

Review

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Intracellular immunity to HIV-1: newly defined retroviral battles inside infected cells

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Abstract

Studies of the human immunodeficiency virus type 1 (HIV-1) continue to enrich eukaryotic biology and immunology. Recent advances have defined factors that function after viral entry and prevent the replication of proviruses in the infected cell. Some of these attack directly viral structures whereas others edit viral genetic material during reverse transcription. Together, they provide strong and immediate intracellular immunity against incoming pathogens. These processes also offer a tantalizing glimpse at basic cellular mechanisms that might restrict the movement of mobile genetic elements and protect the genome.

Background

Although it is highly pathogenic in humans, HIV-1 cannot replicate in most other species [1]. This tropism is determined primarily by whether host cells express the required cofactors. For example, by lacking a functional receptor and appropriate transcriptional machinery, mouse cells do not support infection by HIV-1. Thus, the organism resists the pathogen via a cell-based incompatibility. However, a pathogen can also be restricted by the presence of dominant inhibitory factors. They attack the incoming virus directly and block its integration into the host genome. This situation also pertains to HIV-1 in mouse cells and represents true "intracellular immunity." Importantly, this host response is more rapid than either traditional innate or adaptive immunity and can prevent the establishment of the infection.

Recent advances in our understanding of intracellular immunity have identified two different proteins, the tripartite motif protein 5 α (TRIM5 α) [2] and the apolipoprotein B mRNA-editing enzyme catalytic-polypeptides

3B, 3F and 3G (APOBEC3B, APOBEC3F and APOBEC3G or A3B, A3F and A3G), which collectively inactivate several retroviruses including HIV-1, simian immunodeficiency virus (SIV), hepatitis B virus and some mouse mobile genetic elements [3-7]. This review highlights these recent developments and mentions briefly additional potential blocks to retroviral replication.

Interference and Restriction

Let us begin with some definitions and historical perspectives. Viral "interference" refers to the situation when cells, which are chronically infected with one virus or contain endogenous retroviruses, resist superinfection by other viruses bearing envelopes with a similar target specificity. This block usually results from the loss of the appropriate receptor on the cell surface. A good example of this interference is the Friend virus susceptibility factor 4 (Fv4), also known as Akvr-1, which controls the susceptibility of mice to infection by ecotropic but not other murine leukemia viruses (MLVs) [8]. This gene is located on mouse chromosome 12 [9] within an endogenous defective

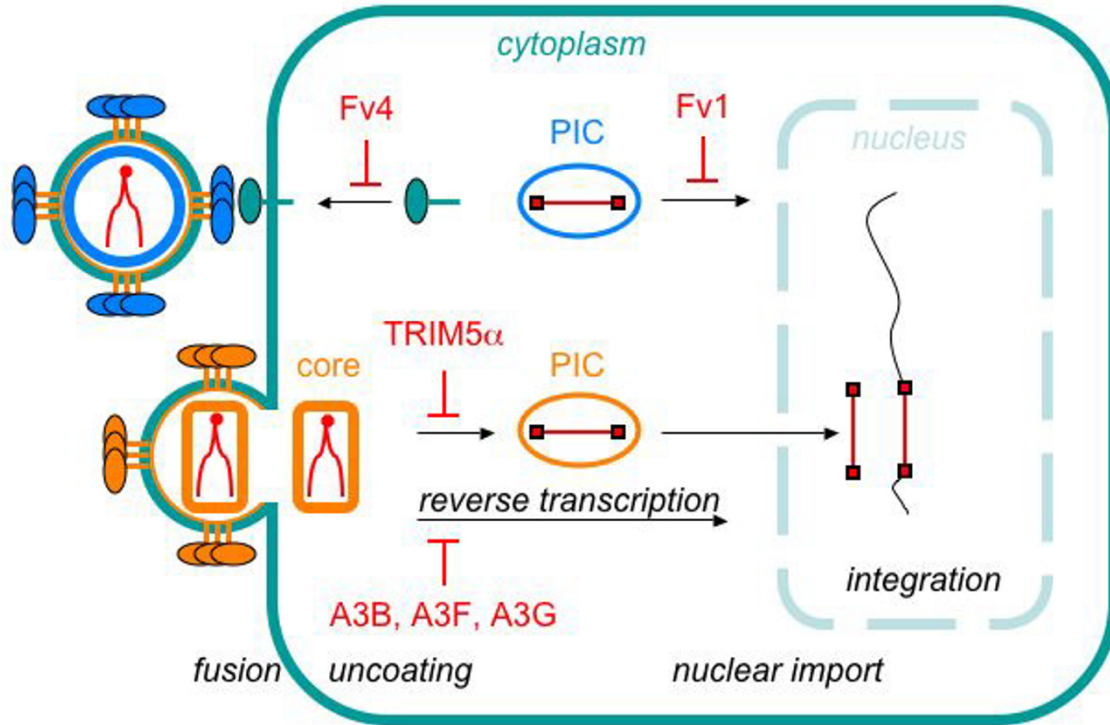


Figure 1

Effective intracellular immunity targets incoming viruses. Whereas the ecotropic murine leukemia virus (MLV) (represented as a viral particle in blue) encounters Fv4 and Fv1 blocks, other retroviruses such as HIV-1, SIV and EIAV (represented as a viral particle in brown) encounter TRIM5 α and cytidine deaminase blocks. Fv4 prevents the entry by ecotropic MLV by sequestering the viral receptor from the cell surface. Fv1 targets MLV CA and stops the nuclear import of the viral preintegration complex (PIC). TRIM5 α also targets retroviral CA and blocks uncoating. hA3B, hA3F and hA3G deaminate cytidines on newly synthesized retroviral cDNA and disrupt viral replication. Capital red letters highlight the points of inhibition. Viral structural components, nucleic acids, RNA and DNA, and intracellular events are represented in different colors.

provirus and encodes a complete envelope [10] that shares very high sequence similarity with those from ecotropic Cas-Br-E virus and Moloney MLV [11]. This envelope then blocks the expression of the cationic amino acid transporter, which is the receptor for these MLVs, on the cell surface (Fig. 1) [12]. Of interest, MLV can only use the murine but not the human form of this receptor for entry.

The term "restriction" refers to intracellular blocks to viral replication. Until now, the best example has been Fv1 [13]. Like Fv4 and the less well-characterized Fv3 and Fv2,

Fv1 also confers resistance of mice to the infection by MLV (Figs. 1 and 2). The Fv1 gene is located on mouse chromosome 4 [14] and encodes a protein that resembles other endogenous retroviral structural group specific antigens (Gag) (Fig. 2) [15]. Of note, during the morphogenesis and release of progeny virions, retroviral Gag polyproteins are processed by the viral protease into distinct subunits, namely matrix (MA), capsid (CA) and nucleocapsid (NC). Whereas MA and CA form the outer shell and inner core of mature viral particles, NC packages viral genomic RNA into the core [16]. After entry and uncoating in newly

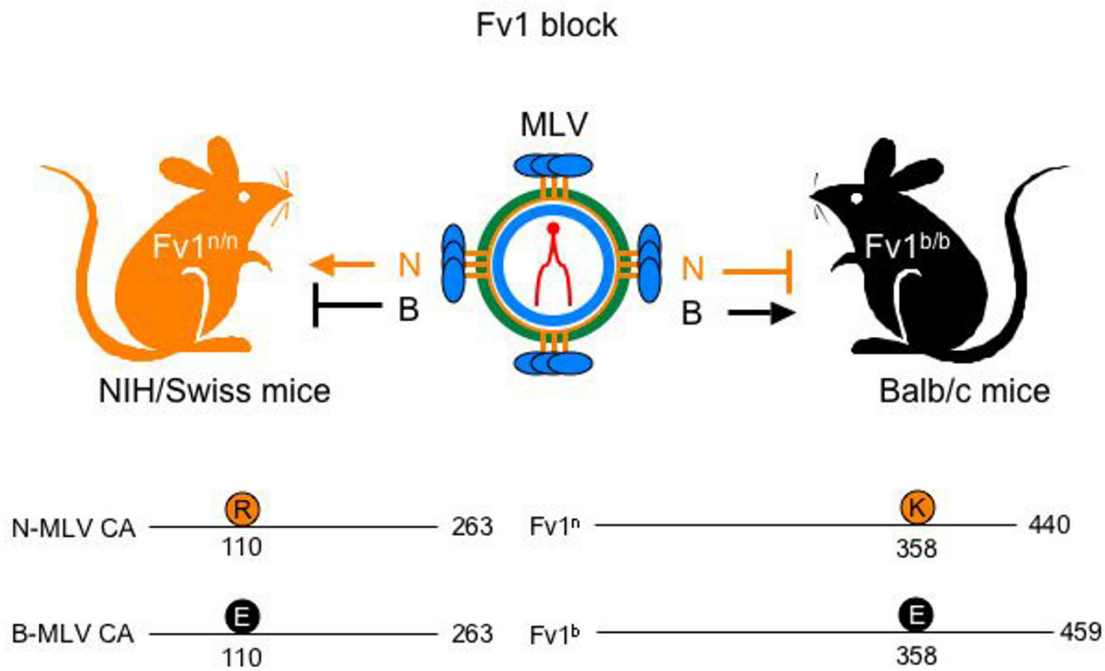


Figure 2

Fv1 block in MLV infection. Ecotropic MLVs (e.g. Friend MLV) fall into two categories with respect to their host range: N-tropic strains infect NIH/Swiss mice (brown) much more efficiently than BALB/c mice (black), whereas B-tropic strains display the opposite preference. Based on their susceptibility to N- or B-tropic virus, mice were classified into Fv1^{n/n} (NIH/Swiss) and Fv1^{b/b} (Balb/c) strains. These viruses differ at a single residue at position 110 in CA (presented below the NIH/Swiss mouse). These changes are matched by residues at position 358 in Fv1ⁿ and Fv1^b proteins (presented below the Balb/c mouse).

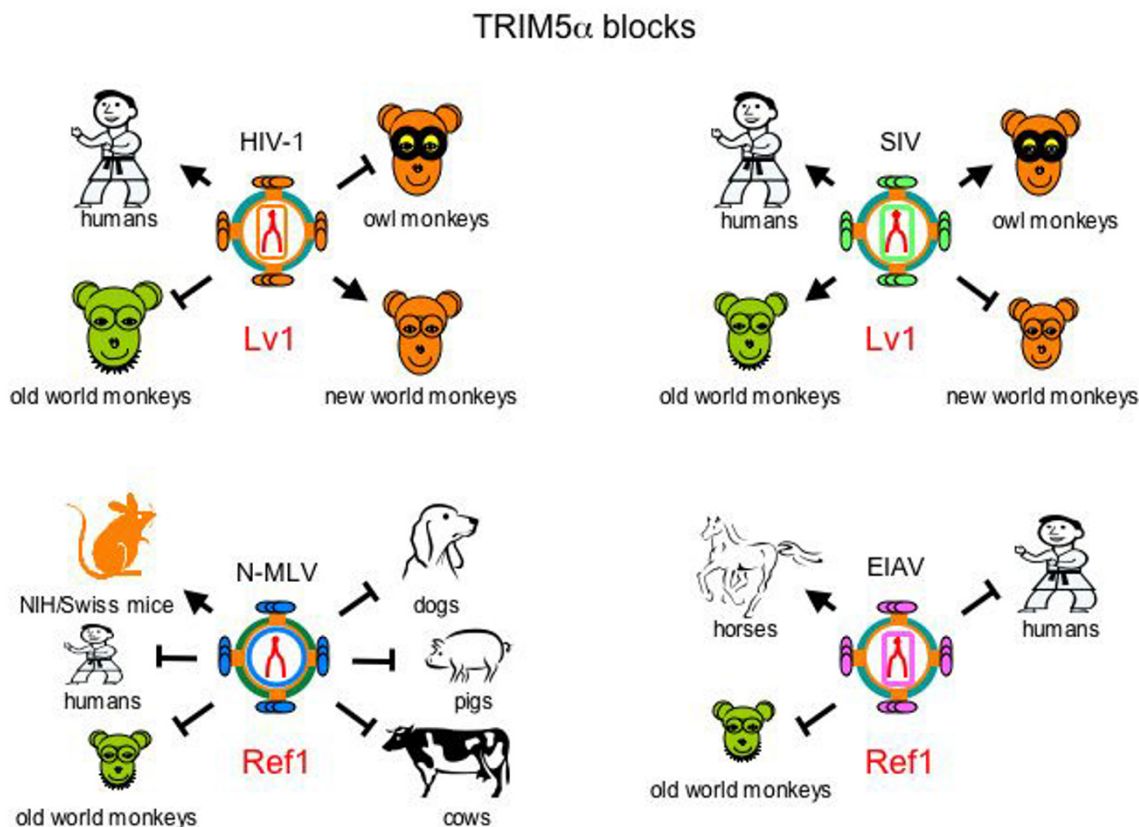
infected cells, many structural proteins remain associated with viral enzymes (reverse transcriptase, RT and integrase, IN) and RNA in a large (2 mDa) preintegration complex (PIC).

Alleles of Fv1 in Balb/c (Fv1^{b/b}) and NIH/Swiss (Fv1^{n/n}) mice result in resistance to N- and B-tropic strains of MLV, respectively, which maps to position 110 in CA (Fig. 2) [17]. A recent structural analysis revealed that this residue is located at the outer face of the core structure of CA with easy access to cellular proteins [18]. On Fv1, the key residue for this restriction was mapped to position 358 (Fig. 2) [19]. Although binding between CA and Fv1 has not been demonstrated, they could interact as higher order structures, especially since CA and Gag form oligomers, in the case of CA, hexagonal lattices of the viral core. As heterozygous Fv1^{n/b} mice block infection by both viruses, resistance is dominant [20]. Conversely, NB-tropic MLV

can infect all these mice. Of interest, this restriction is saturable with high levels of CA from either virus [21], implying that amounts of Fv1 or its cofactor/s are limiting. As described below, one of these cofactors could be TRIM5 α [22]. As a result of these interactions, Fv1 is thought to block the disassembly of CA and the normal movement of the PIC into the nucleus (Fig. 1) [23,24].

TRIM5 α

Fv1 is not the only genetic system conferring intracellular immunity against a retroviral infection. For example, the replication of N-tropic MLV and the equine infectious anemia virus (EIAV, a lentivirus) is also inhibited in human cells [25], as is that of the primate lentiviruses HIV-1 and SIV from rhesus macaques (SIV_{mac}) in cells from different monkeys (Fig. 3) [26-29]. For example, HIV-1 does not grow in old world monkeys, which include African green monkeys and rhesus macaques, and

**Figure 3**

Blocks to retroviral replication by different TRIM5 α proteins from several species. The replication of HIV-1 is blocked by TRIM5 α from old world monkeys and owl monkeys, but not human and new world monkeys (left top panel). The replication of SIV is blocked by TRIM5 α proteins from new world monkeys, but not from humans, old world monkeys, and owl monkeys (right top panel). The replication of N-MLV is prevented by TRIM5 α proteins from dogs, pigs, cows, old world monkeys, and humans, but not mice (left bottom panel). The replication of EIAV is blocked by TRIM5 α from human and old world monkeys, but not horses (right bottom panel). In all cases, arrows indicate no inhibition.

SIV_{mac} does not infect new world monkeys, which include squirrel monkeys and common marmosets (Fig. 3) [26-29].

Interestingly, these blocks resemble Fv1 restriction in several ways. First, viral replication is impaired at the step of reverse transcription [25-28]. Second, CA is also targeted. The residue at position 110 in CA also determines the restriction of N-tropic MLV in human cells [25] and that of HIV-1 in rhesus macaque cells is abrogated when its CA is replaced by that from SIV_{mac} [29]. Third, because heterokaryons between non-restrictive and restrictive cells

maintain the inhibition, this restriction is dominant [27,28]. Finally, these blocks are saturable. However, since no Fv1-related gene could be found in primate cells, blocks to N-tropic MLV and EIAV in human cells were thought to be due to the restriction factor 1 (Ref1) [25], and those to HIV-1 and SIV in monkey cells to the lentivirus susceptibility factor 1 (Lv1) (Fig. 3) [27].

Indeed, Ref1 and Lv1 share additional similarities in blocking retroviral replication. For examples, both restrictions can be attenuated by chemicals that disrupt the integrity of mitochondrial membranes [30,31], and they

can be saturated by the same virus like particles (VLPs) [32]. Using a functional complementation assay, Lv1 was first identified as the rhesus macaque TRIM5 α (macTRIM5 α) gene [2]. Later, by eliminating TRIM5 α transcripts from old world monkey and human cells with small interfering RNA (siRNA), the Lv1 and Ref1 blocks were also abrogated [33]. Further studies revealed that hTRIM5 α (from humans), macTRIM5 α and agmTRIM5 α (from African green monkeys) restrict the replication of different viruses, which were assigned previously to Lv1 and Ref1 (Fig. 3) [22,33-35]. Thus, Ref1 and Lv1 are species-specific variants of TRIM5 α .

The hTRIM5 α protein contains 493 residues (Fig. 4) and belongs to the large tripartite motif (TRIM) family that consists of 37 genes, which include the promyelocytic leukemia (PML or TRIM19) protein [36]. By alternative RNA splicing, they produce 71 different transcripts. For example, the human TRIM5 gene is expressed as hTRIM5 α , β , γ , σ , ϵ , and ζ . Although little is known of their function, they contain three distinctive structural motifs, a RING Zn⁺⁺ finger, one or two B-box Zn⁺⁺ finger, and an α -helical coiled-coil (CC) region (Fig. 4). For this reason, they are also called the RING finger:B box:Coiled-coil (RBCC) family proteins. The RING finger motif features a cysteine-rich consensus, which contains two interleaved Zn⁺⁺-binding sites [37]. Many RING finger proteins act as E3 ubiquitin ligases and play key roles in protein degradation. For example, Ring-box-1 (Rbx1) is an essential component of the Skp1:cullin-1:F-box (SCF) complex. Additionally, TRIM5 σ displays E3 ligase activity in vitro [38]. B-boxes, which consist of one Zn⁺⁺-binding site and a B1 or B2 motif [39], orient the CC motif that mediates protein-protein interactions. Indeed, TRIM proteins form oligomers [36]. In addition, TRIM5 α contains a SPRY domain at its C-terminus (Fig. 4). The SPRY domain was originally identified in the splA kinase of *Dictyostelium* and the rabbit ryanodine receptor [40], and belongs to the subclass of the B30.2 or RFP-like domains. In butyrophilin, the B30.2 domain, which contains 170 residues, is involved in ligand binding [41]. Of interest, TRIM proteins localize to particular cellular compartments where they form discrete structures. Whereas TRIM19 assembles discrete PML oncogenic domains (PODs) in the nucleus, TRIM5 α can form cytoplasmic bodies [36].

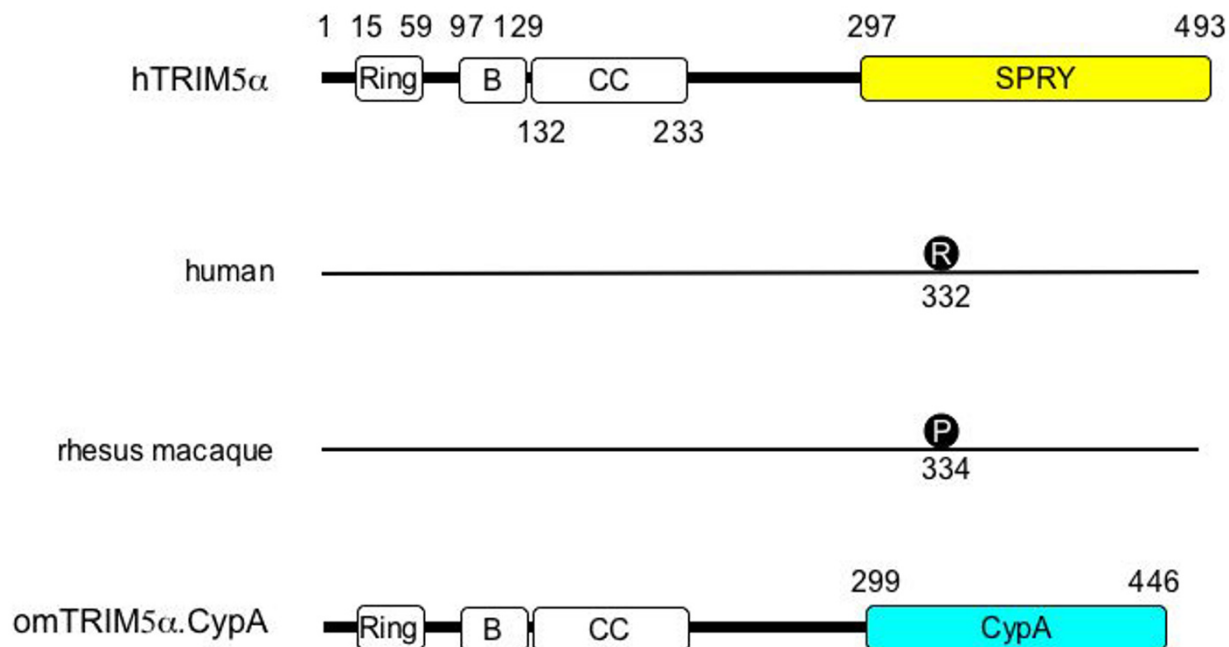
Although they share 87% sequence similarity, only macTRIM5 α but not hTRIM5 α blocks HIV-1 replication [2]. This species-specific restriction was mapped to the SPRY domain [42-44]. Through genetic analysis, it was revealed that this SPRY domain has experienced dramatic mutations during primate evolution [45] and contains four variable regions V1, V2, V3, and V4 [46]. The change of a single residue (R332P) in V1 abolished the inhibition of HIV-1 replication by hTRIM5 α [43,44], which suggests

that the SPRY domain is responsible for its targeting of CA. Although no binding between the SPRY of rhTRIM5 α and HIV-1 CA has been demonstrated, the findings with TRIM5 α from owl monkeys (omTRIM5 α) support such direct interactions [47,48]. A rather complicated story follows. Cyclophilin A (CypA) is an eukaryotic peptidyl-prolyl cis-trans-isomerase. It binds an exposed proline-rich loop in CA of HIV-1 and is critical for its replication in human cells [49,50]. In contrast, the ability to bind CypA restricts HIV-1 replication in owl monkey cells. Owl monkeys are atypical new world monkeys because their Lv1 inhibits HIV-1 but not SIV_{mac}. Although this block to HIV-1 replication is abrogated when the interaction between CA and CypA is prevented by mutations in CA or by cyclosporin A treatment in owl monkey cells, the same manipulations increase effects of Ref1 on HIV-1 in human cells [51]. The explanation for these differences came with the cloning of the omTRIM5 α gene. Instead of the SPRY domain, it contains the complete CypA gene [47,48] (Fig. 4). Thus, owl monkey cells express a fusion protein between omTRIM5 α and CypA (omTRIM5 α .Cyp), which most likely arose from a retrotransposition of the CypA gene into the omTRIM5 α locus by the long interspersed nuclear elements-1 (LINE-1 or L1). In conclusion, CA and omTRIM5 α interact via this CypA domain and restrict HIV-1 replication in owl monkeys.

These studies suggest that Fv1 and TRIM5 α might interact directly with CA to block incoming viruses. However, in contrast to Fv1, which blocks nuclear entry and integration of the provirus [23,24], TRIM5 α inhibits viral replication at a step before reverse transcription (Fig. 1). It is puzzling why such differences exist. An answer might lie in the observation that MLV, but not HIV-1, retains its CA in the reverse transcription complex [52,53]. Thus, the uncoating of HIV-1 could proceed much faster than that of MLV. Once the core structure is destroyed, the reverse transcription complex could become more susceptible to TRIM5 α . TRIM5 α could then trigger the proteasomal degradation of PIC. This model also offers an explanation of the enhancement of viral replication when target cells are treated with proteasomal inhibitors [54]. Further details await studies of other proteins that interact with Fv1 and TRIM5 α , their enzymatic properties and trafficking in cells.

Cytidine deaminases

In addition to Fv1 and TRIM5 α , host cells have developed additional mechanisms to protect themselves from viral invasion. The next important block involves nucleic acid editing of viral reverse transcripts. For a long time, it had been noted that retroviruses contain a high frequency of G to A transitions [55,56]. In certain strains of HIV-1, up to 60% of all guanidines are replaced by adenines [57]. Previously, this G to A hypermutation was attributed to the

**Figure 4**

Schematic representations of hTRIM5 α , macTRIM5 α , and omTRIM5 α . CypA proteins. hTRIM5 α contains 493 residues and four conserved motifs, whose positions are given. They are the RING domain, B box, coiled-coil and SPRY domains. The latter domain is required for species-specific restriction of primate lentiviruses and is diagrammed in red. A key residue in this domain, which is the arginine at position 332 in hTRIM5 α , or the proline at position 334 in macTRIM5 α , is responsible for its species-specific inhibition of lentiviral replication. omTRIM5 α from owl monkeys contains an N-terminal omTRIM5 α sequence to position 299, linked in-frame to the entire CypA gene (147 residues)(omTRIM5 α .CypA).

high error rate of reverse transcriptase and the imbalance in dCTP pools in cells [58]. However, we now know that host cellular cytidine deaminases are responsible.

In parallel, mutant HIV-1 lacking the viral infectivity factor (Vif) (HIV-1 Δ Vif) can only replicate in certain T cell lines, which are called "permissive" cells. In other "non-permissive" cells, only wild type HIV-1 but not HIV-1 Δ Vif can replicate [59,60]. Because heterokaryons between permissive and non-permissive cells do not support the replication of HIV-1 Δ Vif, there exists a dominant inhibitor in these non-permissive cells [61,62]. By subtractive cloning between non-permissive CEM and permissive CEM-SS T cells, the inhibitory factor was identified as the human A3G (hA3G) protein [3]. Later, its close relatives hA3F,

and to a lesser degree, hA3B, were found to possess similar anti-viral activities [4-7].

The human APOBEC family comprises 10 proteins, among which are the founding member APOBEC1 (A1) and the activation induced deaminase (AID) [63]. They contain one (e.g. APOBEC1 and AID) or two (e.g. hA3F and hA3G) Zn⁺⁺-binding deaminase motifs with the consensus sequence His-X-Glu-X₂₃₋₂₈-Pro-Cys-X₂₋₄-Cys (where X denotes any amino acid) [63]. They can target cytosines and convert them to uracils (C to U transitions) on DNA or RNA (e.g. A1) templates. During the second-strand DNA synthesis, these C to U transitions are then converted to those of G to A. For example, by changing C6666 to U6666, A1 introduces a stop codon at position

Table 1: Abilities of APOBEC proteins to inhibit viruses and retrotransposons

Species	APOBEC proteins	HIV-1ΔVif	HIV-2ΔVif	SIVΔVif	MLV	EIAV	HBV	LI	IAP MusD
humans	A3B	+		+	-				
	A3C	-		+	-				
	A3F	+		+			+		
	A3G	+	+	+	+	+	+	-	+
old world monkeys	A3G	+		+	-				
rats	A1	+			-				
mice	A3	+		+	-			-	+

(+) block, (-) do not block

6666 into the apolipoprotein B100 mRNA, which is translated into the truncated apolipoprotein B48 (48 kDa) protein [64]. AID also directs the cytidine deamination at specific "hot spots" to direct somatic hypermutation and isotype class switching in B cells [65]. hA3F and hA3G block retroviral infection in hematopoietic cells. They share overall 70% sequence similarity and form homodimers as well as mixed oligomers [5]. Physiological functions of these proteins are not yet defined, except that hA3G also inhibits the movement of some mouse mobile genetic elements in cells [66]. Thus, they could contribute to the stability of the genome.

APOBEC proteins and viral replication

The mechanisms for antiviral activities of APOBEC proteins have been characterized extensively. In the absence of Vif, hA3F and hA3G are incorporated into virions. They are then transferred from producer to target cells by the virus. Following viral entry and uncoating, reverse transcription is initiated and viral minus-strand cDNA is synthesized. During this process, these APOBEC proteins attack newly synthesized minus-strand cDNAs and introduce C to U transitions [67-70], which block viral replication by several mechanisms [71]. First, since uracils are not tolerated in DNA, they are removed by uracil N-glycosidases (UNG) from DNA and these nicked DNA are further cleaved by the host DNA-repair enzymes like apurinic/apyrimidinic endonuclease-1 (APE1). Fragmented DNA neither integrates nor replicates. Second, should edited proviruses survive and integrate, the new G to A changes on the plus strand DNA also create havoc on viral transcripts. These changes could lead to alternate splicing and the production of nonfunctional proteins. To these ends, hA3G and hA3F have different sequence preferences. Whereas hA3G favors repeated deoxycytidines (GG on the opposite strand) [72], hA3F prefers deoxycytidines followed by deoxythymidines (GA on the opposite strand) [4,7].

The key step for the anti-viral activity of hA3G is its incorporation into virions. Although the encapsidation of

hA3G requires NC of HIV-1 Gag, it is still controversial whether this interaction is mediated by RNA [73-76]. Since both NC and hA3G can bind RNA, this recruitment most likely reflects RNA-protein, as well as protein-protein, interactions [77,78]. Nevertheless, since hA3G blocks the replication of all primate lentiviruses in the absence of Vif (HIV-1, HIV-2, and SIV) [3,79,80], EIAV [69], HBV [81,82], and some mouse mobile genetic elements [66], these interactions must have broad specificities. For example, hA3F has the same effect against HIV-1, SIV and HBV and hA3B and hA3C block SIV (Table 1) [4-7,83,84]. Of interest, the rat but not human A1 proteins block HIV-1 by directly deaminating viral RNA [85].

Vif and APOBEC proteins

In contrast to HIV-1ΔVif, wild-type HIV-1 is not restricted in non-permissive cells. Thus, Vif counteracts the effects of hA3F and hA3G. Indeed, Vif binds and triggers the degradation of these APOBEC proteins in producer cells, thus blocking their incorporation into virions [86-88]. Initially, Vif was demonstrated to interact with cellular proteins Cul5, elonginB, elonginC, and Rbx1 to form a cullin-based E3 ubiquitin ligase complex [89], which displays striking similarities to SCF complex. Later, Vif was found to contain a conserved suppressor of cytokine signaling (SOCS) box-like motif (SLQ(Y/F)LA) that binds elongin C, which in turn recruits elongin B, cullin 5 and Rbx1, thus forming the ElonginB/C-Cul5-SOCS-box (ECS) E3 ubiquitin ligase complex [90,91]. As a consequence of these interactions, APOBEC proteins are polyubiquitylated and degraded [86-88]. In parallel, some groups observed that Vif triggers only a marginal degradation of hA3G, which suggested that Vif could sequester hA3G from encapsidation through a degradation-independent mechanism [79,92].

Although Vif blocks the antiviral activity of hA3G, its activity is highly species-specific (fig. 5). Additionally as presented in Table 2, Vif from HIV-1 blocks A3G proteins from humans and chimpanzees (hA3G and chA3G), but not from old world monkeys, Vif from SIV_{mac} blocks all

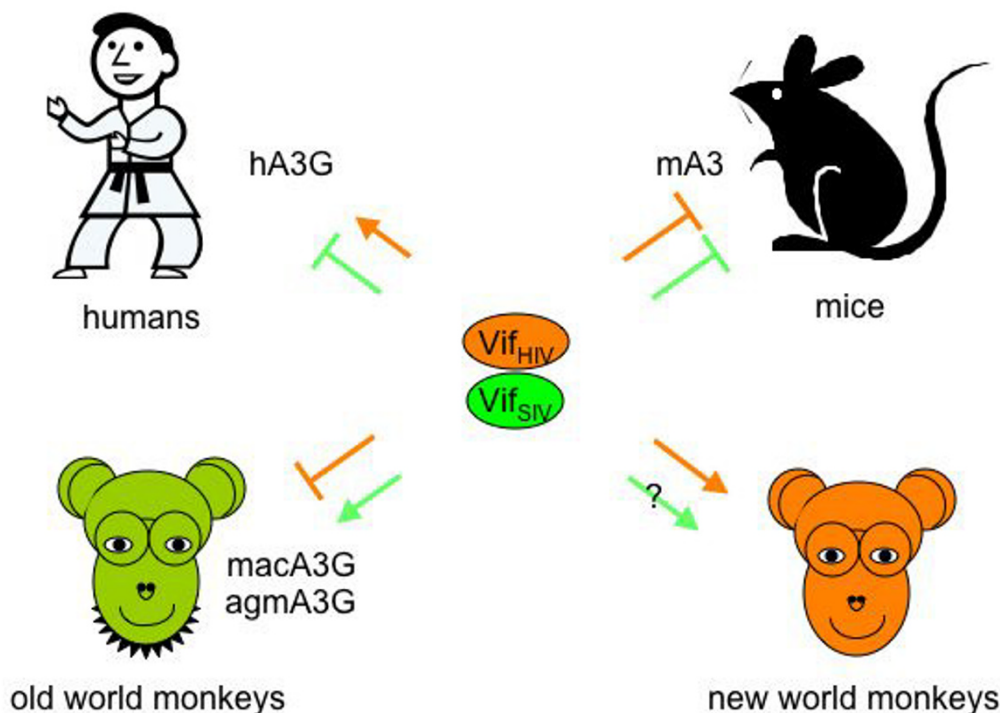


Figure 5

Species-specific inhibition of APOBEC3 (A3) proteins by Vif. HIV-1 and SIV can incorporate A3 proteins from all these species into virions. However, Vif from HIV-1 (Vif_{HIV}, brown), can only inhibit A3 proteins from humans and new world monkeys) but not those from old world monkeys and mice. In contrast, Vif from SIV_{mac} (Vif_{SIV}, green) can inactivate A3 proteins from old and possibly new world monkeys, but not from humans and mice). In this drawing, stick figures represent sources of A3 proteins and not targets of infection.

A3G isoforms from human and non-human primates, and Vif from SIV_{agm} only blocks A3G proteins from monkeys [79]. In addition, hA3F can be inactivated by Vif proteins from HIV-1, HIV-2, and SIV_{mac'} but not from SIV_{agm} [4,5,84]. Moreover, the hA3C can be inactivated by Vif from SIV_{mac} [84] and no Vif protein can inactivate the hA3B, rat A1, or mouse APOBEC3 (mA3) proteins [6]. Efforts have been made to uncover the molecular mechanisms of these species-specific differences, and agmA3G was chosen because it is most similar to hA3G. It was found that Vif from HIV-1 fails to inactivate agmA3G because it contains a lysine rather than aspartate at position 128 (K128D), which is found in hA3G. Although

agmA3G neither binds Vif nor is excluded from virions, the mutant agmA3G protein bearing D128 becomes fully sensitive to Vif from HIV-1 [93-96]. In addition, the reciprocal exchange of D for K at position 128 in hA3G renders it resistant to Vif. Structural comparisons with the related cytidine deaminases from *E.coli* reveal that D128 maps to an α -helical turn on an exposed loop [96]. Since the same K128 residue also exists in A3G from rhesus macaque (macA3G), its sensitivity might also be altered with a similar K128D substitution. Although these studies established the correlation between the ability of Vif to neutralize APOBEC proteins and viral replication, it is unlikely that these species-specific susceptibilities of

Table 2: Species-specific susceptibility of APOBEC proteins to Vif

APOBEC proteins	Species	HIV-1 Vif	HIV-2 Vif	SIV _{agn} Vif	SIV _{mac} Vif
A3G	humans	+	+	-	+
	chimpanzees	+		-	+
	African green monkeys	-		+	+
	rhesus macaques	-		+	+
A3	mice	-		-	-
A3F	humans	+	+	-	+
A3B	humans	-		-	-
A3C	humans	-		+	+
A1	rats	-			

(+) susceptible, (-) not susceptible

APOBEC proteins to Vif are responsible for the transmission of primate lentiviruses to new host species [97].

Viruses that lack Vif and mobile genetic elements

How can viruses that do not encode Vif escape from this intracellular immunity?

As some APOBEC proteins also inhibit the replication of EIAV, HBV, and MLV, there must be additional mechanisms of escape. In the case of EIAV, it encodes an additional enzyme, which is named dUTPase [98]. This enzyme is also produced by herpesviruses, poxviruses, and some other retroviruses. Recently, it was demonstrated that dUTPase from caprine arthritis encephalitis virus (CAEV) could block the misincorporation of dUTP during HIV-1 reverse transcription [99]. Thus, its dUTPase could also protect EIAV from attack by APOBEC proteins. In the case of HBV, it replicates in tissues that do not express hA3G [63]. The situation for MLV is more complicated. Unlike human cells that express seven A3 proteins, the mouse genome contains only one A3 gene. Although mA3 blocks the replication of HIV-1 and SIV, it is less efficiently packaged into and does not inhibit MLV [100]. In contrast, hA3G blocks the replication of MLV. Thus, MLV has adapted to its natural host by a mechanism that remains poorly understood.

What is the situation with mobile genetic elements that resemble retroviruses? In humans and mice, there are several types of retrotransposons [101]. The most abundant are LINE-1 or L1 elements that do not contain long terminal repeats (LTRs). Up to one hundred human and several thousand mouse L1 elements are functional [101]. Although they require reverse transcription, they do not form VLPs and APOBEC proteins do not block their replication [66,102]. In contrast, LTR-containing retrotransposons, which represent up to 10% of the human

genome, form VLPs, bud from intracellular organelles and behave similarly to incoming exogenous retroviruses. Although no active human endogenous retroviruses (HERVs) have been found, in the mouse, there are several hundred active intracisternal A-particles (IAPs) [103] and at least ten copies of MusD [104]. Indeed, sequences of IAPs and MusDs contain frequent G to A transversions in their genomes [66]. In addition, using transient expression assays in cells, hA3G and mA3 inhibit the retrotransposition of IAP and MusD (Table 1) [66]. Thus, APOBEC proteins also block the movement of some mobile genetic elements, most likely in germ cells and during embryogenesis, in mammals.

Other antiviral genes that contribute to intracellular immunity

Besides these predominant blocks to viral replication in cells, additional barriers have been described at levels of transcription and RNA stability, as well as assembly of progeny virions. However, since they do not block the integration of proviruses into the host genome, they play lesser roles in intracellular immunity. First, Murr1 blocks the activation of NF- κ B in resting cells and thus the induction of HIV-1 replication [105]. Second, a sophisticated genetic screen looking for cells that survive attack by MuLV bearing the thymidine kinase (tk) gene (which would otherwise succumb to trifluorothymidine that is phosphorylated by tk) revealed the Zn⁺⁺-finger antiviral protein ZAP that degrades rapidly MLV transcripts [106]. ZAP binds a specific sequence at the 3' end of viral, but not cellular, transcripts and leads to their rapid degradation in the exosome. This mechanism appears analogous to tristetraprolin, which binds AU-rich RNA species (e.g. those coding for cytokine genes) and targets them for rapid degradation in the cytoplasm. Apparently, not only are retroviral transcripts targeted by ZAP, but it destroys Ross River, Semliki, Sindbis and Venezuelan equine encephalitis viruses, all of which belong to the alphavirus family [107].

Although ZAP is extremely efficient against alphaviruses and MuLV, it is not clear what role, if any, it plays against primate retroviruses.

The final level of intracellular immunity deals with viral assembly and release. Again, HIV-1 encodes another accessory viral protein u (Vpu), which facilitates the release of progeny virions from infected cells [108]. Thus, analogous to the situation with Vif, some cells are "permissive" and others are "non-permissive" for viral replication in the absence of Vpu. Heterokaryons between them maintain the non-permissive phenotype, which is dominant. Thus, Vpu must counteract some dominant negative cellular factor, whose identity remains to be determined. Of interest, recent work suggests that Vpu counteracts the two-pore K⁺ (K_{2P}) channel TASK-1, which inhibits the release of many viruses by an unknown mechanism, possibly by changing membrane fluidity [109]. Vpu also facilitates the release of other retroviruses. By mimicking a natural component of TASK-1, Vpu is incorporated into the channel, where it acts as a dominant negative effector. Vpu also binds βTRCP, an E3 ubiquitin ligase, which could accelerate the degradation of TASK-1 in the proteasome [110]. Thus, it is possible that levels and/or polymorphisms of TASK-1 are mostly responsible for this block in the assembly and release of progeny virions. However, additional experiments are required to make this connection and/or to reveal additional players in this last step of the viral replicative cycle in cells.

Intracellular immunity

Several themes emerge from these cell-intrinsic blocks to retroviral replication. First, the inhibition is broad. Thus, not only are retroviruses targeted, but other viruses as well, from HBV and alphaviruses to some mobile genetic elements, which once were viruses themselves. Second, multiple steps in the replicative cycles of these viruses are inhibited, most likely because each mechanism is not completely effective. This finding might reflect small differences between extracellular pathogens and normal cellular homeostatic mechanisms. Alternatively, it might reflect the vast spectrum of different pathogens, all of which must be targeted and destroyed. For retroviruses, the challenge is increased because of their rapid rate of mutations and their quick adaptation to the host. Third, these intracellular blocks are more pronounced and effective in zoonotic infections, where the virus jumps species. Finally, this inhibition is rapid and targets predominantly early steps in the replicative cycles of these viruses. Thus, it tries to prevent the integration of the viral genetic material into the host genome. Whether these inhibitors accomplish this task by targeting viral structures or genetic material to an endosome, exosome or proteasome, the end results are the same, i.e. the elimination of the virus. In this scenario, the outcome depends on the effectiveness

of cellular proteins versus the protective armor of the virus.

Given these observations, one of the simplest new therapeutic interventions could be simply to increase intracellular levels of these antiviral proteins, e.g. TRIM5α, APOBEC proteins, ZAP and/or TASK-1. Thus, if we only understood their normal regulation, it is possible that we could augment their amounts and activities during active infections. Of course, as we do not know their other functions in cells, there are also many potential concerns. For example, would increased levels of APOBEC3G cause editing of genomic DNA during replication, thus facilitating oncogenic transformation? Likewise, would increased amounts of ZAP target critical cellular transcripts for accelerated degradation? Alternatively, one could try to block interactions between Vif and APOBEC proteins and TASK-1 and Vpu. Possibly, by studying their structures, one could design inhibitors for their protein-protein interactions. Moreover, all these processes can also be targeted by gene therapy, by introducing into cells their counterparts from different species and/or by changing binding surfaces of the host proteins so that they no longer interact with Vif or Vpu, for example. If not practical clinically, such genetic manipulation would yield important clues as to which restriction should be targeted by other therapeutic means.

Conclusion

It is remarkable how active are the processes that protect an organism from internal and external challenges. In humans, at least three layers of immunity have developed. Among them, intracellular and innate immune responses act primarily via pattern recognition, whereas adaptive immunity is very sequence and peptide-specific. Nevertheless, many pathogens break through and are integrated into the host genetic material. Thus, some of these defense mechanisms must also survey the movements and effects of these mobile genetic elements. It appears that a fine line has been drawn between control and allowing for some escape as well. As mobile genetic elements contribute to evolution and fitness of all species, they must be kept in check, but not eliminated completely and it is possible that this intricate regulation of hA3G activity in cells reflects this requirement. On the other hand, there is also a high price to pay in terms of mistakes, be they developmental defects or cancer. Nevertheless, the study of these systems that fight extracellular pathogens is likely to reveal fundamental insights into a plethora of cellular processes that contribute to human health and disease.

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References

- Gardner MB, Luciw PA: **Animal models of AIDS.** *Faseb J* 1989, **3(14)**:2593-2606.
- Stremlau M, Owens CM, Perron MJ, Kiessling M, Autissier P, Sodroski J: **The cytoplasmic body component TRIM5 α restricts HIV-1 infection in Old World monkeys.** *Nature* 2004, **427(6977)**:848-853.
- Sheehy AM, Gaddis NC, Choi JD, Malim MH: **Isolation of a human gene that inhibits HIV-1 infection and is suppressed by the viral Vif protein.** *Nature* 2002, **418(6898)**:646-650.
- Zheng YH, Irwin D, Kurosu T, Tokunaga K, Sata T, Peterlin BM: **Human APOBEC3F is another host factor that blocks human immunodeficiency virus type 1 replication.** *J Virol* 2004, **78(11)**:6073-6076.
- Wiegand HL, Doehle BP, Bogerd HP, Cullen BR: **A second human antiretroviral factor, APOBEC3F, is suppressed by the HIV-1 and HIV-2 Vif proteins.** *Embo J* 2004, **23(12)**:2451-2458.
- Bishop KN, Holmes RK, Sheehy AM, Davidson NO, Cho SJ, Malim MH: **Cytidine Deamination of Retroviral DNA by Diverse APOBEC Proteins.** *Curr Biol* 2004, **14(15)**:1392-1396.
- Liddament MT, Brown WL, Schumacher AJ, Harris RS: **APOBEC3F Properties and Hypermutation Preferences Indicate Activity against HIV-1 In Vivo.** *Curr Biol* 2004, **14(15)**:1385-1391.
- Suzuki S: **Fv-4: a new gene affecting the splenomegaly induction by Friend leukemia virus.** *Jpn J Exp Med* 1975, **45(6)**:473-478.
- Ikeda H, Sato H, Odaka T: **Mapping of the Fv-4 mouse gene controlling resistance to murine leukemia viruses.** *Int J Cancer* 1981, **28(2)**:237-240.
- Ikeda H, Laigret F, Martin MA, Repaske R: **Characterization of a molecularly cloned retroviral sequence associated with Fv-4 resistance.** *J Virol* 1985, **55(3)**:768-777.
- Masuda M, Yoshikura H: **Construction and characterization of the recombinant Moloney murine leukemia viruses bearing the mouse Fv-4 env gene.** *J Virol* 1990, **64(3)**:1033-1043.
- Taylor GM, Gao Y, Sanders DA: **Fv-4: identification of the defect in Env and the mechanism of resistance to ecotropic murine leukemia virus.** *J Virol* 2001, **75(22)**:11244-11248.
- Lilly F: **Susceptibility to two strains of Friend leukemia virus in mice.** *Science* 1967, **155(761)**:461-462.
- Rowe WP, Humphrey JB, Lilly F: **A major genetic locus affecting resistance to infection with murine leukemia viruses. 3. Assignment of the Fv-1 locus to linkage group 8 of the mouse.** *J Exp Med* 1973, **137(3)**:850-853.
- Best S, Le Tissier P, Towers G, Stoye JP: **Positional cloning of the mouse retrovirus restriction gene Fv1.** *Nature* 1996, **382(6594)**:826-829.
- Freed EO: **HIV-1 gag proteins: diverse functions in the virus life cycle.** *Virology* 1998, **251(1)**:1-15.
- Kozak CA, Chakraborti A: **Single amino acid changes in the murine leukemia virus capsid protein gene define the target of Fv1 resistance.** *Virology* 1996, **225(2)**:300-305.
- Mortuza GB, Haire LF, Stevens A, Smerdon SJ, Stoye JP, Taylor IA: **High-resolution structure of a retroviral capsid hexameric amino-terminal domain.** *Nature* 2004, **431(7007)**:481-485.
- Bishop KN, Bock M, Towers G, Stoye JP: **Identification of the regions of Fv1 necessary for murine leukemia virus restriction.** *J Virol* 2001, **75(11)**:5182-5188.
- Pincus T, Rowe WP, Lilly F: **A major genetic locus affecting resistance to infection with murine leukemia viruses. II. Apparent identity to a major locus described for resistance to friend murine leukemia virus.** *J Exp Med* 1971, **133(6)**:1234-1241.
- Pincus T, Hartley JW, Rowe WP: **A major genetic locus affecting resistance to infection with murine leukemia viruses. IV. Dose-response relationships in Fv-1-sensitive and resistant cell cultures.** *Virology* 1975, **65(2)**:333-342.
- Keckesova Z, Ylilin LM, Towers GJ: **The human and African green monkey TRIM5 α genes encode Ref1 and Lvl retroviral restriction factor activities.** *Proc Natl Acad Sci U S A* 2004, **101(29)**:10780-10785.
- Jolicoeur P, Rassart E: **Effect of Fv-1 gene product on synthesis of linear and supercoiled viral DNA in cells infected with murine leukemia virus.** *J Virol* 1980, **33(1)**:183-195.
- Yang WK, Kiggans JO, Yang DM, Ou CY, Tennant RW, Brown A, Bassin RH: **Synthesis and circularization of N- and B-tropic retroviral DNA Fv-1 permissive and restrictive mouse cells.** *Proc Natl Acad Sci U S A* 1980, **77(5)**:2994-2998.
- Towers G, Bock M, Martin S, Takeuchi Y, Stoye JP, Danos O: **A conserved mechanism of retrovirus restriction in mammals.** *Proc Natl Acad Sci U S A* 2000, **97(22)**:12295-12299.
- Besnier C, Takeuchi Y, Towers G: **Restriction of lentivirus in monkeys.** *Proc Natl Acad Sci U S A* 2002, **99(18)**:11920-11925.
- Cowan S, Hatzioannou T, Cunningham T, Muesing MA, Gottlinger HG, Bieniasz PD: **Cellular inhibitors with Fv1-like activity restrict human and simian immunodeficiency virus tropism.** *Proc Natl Acad Sci U S A* 2002, **99(18)**:11914-11919.
- Munk C, Brandt SM, Lucero G, Landau NR: **A dominant block to HIV-1 replication at reverse transcription in simian cells.** *Proc Natl Acad Sci U S A* 2002, **99(21)**:13843-13848.
- Owens CM, Yang PC, Gottlinger H, Sodroski J: **Human and simian immunodeficiency virus capsid proteins are major viral determinants of early, postentry replication blocks in simian cells.** *J Virol* 2003, **77(1)**:726-731.
- Berthoux L, Sebastian S, Sokolskaja E, Luban J: **Lvl inhibition of human immunodeficiency virus type 1 is counteracted by factors that stimulate synthesis or nuclear translocation of viral cDNA.** *J Virol* 2004, **78(21)**:11739-11750.
- Berthoux L, Towers GJ, Gurer C, Salomoni P, Pandolfi PP, Luban J: **As(2)O(3) enhances retroviral reverse transcription and counteracts Ref1 antiviral activity.** *J Virol* 2003, **77(5)**:3167-3180.
- Hatzioannou T, Cowan S, Goff SP, Bieniasz PD, Towers GJ: **Restriction of multiple divergent retroviruses by Lvl and Ref1.** *Embo J* 2003, **22(3)**:385-394.
- Hatzioannou T, Perez-Caballero D, Yang A, Cowan S, Bieniasz PD: **Retrovirus resistance factors Ref1 and Lvl are species-specific variants of TRIM5 α .** *Proc Natl Acad Sci U S A* 2004, **101(29)**:10774-10779.
- Perron MJ, Stremlau M, Song B, Ulm W, Mulligan RC, Sodroski J: **TRIM5 α mediates the postentry block to N-tropic murine leukemia viruses in human cells.** *Proc Natl Acad Sci U S A* 2004, **101(32)**:11827-11832.
- Yap MW, Nisole S, Lynch C, Stoye JP: **Trim5 α protein restricts both HIV-1 and murine leukemia virus.** *Proc Natl Acad Sci U S A* 2004, **101(29)**:10786-10791.
- Reymond A, Meroni G, Fantozzi A, Merla G, Cairo S, Luzi L, Riganelli D, Zanaria E, Messali S, Cainarca S, Guffanti A, Minucci S, Pelicci PG, Ballabio A: **The tripartite motif family identifies cell compartments.** *Embo J* 2001, **20(9)**:2140-2151.
- Joazeiro CA, Weissman AM: **RING finger proteins: mediators of ubiquitin ligase activity.** *Cell* 2000, **102(5)**:549-552.
- Xu L, Yang L, Moitra PK, Hashimoto K, Rallabhandi P, Kaul S, Meroni G, Jensen JP, Weissman AM, D'Arpa P: **BTBD1 and BTBD2 colocalize to cytoplasmic bodies with the RBCC/tripartite motif protein, TRIM5 δ .** *Exp Cell Res* 2003, **288(1)**:84-93.
- Torok M, Etkin LD: **Two B or not two B? Overview of the rapidly expanding B-box family of proteins.** *Differentiation* 2001, **67(3)**:63-71.
- Ponting C, Schultz J, Bork P: **SPRY domains in ryanodine receptors (Ca(2+)-release channels).** *Trends Biochem Sciences* 1997, **22(6)**:193-194.
- Jack LJ, Mather IH: **Cloning and analysis of cDNA encoding bovine butyrophilin, an apical glycoprotein expressed in mammary tissue and secreted in association with the milk-fat globule membrane during lactation.** *J Biol Chem* 1990, **265(24)**:14481-14486.
- Sawyer SL, Wu Li, Emerman M, Malik HS: **Positive selection of primate TRIM5 α identifies a critical species-specific retroviral restriction domain.** *Proc Natl Acad Sci U S A* 2005, **102(8)**:2832-2837.
- Stremlau M, Perron M, Welikala S, Sodroski J: **Species-specific variation in the B30.2(SPRY) domain of TRIM5 α determines the potency of human immunodeficiency virus restriction.** *J Virol* 2005, **79(5)**:3139-3145.
- Yap MW, Nisole S, Stoye JP: **A single amino acid change in the SPRY domain of human Trim5 α leads to HIV-1 restriction.** *Curr Biol* 2005, **15(1)**:73-78.
- Sawyer SL, Emerman M, Malik HS: **Ancient adaptive evolution of the primate antiviral DNA-editing enzyme APOBEC3G.** *PLoS Biol* 2004, **2(9)**:E275.

46. Song B, Javanbakht H, Perron M, Park do H, Stremlau M, Sodroski J: **Retrovirus Restriction by TRIM5(alpha) Variants from Old World and New World Primates.** *J Virol* 2005, **79(7)**:3930-3937.
47. 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 U S A* 2004, **101(36)**:13324-13328.
48. Sayah DM, Sokolskaja E, Berthoux L, Luban J: **Cyclophilin A retrotransposition into TRIM5 explains owl monkey resistance to HIV-1.** *Nature* 2004, **430(6999)**:569-573.
49. Thali M, Bukovsky A, Kondo E, Rosenwirth B, Walsh CT, Sodroski J, Gottlinger HG: **Functional association of cyclophilin A with HIV-1 virions.** *Nature* 1994, **372(6504)**:363-365.
50. Franke EK, Yuan HE, Luban J: **Specific incorporation of cyclophilin A into HIV-1 virions.** *Nature* 1994, **372(6504)**:359-362.
51. Towers GJ, Hatzioannou T, Cowan S, Goff SP, Luban J, Bieniasz PD: **Cyclophilin A modulates the sensitivity of HIV-1 to host restriction factors.** *Nat Med* 2003, **9(9)**:1138-1143.
52. Fassati A, Goff SP: **Characterization of intracellular reverse transcription complexes of human immunodeficiency virus type I.** *J Virol* 2001, **75(8)**:3626-3635.
53. Fassati A, Goff SP: **Characterization of intracellular reverse transcription complexes of Moloney murine leukemia virus.** *J Virol* 1999, **73(11)**:8919-8925.
54. Schwartz O, Marechal V, Friguet B, Arenzana-Seisdedos F, Heard JM: **Antiviral activity of the proteasome on incoming human immunodeficiency virus type I.** *J Virol* 1998, **72(5)**:3845-3850.
55. Pathak VK, Temin HM: **Broad spectrum of in vivo forward mutations, hypermutations, and mutational hotspots in a retroviral shuttle vector after a single replication cycle: substitutions, frameshifts, and hypermutations.** *Proc Natl Acad Sci U S A* 1990, **87(16)**:6019-6023.
56. Pathak VK, Temin HM: **Broad spectrum of in vivo forward mutations, hypermutations, and mutational hotspots in a retroviral shuttle vector after a single replication cycle: deletions and deletions with insertions.** *Proc Natl Acad Sci U S A* 1990, **87(16)**:6024-6028.
57. Vartanian JP, Henry M, Wain-Hobson S: **Sustained G-->A hypermutation during reverse transcription of an entire human immunodeficiency virus type I strain Vau group O genome.** *J Gen Virol* 2002, **83(Pt 4)**:801-805.
58. Vartanian JP, Meyerhans A, Sala M, Wain-Hobson S: **G-->A hypermutation of the human immunodeficiency virus type I genome: evidence for dCTP pool imbalance during reverse transcription.** *Proc Natl Acad Sci U S A* 1994, **91(8)**:3092-3096.
59. Gabuzda DH, Lawrence K, Langhoff E, Terwilliger E, Dorfman T, Haseltine WA, Sodroski J: **Role of vif in replication of human immunodeficiency virus type I in CD4+ T lymphocytes.** *J Virol* 1992, **66(11)**:6489-6495.
60. von Schwedler U, Song J, Aiken C, Trono D: **Vif is crucial for human immunodeficiency virus type I proviral DNA synthesis in infected cells.** *J Virol* 1993, **67(8)**:4945-4955.
61. Madani N, Kabat D: **An endogenous inhibitor of human immunodeficiency virus in human lymphocytes is overcome by the viral Vif protein.** *J Virol* 1998, **72(12)**:10251-10255.
62. Simon JH, Gaddis NC, Fouchier RA, Malim MH: **Evidence for a newly discovered cellular anti-HIV-1 phenotype.** *Nat Med* 1998, **4(12)**:1397-1400.
63. Jarmuz A, Chester A, Bayliss J, Gisbourne J, Dunham I, Scott J, Navaratnam N: **An anthropoid-specific locus of orphan C to U RNA-editing enzymes on chromosome 22.** *Genomics* 2002, **79(3)**:285-296.
64. Teng B, Burant CF, Davidson NO: **Molecular cloning of an apolipoprotein B messenger RNA editing protein.** *Science* 1993, **260(5115)**:1816-1819.
65. Muramatsu M, Kinoshita K, Fagarasan S, Yamada S, Shinkai Y, Honjo T: **Class switch recombination and hypermutation require activation-induced cytidine deaminase (AID), a potential RNA editing enzyme.** *Cell* 2000, **102(5)**:553-563.
66. Esnault C, Heidmann O, Delebecque F, Dewannieux M, Ribet D, Hance AJ, Heidmann T, Schwartz O: **APOBEC3G cytidine deaminase inhibits retrotransposition of endogenous retroviruses.** *Nature* 2005, **433(7024)**:430-433.
67. Harris RS, Bishop KN, Sheehy AM, Craig HM, Petersen-Mahrt SK, Watt IN, Neuberger MS, Malim MH: **DNA deamination mediates innate immunity to retroviral infection.** *Cell* 2003, **113(6)**:803-809.
68. Lecossier D, Bouchonnet F, Clavel F, Hance AJ: **Hypermutation of HIV-1 DNA in the absence of the Vif protein.** *Science* 2003, **300(5622)**:1112.
69. Mangeat B, Turelli P, Caron G, Friedli M, Perrin L, Trono D: **Broad antiretroviral defence by human APOBEC3G through lethal editing of nascent reverse transcripts.** *Nature* 2003, **424(6944)**:99-103.
70. Zhang H, Yang B, Pomerantz RJ, Zhang C, Arunachalam SC, Gao L: **The cytidine deaminase CEM15 induces hypermutation in newly synthesized HIV-1 DNA.** *Nature* 2003, **424(6944)**:94-98.
71. Gu Y, Sundquist VI: **Good to CU.** *Nature* 2003, **424(6944)**:21-22.
72. Yu Q, Konig R, Pillai S, Chiles K, Kearney M, Palmer S, Richman D, Coffin JM, Landau NR: **Single-strand specificity of APOBEC3G accounts for minus-strand deamination of the HIV genome.** *Nat Struct Mol Biol* 2004, **11(5)**:435-442.
73. Alce TM, Popik W: **APOBEC3G is incorporated into virus-like particles by a direct interaction with HIV-1 Gag nucleocapsid protein.** *J Biol Chem* 2004, **279(33)**:34083-34086.
74. Cen S, Guo F, Niu M, Saadatmand J, Deflassieux J, Kleiman L: **The interaction between HIV-1 Gag and APOBEC3G.** *J Biol Chem* 2004, **279(32)**:33177-33184.
75. Luo K, Liu B, Xiao Z, Yu Y, Yu X, Gorelick R, Yu XF: **Amino-terminal region of the human immunodeficiency virus type I nucleocapsid is required for human APOBEC3G packaging.** *J Virol* 2004, **78(21)**:11841-11852.
76. Svarovskaia ES, Xu H, Mbisa JL, Barr R, Gorelick RJ, Ono A, Freed EO, Hu WS, Pathak VK: **Human Apolipoprotein B mRNA-editing Enzyme-catalytic Polypeptide-like 3G (APOBEC3G) Is Incorporated into HIV-1 Virions through Interactions with Viral and Nonviral RNAs.** *J Biol Chem* 2004, **279(34)**:35822-35828.
77. Schafer A, Bogerd HP, Cullen BR: **Specific packaging of APOBEC3G into HIV-1 virions is mediated by the nucleocapsid domain of the gag polyprotein precursor.** *Virology* 2004, **328(2)**:163-168.
78. Zennou V, Perez-Caballero D, Gottlinger H, Bieniasz PD: **APOBEC3G incorporation into human immunodeficiency virus type I particles.** *J Virol* 2004, **78(21)**:12058-12061.
79. Mariani R, Chen D, Schrofelbauer B, Navarro F, Konig R, Bollman B, Munk C, Nymark-McMahon H, Landau NR: **Species-specific exclusion of APOBEC3G from HIV-1 virions by Vif.** *Cell* 2003, **114(1)**:21-31.
80. Ribeiro AC, Maia ESA, Santa-Marta M, Pombo A, Moniz-Pereira J, Goncalves J, Barahona I: **Functional Analysis of Vif Protein Shows Less Restriction of Human Immunodeficiency Virus Type 2 by APOBEC3G.** *J Virol* 2005, **79(2)**:823-833.
81. Rosler C, Kock J, Malim MH, Blum HE, von Weizsacker F: **Comment on "Inhibition of hepatitis B virus replication by APOBEC3G".** *Science* 2004, **305(5689)**:1403; author reply 1403.
82. Turelli P, Mangeat B, Jost S, Vianin S, Trono D: **Inhibition of hepatitis B virus replication by APOBEC3G.** *Science* 2004, **303(5665)**:1829.
83. Turelli P, Jost S, Mangeat B, Trono D: **Response to comment on "Inhibition of Hepatitis B Virus Replication by APOBEC3G".** *Science* 2004, **305**:1403b.
84. Yu Q, Chen D, Konig R, Mariani R, Unutmaz D, Landau NR: **APOBEC3B and APOBEC3C are potent inhibitors of simian immunodeficiency virus replication.** *J Biol Chem* 2004.
85. Bishop KN, Holmes RK, Sheehy AM, Malim MH: **APOBEC-mediated editing of viral RNA.** *Science* 2004, **305(5684)**:645.
86. Marin M, Rose KM, Kozak SL, Kabat D: **HIV-1 Vif protein binds the editing enzyme APOBEC3G and induces its degradation.** *Nat Med* 2003, **9(11)**:1398-1403.
87. Sheehy AM, Gaddis NC, Malim MH: **The antiretroviral enzyme APOBEC3G is degraded by the proteasome in response to HIV-1 Vif.** *Nat Med* 2003, **9(11)**:1404-1407.
88. Stopak K, de Noronha C, Yonemoto W, Greene WC: **HIV-1 Vif blocks the antiviral activity of APOBEC3G by impairing both its translation and intracellular stability.** *Mol Cell* 2003, **12(3)**:591-601.
89. Yu X, Yu Y, Liu B, Luo K, Kong W, Mao P, Yu XF: **Induction of APOBEC3 ubiquitination and degradation by an HIV-1 Vif-CuI5-SCF complex.** *Science* 2003, **302(5647)**:1056-1060.
90. Mehle A, Goncalves J, Santa-Marta M, McPike M, Gabuzda D: **Phosphorylation of a novel SOCS-box regulates assembly of the**

- HIV-1 Vif-Cul5 complex that promotes APOBEC3G degradation.** *Genes Dev* 2004, **18(23)**:2861-2866.
91. Yu Y, Xiao Z, Ehrlich ES, Yu X, Yu XF: **Selective assembly of HIV-1 Vif-Cul5-ElonginB-ElonginC E3 ubiquitin ligase complex through a novel SOCS box and upstream cysteines.** *Genes Dev* 2004, **18(23)**:2867-2872.
 92. Kao S, Miyagi E, Khan MA, Takeuchi H, Opi S, Goila-Gaur R, Strebel K: **Production of infectious human immunodeficiency virus type I does not require depletion of APOBEC3G from virus-producing cells.** *Retrovirology* 2004, **1(1)**:27.
 93. Mangeat B, Turelli P, Liao S, Trono D: **A single amino acid determinant governs the species-specific sensitivity of APOBEC3G to Vif action.** *J Biol Chem* 2004, **279(15)**:14481-14483.
 94. Xu H, Svarovskaia ES, Barr R, Zhang Y, Khan MA, Strebel K, Pathak VK: **A single amino acid substitution in human APOBEC3G antiretroviral enzyme confers resistance to HIV-1 virion infectivity factor-induced depletion.** *Proc Natl Acad Sci U S A* 2004, **101(15)**:5652-5657.
 95. Bogerd HP, Doehle BP, Wiegand HL, Cullen BR: **A single amino acid difference in the host APOBEC3G protein controls the primate species specificity of HIV type I virion infectivity factor.** *Proc Natl Acad Sci U S A* 2004, **101(11)**:3770-3774.
 96. Schrofelbauer B, Chen D, Landau NR: **A single amino acid of APOBEC3G controls its species-specific interaction with virion infectivity factor (Vif).** *Proc Natl Acad Sci U S A* 2004, **101(11)**:3927-3932.
 97. Gaddis NC, Sheehy AM, Ahmad KM, Swanson CM, Bishop KN, Beer BE, Marx PA, Gao F, Bibollet-Ruche F, Hahn BH, Malim MH: **Further investigation of simian immunodeficiency virus Vif function in human cells.** *J Virol* 2004, **78(21)**:12041-12046.
 98. Chen R, Wang H, Mansky LM: **Roles of uracil-DNA glycosylase and dUTPase in virus replication.** *J Gen Virol* 2002, **83(Pt 10)**:2339-2345.
 99. Priet S, Gros N, Navarro JM, Boretto J, Canard B, Querat G, Sire J: **HIV-1-associated uracil DNA glycosylase activity controls dUTP misincorporation in viral DNA and is essential to the HIV-1 life cycle.** *Mol Cell* 2005, **17(4)**:479-490.
 100. Kobayashi M, Takaori-Kondo A, Shindo K, Abudu A, Fukunaga K, Uchiyama T: **APOBEC3G targets specific virus species.** *J Virol* 2004, **78(15)**:8238-8244.
 101. Kazazian HHJ: **Mobile elements: drivers of genome evolution.** *Science* 2004, **303(5664)**:1626-1632.
 102. Turelli P, Vianin S, Trono D: **The innate antiretroviral factor APOBEC3G does not affect human LINE-1 retrotransposition in a cell culture assay.** *J Biol Chem* 2004, **279(42)**:43371-43373.
 103. Dewannieux M, Dupressoir A, Harper F, Pierron G, Heidmann T: **Identification of autonomous IAP LTR retrotransposons mobile in mammalian cells.** *Nat Genet* 2004, **36(5)**:534-539.
 104. Ribet D, Dewannieux M, Heidmann T: **An active murine transposon family pair: retrotransposition of "master" MusD copies and ETn trans-mobilization.** *Genome Res* 2004, **14(11)**:2261-2267.
 105. Ganesh L, Burstein E, Guha-Niyogi A, Louder MK, Mascola JR, Klomp LW, Wijmenga C, Duckett CS, Nabel GJ: **The gene product Murr1 restricts HIV-1 replication in resting CD4+ lymphocytes.** *Nature* 2003, **426(6968)**:853-857.
 106. Gao G, Guo X, Goff SP: **Inhibition of retroviral RNA production by ZAP, a CCCH-type zinc finger protein.** *Science* 2002, **297(5587)**:1703-1706.
 107. Bick MJ, Carroll JW, Gao G, Goff SP, Rice CM, MacDonald MR: **Expression of the zinc-finger antiviral protein inhibits alphavirus replication.** *J Virol* 2003, **77(21)**:11555-11562.
 108. Varthakavi V, Smith RM, Bour SP, Strebel K, Spearman P: **Viral protein U counteracts a human host cell restriction that inhibits HIV-1 particle production.** *Proc Natl Acad Sci U S A* 2003, **100(25)**:15154-15159.
 109. Hsu K, Seharaseyon J, Dong P, Bour S, Marban E: **Mutual functional destruction of HIV-1 Vpu and host TASK-1 channel.** *Mol Cell* 2004, **14(2)**:259-267.
 110. Margottin F, Bour SP, Durand H, Selig L, Benichou S, Richard V, Thomas D, Strebel K, Benarous R: **A novel human WD protein, h-beta TrCp, that interacts with HIV-1 Vpu connects CD4 to the ER degradation pathway through an F-box motif.** *Mol Cell* 1998, **1(4)**:565-574.

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