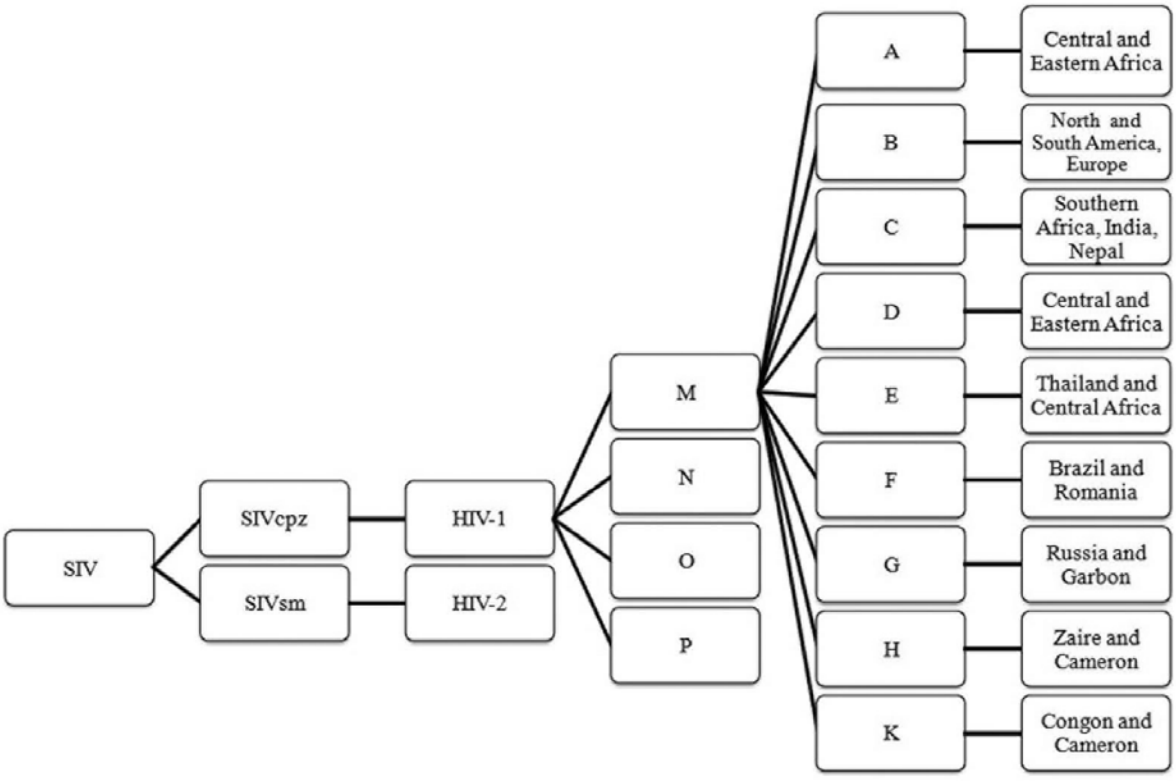

Fig. (2). Hierarchy representing the origin of HIV and its subtypes based on their emergence in different parts of the world. SIV: Simian immunodeficiency Virus, SIVcpz: SIV from chimapanzees, SIVsm: SIV from sooty mangabeys, HIV: Human immunodeficiency virus, M: main or major, N: new and O: outlier sub-group [20, 21].

the primate cells. The Lentivirus susceptibility factor1 (Lv1) and restriction factor1 (Ref1) are such cellular factors that block retroviruses in non-human primate cells and N-MLV in human cells, respectively. During the characterization of Lv1 and Ref1, it was found that TRIM5α is solely responsible for the anti-retroviral activity of Lv1 and Ref1 [29]. Studies had found that it had no homology with Fv1 gene and it belongs to a separate family of proteins known as tripartite motif (TRIM) family [25]. The first structure of TRIM was identified as a Xenopus nuclear factor 7 (XNF7) [34]. Gradually with advancement, various TRIM motifs were identified and their sequences were cloned. The restriction mediated by these factors came into interest when it was found that human cell lines also exhibited resistance towards viruses [35].

STRUCTURE OF TRIM5α

TRIM5α isoform is the largest product amongst the TRIM family and consists of approximately 493 amino acids. It also encompasses B30.2 (SPRY) domain that distinguishes itself from the other isoforms. The TRIM5α gene consists of the N-terminus and the C-terminus. The tripartite motif of TRIM is also known as RBCC domain based on the presence of RING, B-box and Coiled-coil domains (Fig. **3**).

The N-terminus of the gene consists of RING (really interesting new gene) domain, one or two B-boxes and the coiled-coil domain [16, 32]. RING finger proteins are regarded as the most common zinc binding motifs found in eukaryotes [36, 37]. This domain can be found in a large variety of species ranging from yeast to humans; including double strand DNA viruses. RING domain is the cysteine-rich binding domain found to provide E3 ubiquitin ligase activity. It acts as an interaction domain as it plays an important role in enzyme specificity. Ubiquitination is a post-translation modification process that involves modifications of proteins in presence of ubiquitin. It recruits ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2) and ubiquitin ligase (E3) enzyme for the process. E3 enzyme functions as a substrate-recognition molecule and is capable of interacting with both E2 and the substrate. Proteasome enzyme carries out the final degradation process of the ubiquitinated proteins that result in the release of Ubiquitin and the degraded protein. RING proteins are absent in Bacteria and lack of ubiquitination differentiates them from eukaryotes. In the TRIM family, Ubiquitin ligase activity is found in TRIM5δ isoform and several other types of TRIM's such as TRIM18, TRIM32, TRIM63 [25, 32, 37, 38]. Focusing on TRIM5α, poly-ubiquitination and rapid degradation require intact RING and B-box domains; however the rapid formation of the degraded protein does not hinder the antiretroviral activity. Members of TRIM family are targets for specific regulators or adopters in the ubiquitin-dependent protein degradation pathway [39-41]. The B-box domain consisting of the B1 and B2 boxes is known as the interaction domain. The boxes determine the RING-Box ubiquitin ligase substrate specificity. The two B-boxes differ from each other in both number and spacing of conserved cysteine and histidine residues. B1 always precedes B2. The key determinant of TRIM family proteins is the presence of B2 domain [42]. The coiled-coil domain is a hyper-secondary structure formed by twining of multiple α-helices. It is responsible to cause homo and heterodimerization of TRIM proteins and is required for assembling them [43].

The C-terminus of the gene consists of the B30.2 domain, which is involved in binding of protein to the capsid molecule of the incoming retrovirus and controls further replication. The presence of B30.2 domain in TRIM5α imparts specificity to the protein which is absent in other shorter counterparts (TRIM5γ and TRIM5δ). These shorter isoforms act as negative dominants and inhibit restriction when over-expressed [32, 37, 38, 43]. Variation in sequence of PRY/SPRY domain can determine the specificity of TRIM5α to a particular species, and the difference in the sequence of amino acids in the viral capsid protein can determine the viral sensitivity to restriction [44]. Subsequent cloning of TRIM5α from a variety of species led to the finding that species variation in TRIM5α sequence (specific in B30.2 domain) was the reason for species-specific retro-viral restriction and tropism, discussed in later paragraphs.

SPECIFICITY

Interestingly, species-specific investigation of TRIM led to the finding that variation in the sequence of B30.2 domain at the C-terminal end of RBCC, attributed to its species

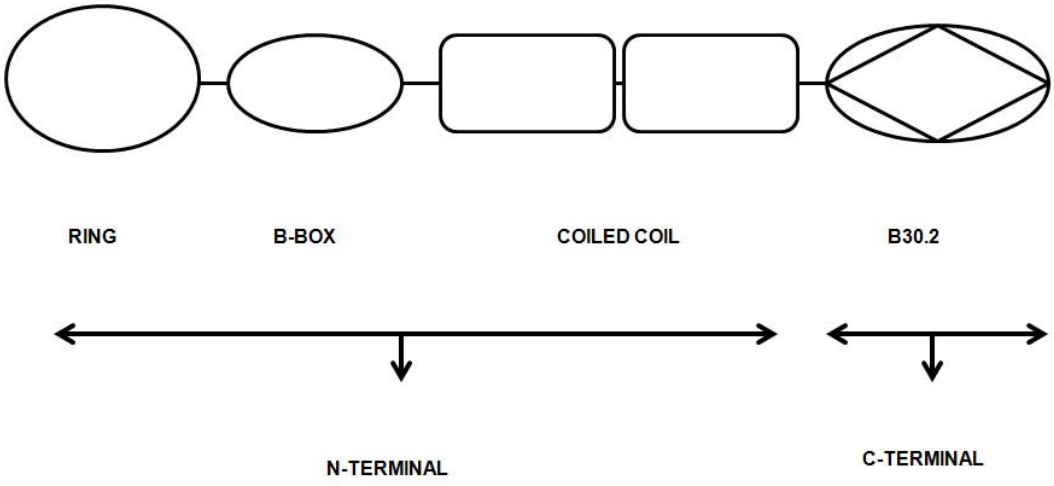

Fig. (3). Structure of TRIM5α.

specificity and tissue tropism. These findings were confirmed further by investigating restriction activity of TRIM5γ isoform (which lacks B30.2 domain) against HIV-1 and SIV. Absence of B30.2 domain was found to be the major factor, hindering anti-HIV-1 and anti-SIV activities [45, 46]. Studies on human and rhesus (Rh) recombinant TRIM5α have also revealed that the major determinant of species-specific restriction against HIV-1 resides in the variable regions of the PRY/SPRY domain. It was found that old world primates exhibit variation specifically in the V_1 (variable) region. A single amino acid change from Arginine (R) to Proline (P) at position 332 on the V_1 site of the human TRIM5α (R332P) can induce strong restriction ability against HIV-1 and SIVmac (SIV of rhesus macaques). Cell culture assays suggested that human TRIM5 alleles had the ability to block the infectivity of SIVsm strains but not of the SIVmac strains [47]. In case of HIV-2 infection, three amino-acid residues Threonine, Phenylalanine and Proline (TFP) at positions 339-341 of Rh-TRIM5α (V_1) were essential to confer restriction against HIV-2 strains. Restriction towards N-MLV by human TRIM5α was conferred by the presence of amino acid residues at positions 409 and 410 in the variable region 3 (V_3) of the PRY-SPRY domain [43, 48, 49]. Studies have suggested that all three variable regions of B30.2 domain of TRIM5α contribute to the specificity of retroviral restriction. Amplification of axon 8 of TRIM5α gene from 12 different primate species and its fusion with RBCC domain of human TRIM5α resulted in chimeras which were checked for restriction against several retroviruses. The restriction pattern of the resulting chimeras has given significant evidence to identify compounds that can bind to specific variable region on B30.2 domain and eventually retarget human TRIM5α to recognize HIV-1[2].

RELATION OF TRIM WITH CYCLOPHILIN

Retrotransposition in the sequence of TRIM5α protein caused expression of the inserted sequence. Widely accepted model of retrotransposition is the TRIMCyp A isoform model. Retrotransposition of Cyclophilin (Cyp A) into the TRIM5α gene sequence resulted in the expression of TRIMCyp A isoform as a consequence of replacement of the B30.2 domain with the Cyp A sequence [38, 50, 51]. Hence, the specificity after the insertion of Cyp A was targeted on the TRIMCyp A domain, instead of the B30.2 domain. This phenomenon highlights the fact that B30.2 domain is the primary determinant, conferring specificity towards retroviral restriction. The activity of TRIMCyp A varies from species to species due to its independent development. In case of *Aotus* (New World Monkeys), TRIMCyp A restricts Human Immunodeficiency Virus (HIV-1) and Feline Immunodeficiency Virus (FIV) [52,53] while in case of *Macaca macaques* (Old World Monkeys), genetic changes caused due to the insertion of Cyp A had resulted in expression of TRIMCyp A but not TRIM5α. Few reports indicate that Old World Monkeys (*Macaca nemestrina*) do not express TRIM5α; instead they transcribe novel isoforms of TRIM5θ and TRIM5η. These isoforms are formed due to single nucleotide polymorphism (SNP) and alternate splicing of the introns and axons [54]. TRIMCyp A exhibits more potent restriction to incoming retrovirus because of its association with Cyp A, which differentiates it from TRIM5α [52, 55]. The potent activity of TRIMCyp A was observed in different species and it was found that retrotransposition caused restriction of both HIV-1 and SIVmac in Spider monkeys while it only restricted the former in Owl monkeys. As rhTRIM5α restricts HIV-1 in rhesus macaques; it is the TRIMCyp A that restricts HIV-1 in the Owl monkeys. It has been suggested that Cyp A improves the anti-viral activity of TRIM5α but is not merely responsible for anti-viral activity [56]. Changes in the amino-acid residues of the Cyp A can alter the conformation or orientation of the distal CypA-binding loop. TRIM-Cyp A retrotransposition in a way can disrupt the activity of TRIM5α. Changes in the Valine86 and Histidine87 residues can alter the conformation of TRIM-CypA binding eventually disrupting the assembly of TRIM5α dimers [57].

MECHANISM OF TRIM5α

Plethora of research done on TRIM5α has suggested that its presence is not the sole factor responsible for restriction. Intermolecular association of the structural domains, formation of dimers and presence of clustered amino acids on the SPRY domain and their replacement in different species, presence or absence of proteosome activity and anti-TRIM mechanism developed in the viruses to inhibit the restriction activity are the factors that have equal importance in determining the anti-retroviral activity [57-59].

Several initial studies have reported that TRIM5α acts at initial stages of retroviral replication; viral capsid uncoating and further restricting formation of reverse transcription products (Fig. **4**) [58, 60]. Recent research in presence of proteosome inhibitors has observed that reverse transcription was restricted in presence of proteosome inhibitors but, there was no alteration in the restriction activity of TRIM5α [61, 62]. Thereafter, scientist found that TRIM5α has several restriction mechanisms. Despite the formation of pre-integration complexes in presence of proteosome inhibitors, it (TRIM5α) was able to restrict the infection. The mechanism behind proteosome independent degradation was speculated to be the presence of E3 ubiquitin ligase activity within TRIM5α, which mediated restriction by inducing proteosomal degradation of the viral cores. The question that aroused was; if reverse transcribed viral cDNA rescued restriction caused by TRIM5α then what was the reason behind their inability to integrate into the chromosomal DNA. It was found that nucleoprotein complexes involved in the reverse transcription of viral cDNA are inherently defective for integration or these complexes had failed to find their chromosomal targets because of their contact with TRIM5α [63]. Hence, it can be inferred that TRIM5α exhibits two-phase mechanism of restriction: first binding to the viral capsid cores and then targeting these cores for proteosomal degradation eventually impairing the accumulation of reverse transcription products. Inhibition of proteosome can lead to formation of reverse transcription products but does not impair the TRIM5α mediated restriction. Cytoplasmic assembling of TRIM5α mediates sequestering of viral cores into these bodies before undergoing proteasomal destruction by the inhibitors. Hence, it can also be inferred that cytoplasmic sequestering of the viral cores by TRIM5α prevents the viral cDNA from intergrating into the nucleus and further integration into the host chromosomal DNA [61-65]. *In vitro* studies have also

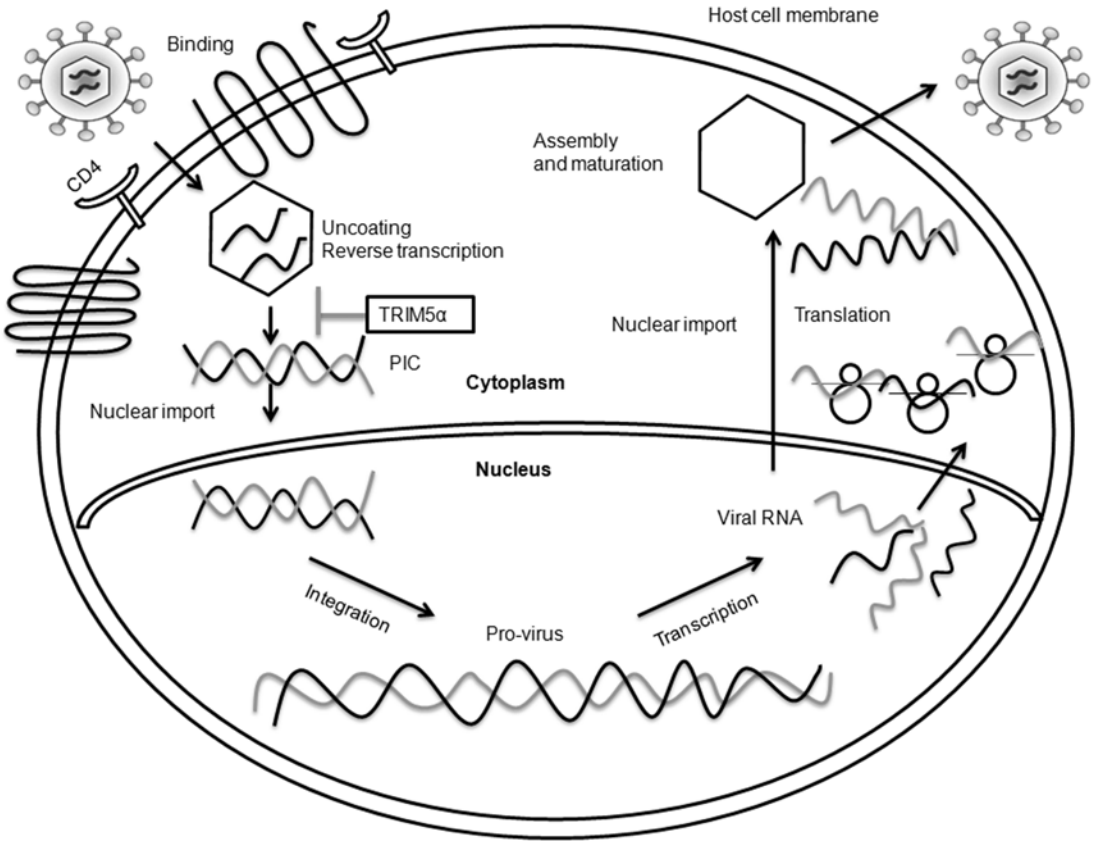

Fig. (4). Tripartite motif (TRIM5α) proteins interfering at initial stages of retroviral replication. Schematic representation of life-cycle of retroviruses and mechanism of TRIM5α acting on initial stage of replication of retrovirus. PIC, Pre-integration complex [25].

revealed that TRIM5α can recognize capsid proteins that have larger viral core, not those that are free capsid proteins. It signifies that viral assembly along with intermolecular association of TRIM5α is an important factor influencing restriction [65]. Additionally, innate immunity exhibited by TRIM5α restriction factor has been recognized as a sensor in the form of pattern recognition receptor that recognizes the pattern of infection caused by the pathogen; referred to as pathogen-associated molecular patterns (PAMP) [66].

SPECIES-SPECIFIC RESTRICTION OF TRIM5α AND ITS ROLE IN CROSS-SPECIES TRANSMISSION

Several hypotheses have been proposed suggesting species-specificity conferred by TRIM5α. Red queen hypothesis and sequential analysis of TRIM5α are the most evident studies, suggesting the role of cross-species transmission of viruses in imparting species-specific restriction to TRIM5α. Red queen hypothesis describes the antagonizing effect developed during the evolution of viruses [67, 68]. Antagonizing effect was observed as a result of replacement of amino acids at the interaction domain (positive selection) of TRIM5α. Sequential analysis of TRIM5α has revealed the importance of 13 amino acids patch in the SPRY domain which offers positive selection of the residues [69]. The ratio of non-synonymous (dN) and synonymous (dS) changes per site along different branches suggested that TRIM5α has been subject to positive selection for at least 133 million years [70]. This supports positive Darwinian selection which describes the presence of selective pressure, favouring change. High dN/dS ratio of SPRY domain when compared to other domains revealed that it had undergone the most intense positive selection. As shown in Fig. (**5**), change in the amino acids at 334 site of SPRY domain and increase in dN/dS ratio can reveal that TRIM5α had evolved during past several years and is undergoing selective pressure to exert its retroviral restriction activity.

Hence, it can be inferred that with gradual evolution, humans have developed several innate mechanisms to defend themselves but, viruses in turn, have also found ways to counteract these restriction factors. However, before the virus infects a new species it has to overcome several hurdles for its survival. Proteomic studies have also suggested that during the process of cross-species transmission drastic amino acid substitutions have occurred in the protein matrix of the virus due to occurrence of strong host-specific selection pressures. These substitutions have made the virus resistant to restriction exhibited by the restriction factors. It was found that Gag-30 in the viral protein matrix of SIVcpz and SIVgor was encoded by Met, which was replaced by Arg in HIV groups of M, N and O. Arg or Lys were further conserved in the strains of HIV-1 [21]. The interchange in the amino acids has been confirmed by reciprocal-transmission studies which involved conversion of Arg to Met in Chimpanzees and increased efficiency in replication of virus in Chimpanzees due to the presence of Met at the

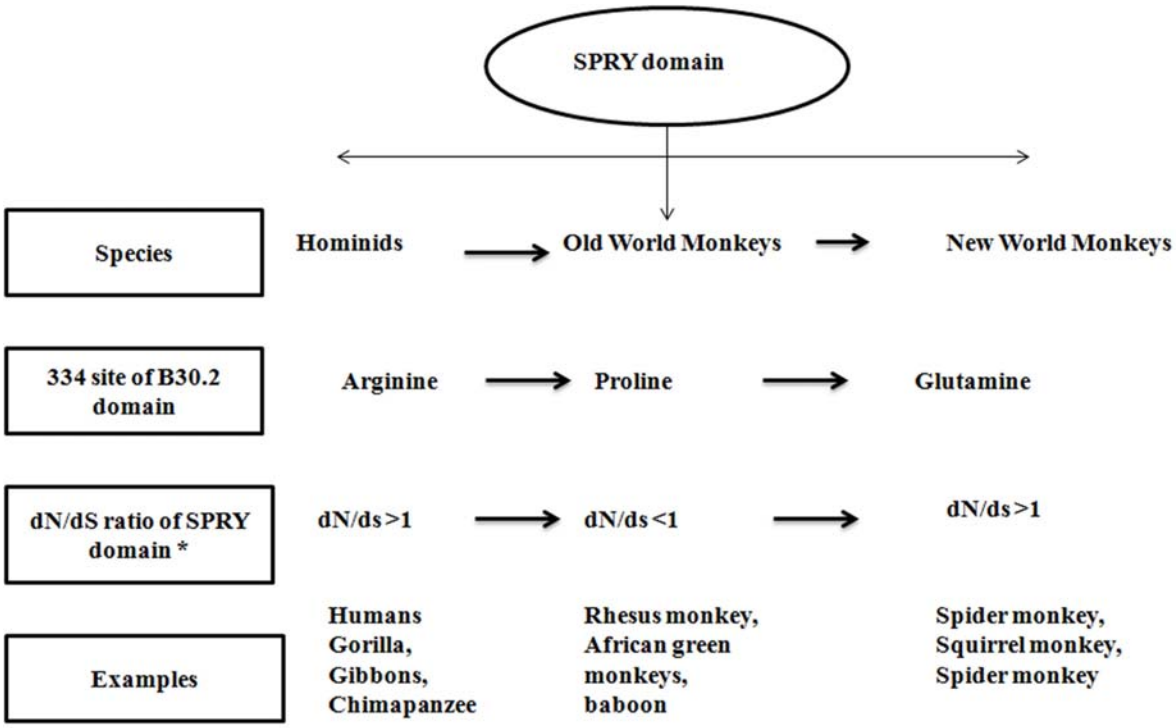

Fig. (5). Species-specific restriction of TRIM5α and its role in cross-species transmission. The figure represents the pattern of change in the amino acids at 334 site of the interaction domain (B30.2 domain) and the dN/dS ratio of the SPRY domain, describing their role in species specificity and cross-species transmission [69, 70]. *dN/dS ratio of SPRY domain indicated is not species-specific.

position 30 [71]. Plethora of research is being done to trace the polymorphisms occurring in the sequence of TRIM5α so that change in the particular amino acid sequence can eventually retarget it to exert restriction against viruses in humans.

CONCLUSION

The daunting spread of HIV and the uncertain prospects of development of an effective vaccine will sustain to pose threat for decades to come. In such a scenario, the study of factors helping to fight against the replication of virus will not only lead to the development of species-targeted drugs but also help to prevent further transmission. Successive generations of Lentiviruses (SIV and HIV) have transformed them from non-pathogenic to pathogenic through the process cross-species transmission. This transmission has not only made the viruses more competent but also has made the cure complex. Tracing the host-specific selection pressures and changes at particular amino-acid sequence provides a scope to restrict the rapid transmission of virus. As several studies have been done to evaluate the adaptations occurring in HIV to counteract the restriction conditions provided by the host; co-relating these studies with the spread of HIV and species-specific change in the amino-acid sequences in restriction factors will be challenging task to combat against the deadly virus. For example, Tetherin being a restriction factor has been widely studied to possess restriction activity by inhibiting budding and release of virions from infected cells. Studies have identified anti-tetherin responses emerging in the virus as a consequence of host-selection pressure. SIVs utilize *Nef* proteins to withdraw Tetherin from cell surface by targeting at its cytoplasmic domain; HIV-1 and SIVs from Dent's monkeys use *Vpu* protein to inhibit Tetherin to bind to its membrane-spanning domain [21]. Further studies identifying such anti-response mechanisms towards TRIM5α will help to identify the key reason behind its inactivity in humans. Hence, evaluating the broad-spectrum of mechanism(s) exhibited by restriction factors will help to predetermine the future risks of zoonotic infections. Additionally, high selection pressure according to positive Darwinian selection has revealed that with increasing evolution, humans are going to face more pressure in developing endogenous defence strategies. Investigation of compounds that can bind to the variable region and retargeting human TRIM5α to recognize HIV-1 can be a milestone in AIDS research. Deeper understanding of restriction factors in different primate species can help to develop a vaccine for AIDS. Surprisingly, the current global AIDS report released by UNAIDS revealed, more than 50% decrease in the incidence of AIDS in India and other Asian countries. Comparing the polymorphism in the variable regions of restriction factors in Asian countries with other countries may discover some hidden facts. Finally, the discovery of restriction factors has eventually paved the path to understand the evolution pattern of AIDS.

LIST OF ABBREVIATIONS

AIDS = Acquired Immunodeficiency Syndrome

HIV = Human Immunodeficiency Virus

TRIM5α = Tripartite Motif Protein Isoform 5 Alpha

APOBEC = Apolipoprotein B mRNA Editing Enzyme, Catalytic Polypeptide-Like

Fv1 = Friend-Virus-Susceptibility Factor 1

SIV = Simian Immunodeficiency Virus

MLV = Murine Leukemia Viruses

Ref1 = Restriction Factor1

XNF7 = Xenopus Nuclear Factor 7

RING = Really Interesting New Gene

FIV = Feline Immunodeficiency Virus

Cyp A = Cyclophilin A

SNP = Single Nucleotide Polymorphism

PIC = Pre-Integration Complex

FRET = Fluorescence Resonance Energy Transfer

INF = Interferon

CONFLICT OF INTEREST

The author(s) declare that they have no conflict of interest.

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PATIENT CONSENT

Declared none.

HUMAN/ANIMAL RIGHTS

Declared none.

REFERENCES

[1] http://www.unaids.org, Accessed on 4 March 2013.
[2] Wessner DR. The Origin of Viruses. Nature Education 2010; 3: 37.
[3] Okhura S, Yap MW, Sheldon T, Stoye JP. All three variable regions of the TRIM5α B30.2 domain can contribute to specificity of retrovirus restriction. J Virol 2010; 80: 8554-65.
[4] Chatterji U, Bodardt MD, Gaskill P, Sheeter D, Fox H, Gallay PA. TRIM5alpha accelerates degradation of cytosolic capsid associated with productive HIV-1 entry. J Biol Chem 2006; 28: 37025-33.
[5] Sawyer EL, Wu LI, Akey JM, Emerman M, Malik HS. High-frequency persistence of an impaired allele of the retroviral defence gene TRIM5alpha in humans. Curr Biol 2006; 16: 95-100.
[6] Johnson WE, Sawyer SL. Molecular evolution of the antiretroviral TRIM5 gene. Immunogenetics 2009; 61: 163-76.
[7] Emiliani C. Extinction and Viruses. Biosystems 1993; 31: 155-9
[8] Longo D, Fauci A, Kasper D, Hauser S, Jameson J, Loscalzo J. Harrison Principles of Modern Medicine. McGraw-Hill, Singapore 2011.
[9] Coffin JM, Hughes SH, Varmus HE. Retroviruses. Cold Spring Harbor. New York 1997.
[10] Katz RA, Greger JG, Skalka AM. Effects of cell cycle on early events in retroviral replication. J Cell Biochem 2006; 94: 880-9.
[11] Brunton LL, Lazo JS, Parker KL. Goodman and Gilman's The Pharmacological Basis of Therapeutics. Mac-Graw-Hill, United States 2006.
[12] Blankson JN, Persaud D, Siliciano RF. The challenge of viral reservoirs in HIV-1 infection. Ann Rev Med 2002; 53: 557-93.
[13] Dimmock NJ, Easton AJ, Leppord KN. Introduction to Modern Virology. Blackwell, USA 2007.
[14] Jarrett OH. Retroviruses. Arch Dis Child 1987; 62: 628-30.
[15] Bieniasz PD. Restriction factors: A defence against retroviral infection. Trends Microbiol 2003; 11: 286-91.
[16] Hatziioannou T, Beiniasz PD. Antiretroviral Restriction Factors. Curr Opin Virol 2011; 1: 526-532.
[17] Sorin M, Kalpana GV. HIV-1 Dynamics in the host cell: A review of Viral and Host protein Interactions and Potential Therapeutic Targets for HIV-1 Infection. Einstein J of Biol Med 2006; 22: 10-24.
[18] Sedwick C. Trimming SIV Transmission between Species. PLoS Biol 2008; 8: e1000463.
[19] Locatelli S, Peeters M. Cross-species transmission of Simian retroviruses: how and why they could lead to the emergence of new diseases in human population. AIDS 2012; 26: 659-73.
[20] Stansell E, Canis K, Haslam S, Dell A, Desrosiers RC. Simian Immunodeficiency Virus from the Sooty Mangabey and Rhesus Macaque Is Modified with O-Linked Carbohydrate. J Virol 2011; 85: 582-95.
[21] Sharp PM, Hahn BH. Origins of HIV and the AIDS pandemic. Cold Spring Harbor, New York 2011.
[22] Santiago ML, Rodenburg CM, Kamenya S, *et al*. SIVcpz in wild chimpanzees. Science 2001; 295-465
[23] Johnson WE, Sawyer SL. Molecular evolution of the antiretroviral TRIM5 gene. Immmunogenetics 2009; 61: 163-76.
[24] Wolf D, Goff SP. Host restriction factors blocking retroviral replication. Annu Rev Genet 2008; 42: 143-63.
[25] Nisole S, Stoye JP, Saib A. TRIM family proteins: Retroviral restriction and antiviral defence. Nat Rev Microbiol 2005; 3: 799-808.
[26] Huthoff H, Towers GJ. Restriction of retroviral replication by APOBEC3G/F and TRIM5α. Trends Microbiol 2008; 16: 612-9.
[27] Neil SJ, Eastman SW, Jouvenet N, Bieniasz PD. HIV-1 Vpu promotes release and prevents endocytosis of nascent retrovirus particles from the plasma membrane. PLoS Pathog 2006; 2: e39.
[28] Gao G, Guo X, Goff SP. Inhibition of RNA production by ZAP, a CCCH-type zinc finger protein. Science 2002; 297: 1703-6.
[29] Hatziioannou T, Perez-Caballero D, Yang A, Cowan S, Bieniasz PD. Retrovirus resistance factors Ref1 and Lv1 are species-species variants of TRIM5α. Proc Natl Acad Sci USA 2004; 101: 10774-9.
[30] Best S, Le Tissier P, Towers G, Stoye JP. Positional cloning of the mouse retrovirus restriction gene Fv1. Nature 1996; 382: 826-9.
[31] Pincus T, Hartley JW, Rowe WP. A major genetic locus affecting resistance to infection with murine leukemia viruses. IV. Dose-relationships in Fv-1 sensitive and resistance cell cultures. Virology 1975; 65: 333-42.
[32] Stremlau M, Perron M, Welikala S, Sodroski J. Species-Specific variation in the B30.2 (SPRY) domain of TRIM5-Determines the potency of human immunodeficiency virus restriction. J Virol 2005; 79: 3139-45.
[33] Stremlau M, Owens CM, Perron MJ, Kiessling M, Autissier P, Sodroski J. The cytoplasmic body component TRIM5alpha restricts HIV-1 infection in Old World monkeys. Nature 2004; 427: 848-53.
[34] Reddy BA, Kloc M, Etkin L. The cloning and characterization of a maternally expressed novel zinc finger nuclear phosphoprotein (xnf7) in Xenopus laevis. Dev Biol 1991; 148: 107-16.
[35] Towers G, Bock M, Martin S, Takeuchi Y, Stoye JP, Danos O. A conserved mechanism of retrovirus restriction in mammals. Proc Natl Acad Sci USA 2000; 97: 12295- 9.
[36] Saurin AJ, Borden KL, Boddy MN, Freemont PS. Does this have a familiar RING? Trends Biochem Sci 1996; 21: 208-14.
[37] Freemont PS. RING for destruction? Curr Biol 2000; 10: R84-7.
[38] Sokolskaja E, Berthoux L, Luban J. Cyclophilin A and TRIM5α Independently Regulate Human Immunodeficiency Virus Type 1 infectivity in Human Cells. J Virol 2006; 80: 2855-62.
[39] Sebastian S, Luban J. TRIM5alpha selectively binds a restriction-sensitive retroviral capsid. Retrovirology 2005; 2: 40.
[40] Diaz-Griffero F, Li X, Javanbakht H, *et al*. Rapid turnover and polyubiquitylation of the retroviral restriction factor TRIM5. Virology 2006; 349: 300-15.
[41] Asaoka K, Ikeda K, Hishinuma T, Horie-Inoue K, Takeda S, Inoue S. A retrovirus restriction factor TRIM5a is transcriptionally regulated by interferons. Biochem Biophys Res Commun 2005; 338: 1950-6.
[42] Borden KL, Lally JM, Martin SR, O'Reilly NJ, Solomon E, Freemont PS. *In vivo* and *In vitro* characterization of the B1 and B2

zinc-binding domains from the acute promyelocytic leukemia protooncoprotein PML. Proc Natl Acad Sci USA 1995; 93: 1601-6.
[43] Reymond A, Meroni G, Fantozzi A, *et al*. The tripartite motif family indentifies cell compartments. EMBO J 2004; 20: 2140-51.
[44] Nakayama EE, Shioda T. TRIM5α and species tropism of HIV/SIV. Front Microbiol 2012; 3: 13.
[45] Sawyer SL, Wu LI, Emerman M, Malik HS. Positive selection of primate TRIM5alpha identifies a critical species-species retroviral restriction domain. Proc Natl Acad Sci USA 2005; 102: 2832-7.
[46] Yap MW, Nisole S, Stoye JP. A single amino acid change in the SPRY domain of human TRIM5α leads to HIV-1 restriction. Curr Biol 2005; 15: 73-8.
[47] Maillard P, Ecco G, Ortiz M, Trono D. The specificity of TRIM5α-mediated restriction is influenced by its coiled-coil domain. J Virol 2012; 84: 5709-801.
[48] Kono K, Song H, Shingai Y, Shioda T, Nakayama EE. Comparison of anti-viral activity of rhesus monkey and cynomolgus monkey TRIM5apha against human immunodeficiency virus type 2 infection. Virology 2008; 373: 447-56.
[49] Perron MJ, Stremlau M, Song B, Ulm W, Mulligan RC, Sodroski J. TRIM5alpha mediates the postentry block to N-tropic murine leukemia viruses in human cells. Proc Natl Acad Sci USA 2004; 101: 11827-32.
[50] Dietrich E, Brennan G, Ferguson B, Wiseman RW, O'Connor D, Hu SL.Variable Prevalance and Functional Diversity of the Antiretroviral Restriction Factor TRIMCyp in *Macaca fascicularis*. J Virol 2011; 85: 9956-63.
[51] Berube J, Bouchard A, Berthoux L. Both TRIM5α and TRIMCyp have only week antiviral activity in canine D17 cells. Retrovirology 2007; 4: 68.
[52] Brennan G, Kozyrev Y, Hu SL. TRIMCyp expression in Old World primates Macaca nemestrina and *Macaca fascicularis*. Proc Natl Acad Sci USA 2008; 105: 3569-74.
[53] Saito A, Kawamoto Y, Higashino A, *et al*. Allele frequency of antiretroviral host factor TRIMCyp in wild-caught cynomolgus macaques (*Macaca fascicularis)*. Front Microbiol 2012; 3: 314.
[54] Brennan G, Kozyrev Y, Kodama T, Hu SL. Novel TRIM5 isoforms expressed by Macaca nemestrina. J Virol 2007; 81: 12210-7.
[55] Nisole S, Lynch C, Stoye JP, Yap MW. A TRIM5-cyclophilin A fusion protein found in owl monkey kidney cells can restrict HIV-1. Proc Natl Acad Sci USA 2004. 101: 13324-28.
[56] Stremlau M, Song B, Javanbakht H, Perron M, Sodroski J. Cyclophilin A: An auxiliary but not necessary cofactor for TRIM5α restriction of HIV-1. Virology 2006; 351: 112-20.
[57] Pacheco B, Finzi A, Stremlau M, Sodroski J. Adaptation of HIV-1 to cells expressing rhesus monkey TRIM5α. Virology 2010; 408: 204-12.
[58] Strebel K, Luban J, Jeang KT. Human cellular restriction factors that target HIV-1 replication. BMC Med 2009; 7: 48.
[59] Sebastian S, Grutter C, de Castillia CS, *et al*. An invariant surface patch on the TRIM5alpha PRYSPRY domain is required for retroviral restriction but dispensable for capsid binding. J Virol 2009; 83: 3365-73.
[60] Stremlau M, Perron M, Lee M, *et al*. Specific recognition and accelerated uncoating of retroviral capsids by the TRIM5α restriction factor. Proc Natl Acad Sci USA 2006; 103: 5514-9.
[61] Sastri J, Campbell EM. Recent Insights into the mechanism and consequences of TRIM5α retroviral restriction. AIDS Res Hum Retroviruses 2011; 27: 231-8.
[62] Salomons FA, Acs K, Dantuma NP. Illuminating the ubiquitin/proteosome system. Exp Cell Res 2010; 316: 1289-95.
[63] Anderson JL, Campbell EM, Wu X, *et al*. Proteasome inhibition reveals that a function preintegration complex intermediate can be generated during restriction by diverse TRIM5α proteins. J Virol 2006; 80: 9754-60.
[64] Campbell EM, Perez O, Anderson JL, Hope TJ. Visualization of a proteosome independent intermediate during restriction of HIV-1 by rhesus TRIM5α. J Cell Biol 2008; 180: 549-61.
[65] Yamauchi K, Wada K, Tanji K, Tanaka M, Kamitani T. Ubiquitination of E3 ubiquitin ligase TRIM5alpha and its potential role. FEBS J 2008; 275: 1540-55.
[66] Kawai T, Akira S. Regulation of innate immune signaling pathways by the tripartite motif (TRIM) family proteins. EMBO Mol Med 2001; 3: 513-27.
[67] Rold CJ, Aiken C. Proteasomal degradation of TRIM5alpha during retrovirus restriction. PLoS Pathog 2008; 4: e1000074.
[68] Towers GJ. The control of viral infection by tripartite motif proteins and cyclophilin A. Retrovirology 2007; 4: 40.
[69] Liu HL, Wang YQ, Liao CH, Kuang YQ, Zheng YT, Su B. Adaptive evolution of primate TRIM5aplha, a gene restricting HIV-1 infection. Gene 2005; 362: 109-16.
[70] Sawyer SL, Wu LI, Emerman M, Malik HS. Positive selection of primate TRIM5alpha identifies a critical species-specific retroviral restriction domain. Proc Natl Acad Sci USA 2005; 102: 2832-7.
[71] Mwaengo DM, Novembre FJ. Molecular cloning and characterization of viruses isolated from chimpanzees with pathogenic human immunodeficiency virus type 1 infection. J Virol 1998; 72: 8976-87.

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