Published in final edited form as:
Vet Immunol Immunopathol. 2011 October 15; 143(0): 179–189. doi:10.1016/j.vetimm.2011.06.002.

Retroviral restriction and dependency factors in primates and carnivores

Hind J. Fadel and **Eric M. Poeschla**
Department of Molecular Medicine and Division of Infectious Diseases, Mayo Clinic College of Medicine, Rochester, MN, USA

Abstract

Recent studies have extended the rapidly developing retroviral restriction factor field to cells of carnivore species. Carnivoran genomes, and the domestic cat genome in particular, are revealing intriguing properties vis-à;-vis the primate and feline lentiviruses, not only with respect to their repertoires of virus-blocking restriction factors but also replication-enabling dependency factors. Therapeutic application of restriction factors is envisioned for human immunodeficiency virus (HIV) disease and the feline immunodeficiency virus (FIV) model has promise for testing important hypotheses at the basic and translational level. Feline cell-tropic HIV-1 clones have also been generated by a strategy of restriction factor evasion. We review progress in this area in the context of what is known about retroviral restriction factors such as TRIM5alpha, TRIMCyp, APOBEC3 proteins and BST-2/Tetherin.

Keywords

TRIM5alpha; TRIMCyp; APOBEC3; restriction factor; carnivores; lentivirus; HIV-1; FIV; AIDS

I. Introduction

Exogenous lentiviruses are known to infect Catarrhine primates (Old World monkeys and apes), several ungulate species and diverse felids. Recently identified endogenous lentivirus sequences provide evidence for past infections of Leporidae (rabbits and hares) and Strepsirrhine primates (lemurs) (Fletcher et al., 2010; Gifford et al., 2008; Gilbert et al., 2009; Katzourakis et al., 2007; Keckesova et al., 2009). Despite these past and present invasions of diverse Mammalia, each of the extant lentiviruses has a narrowly restricted host range. Even between closely related species, transmission is highly limited in both natural and experimental settings. This stands in contrast to other RNA viruses that can infect and cause disease in widely divergent mammalian taxa. For example, the human orthomyxovirus pathogen influenza A can be studied in common laboratory model animals such as mice and ferrets.

Overt lentivirus pathology appears to correlate with comparatively recent acquisition, e.g., the emergence of the HIV-1 main group by transmission of SIVcpz from Chimpanzees in West Africa approximately a century ago (Gao et al., 1999). Among nonprimate lentiviruses, analogous examples are visna virus transmission to genetically isolated Icelandic sheep (Sigurdsson et al., 1957) and FIV-related lentiviruses, which have likely

Correspondence: fadel.hind@mayo.edu, emp@mayo.edu; Tel: 507-538-1188. Mailing address: Department of Molecular Medicine, Guggenheim 18, Mayo Clinic, 200 First St SW, Rochester MN 55905.

All authors declare that there is no conflict of interest.

been endemic in the Panthera lineage for hundreds of thousands and perhaps several million years (Antunes et al., 2008; Pecon-Slattery et al., 2008; Troyer et al., 2008). While there is some evidence for chronic immune disease in African lions (Roelke et al., 2009), FIV is clearly pathogenic to a degree comparable to HIV-1 only in the domestic cat, in which the bulk of evidence indicates relatively recent acquisition, sometime after domestication ca. 9,000 yr ago (Pecon-Slattery et al., 2008; Troyer et al., 2008).

Current evidence suggests that the most common scenario for lentiviruses is one of extended periods of confinement to a single species punctuated by relatively rare sustainable acquisition by a new species, which occurs in association with evolved changes in key viral proteins [see, for example, recent proposals for viral adaptations critical to the SIVcpz-to-HIV-1 transition (Kirchhoff, 2009; Sauter et al., 2009)]. This pattern reflects requirements for specific host cell factors utilized by the viruses (dependency factors) and blocks posed by a suite of species-specific defense proteins (restriction factors). The latter can interdict a virus immediately, without requiring downstream transcriptional responses, cytokines or other cells. The term “intrinsic immunity” has been used to differentiate this from more slowly acting immune responses (Bieniasz, 2004; Huthoff and Towers, 2008). For HIV-1, restriction factors of interest now most prominently include TRIM5alpha (Stremlau et al., 2004), the related TRIMcyp (Nisole et al., 2004; Sayah et al., 2004), APOBEC3G/F (Sheehy et al., 2002), and BST-2/Tetherin (Neil et al., 2008; Van Damme et al., 2008), although other intracellular restriction activities exist for retroviruses.

Lentiviruses have evolved counter-defenses, such as capsids that evade TRIM5 protein engagement (Towers, 2007; Towers et al., 2003), Vif proteins that target APOBEC3 proteins for destruction in the cellular proteasome (Sheehy et al., 2002; Stern et al., 2010), central plus strand initiation that acts kinetically to reduce the time viral DNA is exposed to APOBEC3 proteins (Hu et al., 2010) and anti-Tetherins such as Vpu (Neil et al., 2008; Van Damme et al., 2008) and Nef (Sauter et al., 2009; Zhang et al., 2009). There is evidence that host populations and retroviruses have undergone repeated rounds of reactive counter-selection for and against restriction factor evasion during their respective evolutions (Lim et al., 2010a; Malim and Emerman, 2008; Sawyer et al., 2004; Sawyer et al., 2005). The positive selection engendered under this warfare and counter-warfare scenario can be stated as the Red Queen hypothesis (Huthoff and Towers, 2008; van Valen, 1973). For HIV-1, evolution of specific Vpu, Vif and Nef functions appears to have contributed to the adaptations of chimpanzee lentiviruses to humans, one of which became pandemic as the M or main group (Malim and Emerman, 2008; Sharp and Hahn, 2010). HIV-1 has lost the ability to be pathogenic in the reverse direction, to chimpanzees. Research on restriction factors has potential to help yield an animal model or models for HIV-1 (Ambrose et al., 2007; Hatziioannou et al., 2009; Hatziioannou et al., 2006; Stern et al., 2010) and to be applied therapeutically (Dietrich et al., 2010; Neagu et al., 2009).

II. Specific Restriction Factors

1. Tripartite motif (TRIM) proteins

TRIM5alpha acts by engaging the retroviral capsid in the cytoplasm of the target cell, shortly after entry and before nuclear import (Stremlau et al., 2004). Reverse transcription becomes impaired, but the precise mechanism for the subsequent derailment of viral progress is not certain at present. As discussed below, candidate mechanisms center on proteasome activity and dysregulated uncoating. This protein is part of a larger TRIM protein family with 68 known members encoded by the human genome (Nisole et al., 2005). The PRY/SPRY (or B30.2) domain in the C terminus of TRIM5alpha mediates binding to the capsid of the incoming virion, thus acting as a pattern recognition receptor (Mische et al., 2005; Sebastian and Luban, 2005; Stremlau et al., 2006a). The N-terminal segment has a

RING domain with E3-ubiquitin ligase activity (Diaz-Griffero et al., 2006a), a B-Box-2 domain and a coiled-coil domain.

In the presence of a restricting TRIM5alpha protein, the HIV-1 core does not complete reverse transcription and undergoes rapid proteasomal degradation (Diaz-Griffero et al., 2006a; Stremlau et al., 2006a). While it seems likely that under normal circumstances the proteasome is involved in viral fate, the situation is nevertheless not straightforward at present. If the proteasome is inhibited pharmacologically, reverse transcription completes but the infection process through to integration does not (Anderson et al., 2006; Campbell et al., 2008; Perez-Caballero et al., 2005; Wu et al., 2006). The arrested complex is integration-competent when tested on in vitro targets, however (Anderson et al., 2006). Thus, a reverse transcription blockade is not strictly needed for antiviral activity, and restriction activity can be uncoupled from proteasome inhibition (Perez-Caballero et al., 2005; Wu et al., 2006). Premature viral uncoating has been implicated as a primary mechanism of antiviral activity (Diaz-Griffero et al., 2006a; Perron et al., 2007; Stremlau et al., 2006a). Assaying uncoating in the presence of proteasome inhibitors is inherently complex to interpret because it appears to rescue virions that are degraded independently of TRIM5alpha and it results in major re-distribution of TRIM5alpha cytoplasmic aggregates (Diaz-Griffero et al., 2007; Diaz-Griffero et al., 2006a). FIV is strongly restricted by rhesus macaque TRIM5alpha and weakly by human TRIM5alpha (Diaz-Griffero et al., 2007; Saenz et al., 2005). Cows, rabbits and hares expressTRIM5 orthologs that inhibit replication of several retroviruses including HIV-1 (Fletcher et al., 2010; Keckesova et al., 2009; Schaller et al., 2007; Si et al., 2006; Ylinen et al., 2006).

Another cellular protein, Cyclophilin A (CypA), interacts with the HIV-1 capsid (Luban et al., 1993); reviewed in (Luban, 2007; Sokolskaja and Luban, 2006). CypA, which is the intracellular receptor for cyclosporine A, is a peptidyl-prolyl *cis-trans* isomerase that catalyses the conversion of the peptidyl-prolyl bond at G89-P90 in the HIV-1 capsid, increasing the rate of isomerization by two logs but without changing the steady state *cis-trans* ratio (Bosco et al., 2002; Gitti et al., 1996). The connection of this activity to restriction or uncoating is not entirely clear. At present, CypA and TRIM5alpha are thought to regulate infection independently, with cypA perhaps protecting HIV-1 from an unknown antiviral activity in human cells or in general modulating host factors that positively or negatively interact with capsid; this interesting, complex issue is treated in more detail in (Luban, 2007; Sokolskaja and Luban, 2006; Strebel et al., 2009; Stremlau et al., 2006b).

However, insertion of CypA into the TRIM5alpha locus so that it replaces the capsid binding function of the B30.2 domain has occurred by retrotransposition events in nonhuman primates. Remarkably, this has happened entirely independently in old and new world monkey species, which suggests potent selective advantages were conferred, presumably during culling of populations by ancient viral epidemics (Brennan et al., 2008; Liao et al., 2007; Newman et al., 2008; Nisole et al., 2004; Sayah et al., 2004; Stoye and Yap, 2008; Virgen et al., 2008; Wilson et al., 2008). In the new world (owl monkey) case (Nisole et al., 2004; Sayah et al., 2004), insertion between exons 7 and 8 created a TRMcyp fusion protein, with exon 7 spliced to CypA, whereas in old world macaque species, splicing fuses cypA to the end of exon 6. Viral specificity varies, with the owl monkey protein inhibiting FIV and HIV-1, but not SIVmac or EIAV (Diaz-Griffero et al., 2007; Diaz-Griffero et al., 2006b; Nisole et al., 2004; Sayah et al., 2004). In contrast, the *Macaca* genus TRMcyps do not restrict HIV-1, SIVmac or EIAV, but are active against FIV, HIV-2 and SIVagmTan, with the specificity mapping to a histidine or arginine at amino acid 69 (Stoye and Yap, 2008; Virgen et al., 2008; Wilson et al., 2008). Thus, among lentiviruses, the FIV capsid is uniquely vulnerable to both the owl monkey and macaque TRIMcyps, as well as to

macaque TRIM5alpha. We return below to the possibility that this can be exploited in the FIV/cat model.

2. APOBEC3 proteins

In contrast to TRIM proteins, APOBEC3G (A3G) and other antiviral A3 proteins first engage the virus in the producer cell but, as for TRIM proteins, the effect is to interdict a single round of replication without a need for associated signaling, new transcription or effector cell recruitment. [Levels of these and other restriction factor proteins are interferon-inducible, however (Asaoka et al., 2005; Carthagena et al., 2008; Koning et al., 2009; Neil et al., 2007; Refsland et al., 2010; Sakuma et al., 2007)].

In human cells, Vif-deficient HIV-1 is inhibited by A3G (Sheehy et al., 2002), which is encapsidated into virions through interactions with Gag and viral and/or small cellular RNAs (Khan et al., 2005; Luo et al., 2004; Malim, 2009; Schafer et al., 2004; Svarovskaia et al., 2004; Xu et al., 2004; Zennou et al., 2004). A3 proteins are cytidine deaminases. During reverse transcription, APOBEC3G deaminates minus strand cytidines to uridine, such that deleterious G → A mutations accumulate on the plus strand (Bishop et al., 2004; Harris et al., 2003; Mangeat et al., 2003; Mariani et al., 2003; Zhang et al., 2003). APOBEC3G has also been reported to interfere with reverse transcription at various steps (Bishop et al., 2006; Guo et al., 2007; Iwatani et al., 2007; Li et al., 2007; Mbisa et al., 2007). In particular, APOBEC3G and F have been reported to restrict in a deaminase-independent manner, although the contribution to overall antiviral activity is an unsettled issue (Bishop et al., 2006; Bishop et al., 2008; Holmes et al., 2007; Miyagi et al., 2007; Navarro et al., 2005; Newman et al., 2005; Schumacher et al., 2008). Impairment of HIV-1 reverse transcript elongation has been suggested to be a dominant mechanism (Bishop et al., 2008).

All lentiviruses except EIAV encode a Vif protein for the purpose of evading A3 restriction. Vif proteins of primate lentiviruses function primarily to deplete cellular APOBEC3G/F by recruiting an E3 ubiquitin ligase complex, thereby inducing APOBEC3G polyubiquination and proteasomal degradation (Conticello et al., 2003; Marin et al., 2003; Mehle et al., 2004; Sheehy et al., 2003; Stopak et al., 2003; Yu et al., 2003). This was recently shown to also be the case for FIV Vif (Stern et al., 2010).

A3 genomic repertoires are illustrated in Fig. 1. Based on variations in zinc-coordinating (Z) DNA cytosine deaminase motifs (H-x_1-E$x_{25–31}$-C-x2–4-C), A3 proteins can be grouped into three phylogenetic “Z domain” clusters: Z1, Z2, and Z3 (LaRue et al., 2009; LaRue et al., 2008). In the artiodactyl A3 repertoire, sheep and cattle have three *A3* genes, A3Z1, A3Z2 and A3Z3, which encode for at least four active proteins (A3Z1, A3Z2, A3Z3 and A3Z2-Z3), while the porcine lineage has a deletion of the orthologous A3Z1 gene and therefore encodes three proteins (LaRue et al., 2009; LaRue et al., 2008). The aggregate genome data suggest that the ancestral mammalian repertoire for artiodactyls, carnivorans and primates had a Z1, Z2, Z3 composition, with subsequent gene duplication and loss events. Primate A3 gene expansion (Fig. 1) likely occurred over 25 million years ago (LaRue et al., 2008). All A3s are thought to have evolved under substantial, iterative positive selective pressure, leading to highly individual present-day repertoires in which specific functional orthology cannot be inferred across species (LaRue et al., 2008). For example, Z domain composition (Z1, Z2, Z3 permutations) does not correlate with anti-retroviral activity.

3. BST-2/Tetherin

BST-2/Tetherin (CD317) is an integral membrane protein with an amino-terminal cytoplasmic tail followed by a single transmembrane domain, an extracellularly coiled-coil domain and a GPI membrane anchor at the C terminus (Neil et al., 2008; Van Damme et al.,

2008). These different structural domains of Tetherin, though not the primary sequence *per se*, are essential for its activity (Perez-Caballero et al., 2009). Tetherin protein inhibits the release of retrovirus particles and is antagonized by the HIV-1 accessory proteins Vpu (Neil et al., 2008; Van Damme et al., 2008) and Nef (Sauter et al., 2009; Yang et al., 2010; Zhang et al., 2009). Tetherin also inhibits the release of other enveloped viruses such filo-, herpes and arenaviruses, which encode distinct antagonists (Bartee et al., 2006; Jouvenet et al., 2009; Kaletsky et al., 2009; Mansouri et al., 2009; Sakuma et al., 2009; Tokarev et al., 2009). In the case of HIV-2, Env fulfills this function (Hauser et al., 2010; Le Tortorec and Neil, 2009).

III. HIV-1 Animal Models and Restriction

1. Recent advances in non-human primates

Although the SIVs that infect African monkeys do not induce AIDS in their natural hosts, infection of captive rhesus macaques with the sooty mangabey virus does (Daniel et al., 1985; Letvin et al., 1985). Cloned versions (SIVmac, which is closely related to HIV-2 but not HIV-1) have been derived (Kestler et al., 1990; Naidu et al., 1988) and allowed genetic manipulation (Kestler et al., 1991). Various versions of these viruses have provided the most useful animal model for elucidating AIDS pathogenesis for over two decades. Conversely, the lack of evident pathogenicity in naturally SIV-infected nonhuman primates despite prolific in vivo replication (e.g., SIVagm) has given rise to important and still extant questions about the key drivers of disease (Broussard et al., 2001; Lim and Emerman, 2009). Macaque models were made more directly HIV-1-relevant by construction of SIVmac variants (SHIVs) that incorporate HIV-1 *tat*, *rev*, *vpu* and *env* (Shibata et al., 1991). Applications of restriction factor science in this area are now showing considerable promise towards the still unmet goal of a true HIV-1 disease model. For example, HIV-1 clones with capsid and Vif modifications that mediate evasion of TRIM5 and APOBEC3 restrictions have yielded substantial viremia in particular macaque specie for up to six months (Hatziioannou et al., 2009; Hatziioannou et al., 2006; Igarashi et al., 2007; Kamada et al., 2006). Some remaining limitations of macaque models include the relative scarcity and expense of these nonhuman primates, a breeding time of 5–6 months, enzootic rhesus macaque infection with B virus (a uniformly lethal human pathogen that complicates handling), and the inability so far to use even the most recent simianized (Capsid segment and/or Vif-substituted) versions of HIV-1 to produce two hallmarks of human infection: disease and chronic, sustained viral replication (Ambrose et al., 2007).

2. Rodents, rabbits and hares

Numerous attempts have been made to model HIV-1 in traditional small non-primate laboratory animals and to propagate the virus in the cell lines of these animals. Other than immuno-deficient mice with human hematopoietic cell allografts, attempts to generate such a model have been disappointing. Engineering rodents for intrinsic susceptibility to HIV-1 infection appears to present fundamental difficulties. The introduction of human CD4 and a chemokine coreceptor into murine cells allows viral entry (Feng et al., 1996) and expression of human cyclin T1 enables Tat-dependent proviral transcription (Wei et al., 1998). However, various impediments to proper viral assembly, particle infectivity and post-entry infectivity in rodent cells have been obstacles (Baumann et al., 2004; Bieniasz and Cullen, 2000; Goffinet et al., 2009; Goffinet et al., 2010; Keppler et al., 2002; Keppler et al., 2001; Mariani et al., 2001; Michel et al., 2009; Swanson et al., 2004; Tervo et al., 2008). Leporidae (rabbit and hare) cells encode TRIM5alpha orthlogs that broadly restrict retroviruses, including HIV-1, HIV-2, FIV, EIAV and N-MLV (Fletcher et al., 2010; Schaller et al., 2007). Productive spreading replication of HIV-1 has not been demonstrated in any rabbit cells. However, rabbit TRM5alpha did not restrict SIVmac post-entry (Schaller

et al., 2007), and incorporating the first 150 amino acids of SIVmac239 capsid into HIV-1 relieved the post-entry block to the latter virus (Tervo and Keppler, 2010). Rabbit T cells but not macrophages supported the production of HIV-1 with human cell-comparable infectivity (Tervo and Keppler, 2010).

IV- Carnivoran restriction and dependency factor gene repertoires

We next consider the mammalian order Carnivora with respect to its two suborders, the Feliformia and the Caniformia, and review singular aspects of their restriction repertoires and susceptibility to lentiviral infection.

1. Feliformia and retroviruses

Three exogenous retroviruses infect domestic cats: Feline leukemia virus (FeLV), feline foamy virus (FFV), and feline immunodeficiency virus (FIV) (Jarrett et al., 1968; Pedersen et al., 1987; Winkler et al., 1997). The cat genome also contains endogenous retroviruses, such as the replication-competent RD114 virus (Sarma et al., 1973) and endogenous FeLVs (Polani et al., 2010; Roca et al., 2004). FIV, in a similar fashion to HIV-1, causes depletion of CD4-positive T cells in the domestic cat and a syndrome with high similarity to human AIDS (Ackley et al., 1990; Elder et al., 2010). It is the only non-primate lentivirus that does so. Both HIV-1 and FIV use the CXCR4 chemokine as a coreceptor for entry, but the primary receptor for FIV is CD134 rather than CD4 (Feng et al., 1996; Poeschla and Looney, 1998; Shimojima et al., 2004; Willett et al., 1997a; Willett et al., 1997b). Viruses highly related to domestic cat FIV infect various other feline species, including the *Panthera* and *Puma* genera, where chronic immune system consequences have been documented (Roelke et al., 2009; Roelke et al., 2006; Troyer et al., 2008).

Retrovirolgists have known for some time that domestic cat cell lines were relatively easily transduced with pseudotyped gammaretroviral and lentiviral vectors. Indeed, cat and dog cell lines have frequently been used as permissive “null” background lines for HIV-1 entry receptor testing (McKnight et al., 1994) and more recently for testing antiviral properties of introduced primate TRIM5 proteins (Keckesova et al., 2004). Life cycle steps from the post-entry uncoating stage through to integration are not restricted in domestic cat cell lines. N- and B-MLV are equivalently infectious. In a recent study, McEwan et al. determined a main reason for this: the genomes of all Feliformia encode a TRIM5alpha gene with a truncated and thus inactive B30.2 capsid binding domain (McEwan et al., 2009). This protein does not restrict HIV-1, SIVmac, or N-tropic murine leukemia virus (N-MLV) due to a stop codon in exon eight, 5’ to the V1 region of the B30.2 domain (McEwan et al., 2009). The mutation arose after the Caniformia-Feliformia split approximately 54 million years ago, since exon 8 in two Caniformia species tested (dog and mink) did not have it (though the dog gene is known to be inactivated by other means as discussed below) (McEwan et al., 2009). However, it is certifiably ancient, being present in all Feliformia species, even hyena and fossa, consistent with an origin before the Felidae and Hyaenidae diverged over 40 million years ago (McEwan et al., 2009). Note that other post-entry restrictions exist in some felids. For example, primate lentiviruses encounter a strong post-entry block in lion cells (W. McEwan and B. Willett, personal communication).

Neither *Felis catus* nor *Homo sapiens* has a TRIMcyp protein. As noted above, FIV is restricted by rhesus TRIM5alpha as well as by owl monkey TRIMcyp and macaque TRIMcyps, while HIV-1 is restricted by the first two of these. This suggests the possibility that such proteins or re-engineered versions of them could be used in human or feline gene therapy, and also that the approach could be modeled in the cat. Two groups have recently made progress in this area, with “humanized” and “felinized” TRIMcyps respectively (Dietrich et al., 2010; Neagu et al., 2009). Both modeled the proteins after non-human

primate TRIMcyps. Dietrich et al. discuss this research in more detail elsewhere in this volume [••]. A plus is that since both partners in these chimeras pre-exist in the human and the cat proteomes, the immune responses, if any, to the therapeutic protein are likely to be limited to the fusion junction. A caveat to be considered in such an approach is that fusing the biologically potent CypA domain to the TRIM5 N-terminal domains in a species that has not co-evolved potentially needed compensatory adaptations in other cellular systems could prove to have unpredictable deleterious effects. These aspects and the efficacy and durability of restriction factor-based gene therapy in general have potential to be tested in the cat. Finally, whether introduction of a single restriction factor would protect, and at which of three broadly considered levels -- transmission, systemic viremia, disease -- is not clear. For example, there are macaque and sooty mangabey TRIM5 alleles that do not block primate immunodeficiency virus transmission outright but can limit replication in vivo and which appear to have exerted specific selection pressure on the capsid protein (Kirmaier et al., 2010; Lim et al., 2010b). These are exciting questions for further research.

In contrast to the situation with TRIM5, feline species encode active APOBEC3 proteins (Fig. 1). The domestic cat genome has four A3 genes that encode for 5 known proteins: fA3Ca-c, fA3H and fA3CH (Münk et al., 2008; Munk et al., 2009; Münk et al., 2007). These proteins are termed fA3Z2c, fA3Z2a, fA3Z2b, fA3Z3 and fA3Z2b-Z3 respectively in the Z domain-based classification of LaRue et al. (LaRue et al., 2009). (Human A3F and A3G proteins are named A3Z2e-Z2f and A3Z2g-Z1c respectively in this system). fA3CH (fA3Z2b-Z3) is obtained by alternative splicing and read-through transcription (Münk et al., 2008; Zielonka et al., 2010). There are no double domain feline A3 proteins that are analogous in Z domain composition to human A3G (Z2-Z1) or A3F (Z2-Z2). The three closely related fA3Cs (fA3Ca, fA3Cb and fA3Cc) are active against Δ*bet* feline foamy virus (Lochelt et al., 2005) but not Δ*vif* FIV (Münk et al., 2008; Stern et al., 2010). The foamy virus Bet protein acts analogously to Vif in preventing fA3Ca,b,c (fA3Z2c,a,b) restriction (Münk et al., 2008). The two other proteins (fA3H and fA3CH) have anti-lentiviral effects, as they restrict Δ*vif* FIV and *vif*-intact HIV-1 and induce G to A hypermutation (Münk et al., 2008; Münk et al., 2007; Stern et al., 2010). fA3CH, the only two-domain feline A3 protein, is an unusual hybrid encoded by exons 1–3 of fA3Ca, exon 4 of fA3Cb and exons 2–5 of fA3H (Münk et al., 2008). More recently, additional Z2–Z3 variants were identified (Zielonka et al., 2010). Interestingly, A3 proteins from diverse free-ranging feline species are sensitive to the Vif protein of domestic cat FIV, suggesting A3 restriction is not an obstacle to inter-feline transmission of this virus (Zielonka et al., 2010). The latter study also reported that human A3G and A3F diminish FIV particle infectivity.

2. Generation of feline cell-tropic HIV-1 by APOBEC3 protein evasion

Domestic cat cells produce HIV-1 with low infectivity, which is associated with minus strand deamination by two of the five fA3 proteins; the greatest activity is attributable to the two-domain fA3CH, with fA3H making a lesser yet substantial contribution; in contrast the three fA3C proteins (a–c) are not appreciably restricting of HIV-1 (Münk et al., 2008; Münk et al., 2007; Stern et al., 2010). FIV Vif acts similarly to primates Vifs by decreasing levels of fA3s in a proteasome-dependent manner (Stern et al., 2010).

Focusing on the lack of significant post-entry restricting activity in a number of domestic cat cell lines and the clear evidence of fA3 activity against primate lentiviruses, we recently asked what limits spreading HIV-1 replication in feline cells (Stern et al., 2010). As noted above, transgenic mouse models of HIV-1 infection are prevented not only by restriction (Baumann et al., 2004; Doehle et al., 2005; Mariani et al., 2003), but by stringent blocks to proper viral assembly that appear to reflect a lack of functional dependency factors (Bieniasz and Cullen, 2000; Mariani et al., 2001; Swanson et al., 2004). We noted that feline

fibroblasts, T cell lines and primary peripheral blood mononuclear cells supported early and late HIV-1 life cycle phases equivalently to human cells (Stern et al., 2010). Consistent with their A3 activities, HIV-1 produced in such cells had low infectivity. However, stable expression of FIV Vif alone (as a codon-optimized GFP fusion protein) in HIV-1 entry receptor-complemented CrFK cells enabled spreading replication of the virus at levels commensurate to those observed in human cell lines. In addition, FIV Vif co-localized with feline APOBEC3 (fA3) proteins, targeted them for degradation and prevented G → A hypermutation of the HIV-1 cDNA by fA3CH and fA3H.

In interesting and unexpected contrast, SIVmac Vif had substantial anti-fA3 activities, which were complete against fA3CH and partial against fA3H while HIV-1 Vif was inactive against fA3s as expected. These results provide the first evidence that a primate Vif can counteract a non-primate A3 (Stern et al., 2010). Further examples of Vif proteins acting to promote degradation of A3 proteins in this way – i.e., in non-cognate species and across mammalian suborders – were reported by LaRue et al. (LaRue et al., 2010). Interestingly, both primate lentiviral Vifs co-localized with fA3s and could be pulled down from cell lysates by fA3CH but with HIV-1 Vif this does not result in A3 degradation or relief of restriction (Stern et al., 2010). Whatever cellular factors FIV Vif recruits to target fA3H or fA3CH for degradation (e.g., feline equivalents of Cul5, elongin B/C), it appears that HIV-1 Vif is unable to correctly establish a functional complex.

To complete the picture, we constructed HIV-1 molecular clones that encode FIV Vif or SIVmac Vif (Stern et al., 2010). Both of these viruses (HIV-1^{VF} and HIV-1^{VS}) replicated productively in HIV-1 receptor-expressing CrFK cells and they could be passaged serially to uninfected cells. These viruses are analogous in concept to recent pigtail macaque-enabled HIV-1 clones in that in both cases only *vif* modification was needed to enable spreading replication (Hatziioannou et al., 2009). The obvious difference for the feline cell-competent viruses is that the entry receptors do not exist in the cat, which has so far precluded animal testing. Zielonka et al. also recently inserted FIV *vif* into HIV-1 (Zielonka et al., 2010). The FIV *vif* gene cDNA was inserted immediately downstream of an engineered TAG stop codon in the HIV-1 *vif* reading frame. Whether internal initiation of translation of the feline Vif protein occurred or the AG dinucleotide in the stop codon acted as a splice acceptor is not clear, but this virus also replicated in receptor-complemented CrFK cells.

These studies have therefore revealed that except for entry receptors, the cat genome can supply the dependency factors needed for productive replication of HIV-1. The main restriction can be countered by *vif* chimerism. More subtle or cell type-specific restrictions could turn out to be limiting. Nevertheless it can be speculated that if transgenic expression of HIV-1 entry receptors in the proper hematopoietic lineages of the cat could be enabled, this might have potential to eventually produce a feline HIV-1 model. In principle, transgenesis could also be applied to restriction factor gene therapy modeling.

3. The Caniformia

In contrast to the cat, exogenous dog retroviruses have not been identified and in general Caniformia cells are much less characterized for retroviral restriction. However, similarly to domestic cat cells, dog cell lines appear to lack discernible post-entry restriction activity of the TRIM5α type although B-tropic MLV has been reported to be more infectious than N-MLV in some lines (Towers et al., 2000). In this species and perhaps other Caniformia, TRIM5alpha disruption has occurred not by a stop codon, but by the insertion of an apparently unrelated gene (*PNRC1*) that prevents expression at the level of transcription rather than translation (Sawyer et al., 2007). Thus, two independent TRIM5α disruption events have taken place during carnivore evolution.

Phylogenetic studies have indicated that the dog genome encodes Z1 and Z3 APOBEC3 proteins, which are so far less characterized (LaRue et al., 2008; Münk et al., 2008; OhAinle et al., 2006). The canine Z3 protein (alternatively called A3H) has been reported to have activity against FIV and SIVagm (Münk et al., 2008). Canine chronic lymphocytic cells (CLL) that express the FIV entry receptor CD134 were reported to support productive replication of FIV (Willett et al., 2006). When marmoset and human CD4 and CXCR4 receptors were introduced into canine fetal thymus (Cf2Th) cells, HIV-1 could be serially passaged in these cells lines, leading to the adaptation of HIV-1 envelope glycoproteins to these New World monkey receptors and productive replication (Kolchinsky et al., 1999; Pacheco et al., 2008). Studies of cell lines from other Caniformia, e.g. *Mustelidae* (weasels), have suggested that they also do not restrict N-MLV (Towers et al., 2000) or HIV-1 (Koito et al., 2003a; Koito et al., 2003b) post-entry. Koito et al. reported that receptor-complemented mink cells supported early and late HIV-1 gene expression and viral replication (Koito et al., 2003a). Serial passage and exponential amplification of HIV-1 in mink or other Mustelidae cells remains to be demonstrated.

V. Conclusions and perspectives

Taken together, all of these studies in cells of species that span the Feliformia and Caniformia suborders indicate that carnivore species present interesting prospects for further understanding host defenses against lentiviruses and perhaps for exploiting them. The similarities of FIV to HIV-1 in genetic structure, the close resemblance of the two AIDS syndromes, and the unusually broad susceptibility of FIV to multiple primate restriction factor variants, suggest that cat has favorable characteristics for testing basic and translational hypotheses about restriction factors in vivo.

Considering the other side of the coin, while the prospect of modeling HIV-1 disease in any carnivore species is a speculative one at present, there are nevertheless reasons to start considering the possibilities. Recent studies reveal that the cat proteome, in clear distinction to that of the mouse, contains the essential HIV-1 dependency factors for productive replication if viral entry is enabled. HIV-1 assembly proceeds normally and the post-entry pathway to integration is not significantly hindered in cat cells so far tested. In addition to the clear viral phenotypic data, it has been further established that functional genes that encode known murine and primate (Fv1/TRIM) post-entry restriction mechanisms are not present in this species. Similarly, recent experiments show that the potent restrictions mediated by APOBEC3 proteins can be abrogated in both macaque and cat cells by *vif* gene substitution. Further engineering of HIV-1 molecular clones for restriction factor evasion in cells of macaques and carnivores may be possible. Progress in carnivores will benefit from additional characterization of restriction mechanisms in relevant target cells of different species and development of procedures for germline modification of such animals.

Acknowledgments

E.M.P. receives funding from NIH AI77344 and H. Fadel was funded in part by a Mayo Clinic Rosenow Fellowship Award.

References

Ackley CD, Yamamoto JK, Levy N, Pedersen NC, Cooper MD. Immunologic abnormalities in pathogen-free cats experimentally infected with feline immunodeficiency virus. J. Virol. 1990; 64:5652–5655. [PubMed: 1976826]

Ambrose Z, KewalRamani VN, Bieniasz PD, Hatziioannou T. HIV/AIDS: in search of an animal model. Trends Biotechnol. 2007:333–337. [PubMed: 17574286]

Anderson JL, Campbell EM, Wu X, Vandegraaff N, Engelman A, Hope TJ. Proteasome inhibition reveals that a functional preintegration complex intermediate can be generated during restriction by diverse TRIM5 proteins. J. Virol. 2006; 80:9754–9760. [PubMed: 16973579]

Antunes A, Troyer JL, Roelke ME, Pecon-Slattery J, Packer C, Winterbach C, Winterbach H, Hemson G, Frank L, Stander P, Siefert L, Driciru M, Funston PJ, Alexander KA, Prager KC, Mills G, Wildt D, Bush M, O'Brien SJ, Johnson WE. The evolutionary dynamics of the lion Panthera leo revealed by host and viral population genomics. PLoS Genet. 2008; 4:e1000251. [PubMed: 18989457]

Asaoka K, Ikeda K, Hishinuma T, Horie-Inoue K, Takeda S, Inoue S. A retrovirus restriction factor TRIM5alpha is transcriptionally regulated by interferons. Biochem. Biophys. Res. Commun. 2005:1950–1956. [PubMed: 16289103]

Bartee E, McCormack A, Fruh K. Quantitative membrane proteomics reveals new cellular targets of viral immune modulators. PLoS Pathog. 2006; 2:e107. [PubMed: 17238276]

Baumann JG, Unutmaz D, Miller MD, Breun SK, Grill SM, Mirro J, Littman DR, Rein A, KewalRamani VN. Murine T cells potently restrict human immunodeficiency virus infection. J. Virol. 2004; 78:12537–12547. [PubMed: 15507641]

Bieniasz PD. Intrinsic immunity: a front-line defense against viral attack. Nat. Immunol. 2004:1109–1115. [PubMed: 15496950]

Bieniasz PD, Cullen BR. Multiple blocks to human immunodeficiency virus type 1 replication in rodent cells. J. Virol. 2000; 74:9868–9877. [PubMed: 11024113]

Bishop KN, Holmes RK, Malim MH. Antiviral potency of APOBEC proteins does not correlate with cytidine deamination. J. Virol. 2006; 80:8450–8458. [PubMed: 16912295]

Bishop KN, Holmes RK, Sheehy AM, Davidson NO, Cho SJ, Malim MH. Cytidine deamination of retroviral DNA by diverse APOBEC proteins. Curr. Biol. 2004; 14:1392–1396. [PubMed: 15296758]

Bishop KN, Verma M, Kim EY, Wolinsky SM, Malim MH. APOBEC3G inhibits elongation of HIV-1 reverse transcripts. PLoS Pathog. 2008; 4:e1000231. [PubMed: 19057663]

Bosco DA, Eisenmesser EZ, Pochapsky S, Sundquist WI, Kern D. Catalysis of cis/trans isomerization in native HIV-1 capsid by human cyclophilin A. Proc. Natl. Acad. Sci. U S A. 2002; 99:5247–5252. [PubMed: 11929983]

Brennan G, Kozyrev Y, Hu SL. TRIMCyp expression in Old World primates Macaca nemestrina and Macaca fascicularis. Proc. Natl. Acad. Sci. U S A. 2008; 105:3569–3574. [PubMed: 18287033]

Broussard SR, Staprans SI, White R, Whitehead EM, Feinberg MB, Allan JS. Simian immunodeficiency virus replicates to high levels in naturally infected African green monkeys without inducing immunologic or neurologic disease. J. Virol. 2001; 75:2262–2275. [PubMed: 11160730]

Campbell EM, Perez O, Anderson JL, Hope TJ. Visualization of a proteasome-independent intermediate during restriction of HIV-1 by rhesus TRIM5alpha. J. Cell Biol. 2008; 180:549–561. [PubMed: 18250195]

Carthagena L, Parise MC, Ringeard M, Chelbi-Alix MK, Hazan U, Nisole S. Implication of TRIM alpha and TRIMCyp in interferon-induced anti-retroviral restriction activities. Retrovirology. 2008; 5:59. [PubMed: 18613956]

Conticello SG, Harris RS, Neuberger MS. The Vif protein of HIV triggers degradation of the human antiretroviral DNA deaminase APOBEC3G. Curr. Biol. 2003; 13:2009–2013. [PubMed: 14614829]

Daniel MD, Letvin NL, King NW, Kannagi M, Sehgal PK, Hunt RD, Kanki PJ, Essex M, Desrosiers RC. Isolation of T-cell tropic HTLV-III-like retrovirus from macaques. Science. 1985; 228:1201–1204. [PubMed: 3159089]

Diaz-Griffero F, Kar A, Lee M, Stremlau M, Poeschla E, Sodroski J. Comparative requirements for the restriction of retrovirus infection by TRIM5alpha and TRIMCyp. Virology. 2007; 369:400–410. [PubMed: 17920096]

Diaz-Griffero F, Li X, Javanbakht H, Song B, Welikala S, Stremlau M, Sodroski J. Rapid turnover and polyubiquitylation of the retroviral restriction factor TRIM5. Virology. 2006a; 349:300–315. [PubMed: 16472833]

Diaz-Griffero F, Vandegraaff N, Li Y, McGee-Estrada K, Stremlau M, Welikala S, Si Z, Engelman A, Sodroski J. Requirements for capsid-binding and an effector function in TRIMCyp-mediated restriction of HIV-1. Virology. 2006b; 351:404–419. [PubMed: 16650449]

Dietrich I, Macintyre A, McMonagle E, Price AJ, James LC, McEwan WA, Hosie MJ, Willett BJ. Potent lentiviral restriction by a synthetic feline TRIM5 cyclophilin A fusion. J. Virol. 2010; 84:8980–8985. [PubMed: 20554781]

Doehle BP, Schafer A, Wiegand HL, Bogerd HP, Cullen BR. Differential sensitivity of murine leukemia virus to APOBEC3-mediated inhibition is governed by virion exclusion. J. Virol. 2005; 79:8201–8207. [PubMed: 15956565]

Elder JH, Lin YC, Fink E, Grant CK. Feline immunodeficiency virus (FIV) as a model for study of lentivirus infections: parallels with HIV. Curr. HIV Res. 2010; 8:73–80. [PubMed: 20210782]

Feng Y, Broder CC, Kennedy PE, Berger EA. HIV-1 entry cofactor: functional cDNA cloning of a seven-transmembrane, G protein-coupled receptor [see comments]. Science. 1996; 272:872–877. [PubMed: 8629022]

Fletcher AJ, Hue S, Schaller T, Pillay D, Towers GJ. Hare TRIM5alpha Restricts Divergent Retroviruses and Exhibits Significant Sequence Variation from Closely Related Lagomorpha TRIM5 Genes. J. Virol. 2010; 84:12463–12468. [PubMed: 20861252]

Gao F, Bailes E, Robertson DL, Chen Y, Rodenburg CM, Michael SF, Cummins LB, Arthur LO, Peeters M, Shaw GM, Sharp PM, Hahn BH. Origin of HIV-1 in the chimpanzee Pan troglodytes troglodytes. Nature. 1999; 397:436–441. [PubMed: 9989410]

Gifford RJ, Katzourakis A, Tristem M, Pybus OG, Winters M, Shafer RW. A transitional endogenous lentivirus from the genome of a basal primate and implications for lentivirus evolution. Proc. Natl. Acad. Sci. U S A. 2008; 105:20362–20367. [PubMed: 19075221]

Gilbert C, Maxfield DG, Goodman SM, Feschotte C. Parallel germline infiltration of a lentivirus in two Malagasy lemurs. PLoS Genet. 2009; 5:e1000425. [PubMed: 19300488]

Gitti RK, Lee BM, Walker J, Summers MF, Yoo S, Sundquist WI. Structure of the amino-terminal core domain of the HIV-1 capsid protein. Science. 1996; 273:231–235. [PubMed: 8662505]

Goffinet C, Allespach I, Homann S, Tervo HM, Habermann A, Rupp D, Oberbremer L, Kern C, Tibroni N, Welsch S, Krijnse-Locker J, Banting G, Krausslich HG, Fackler OT, Keppler OT. HIV-1 antagonism of CD317 is species specific and involves Vpu-mediated proteasomal degradation of the restriction factor. Cell Host Microbe. 2009; 5:285–297. [PubMed: 19286137]

Goffinet C, Schmidt S, Kern C, Oberbremer L, Keppler OT. Endogenous CD317/Tetherin limits replication of HIV-1 and murine leukemia virus in rodent cells and is resistant to antagonists from primate viruses. J. Virol. 2010; 84:11374–11384. [PubMed: 20702620]

Guo F, Cen S, Niu M, Yang Y, Gorelick RJ, Kleiman L. The interaction of APOBEC3G with human immunodeficiency virus type 1 nucleocapsid inhibits tRNA3Lys annealing to viral RNA. J.Virol. 81:11322–11331. [PubMed: 17670826]

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; 113:803–809. [PubMed: 12809610]

Hatziioannou T, Ambrose Z, Chung NP, Piatak M Jr, Yuan F, Trubey CM, Coalter V, Kiser R, Schneider D, Smedley J, Pung R, Gathuka M, Estes JD, Veazey RS, KewalRamani VN, Lifson JD, Bieniasz PD. A macaque model of HIV-1 infection. Proc. Natl. Acad. Sci. U S A. 2009; 106:4425–4429. [PubMed: 19255423]

Hatziioannou T, Princiotta M, Piatak M Jr, Yuan F, Zhang F, Lifson JD, Bieniasz PD. Generation of simian-tropic HIV-1 by restriction factor evasion. Science. 2006; 314:95. [PubMed: 17023652]

Hauser H, Lopez LA, Yang SJ, Oldenburg JE, Exline CM, Guatelli JC, Cannon PM. HIV-1 Vpu and HIV-2 Env counteract BST-2/tetherin by sequestration in a perinuclear compartment. Retrovirology. 2010; 7:51. [PubMed: 20529266]

Holmes RK, Koning FA, Bishop KN, Malim MH. APOBEC3F can inhibit the accumulation of HIV-1 reverse transcription products in the absence of hypermutation. Comparisons with APOBEC3G. J. Biol. Chem. 2007; 282:2587–2595. [PubMed: 17121840]

Hu C, Saenz DT, Fadel HJ, Walker W, Peretz M, Poeschla EM. The HIV-1 central polypurine tract functions as a second line of defense against APOBEC3G/F. J. Virol. 2010; 84:11981–11993. [PubMed: 20844042]

Huthoff H, Towers GJ. Restriction of retroviral replication by APOBEC3G/F and TRIM5alpha. Trends Microbiol. 2008; 16:612–619. [PubMed: 18976920]

Igarashi T, Iyengar R, Byrum RA, Buckler-White A, Dewar RL, Buckler CE, Lane HC, Kamada K, Adachi A, Martin MA. Human immunodeficiency virus type 1 derivative with 7% simian immunodeficiency virus genetic content is able to establish infections in pig-tailed macaques. J. Virol. 2007; 81:11549–11552. [PubMed: 17670817]

Iwatani Y, Chan DS, Wang F, Maynard KS, Sugiura W, Gronenborn AM, Rouzina I, Williams MC, Musier-Forsyth K, Levin JG. Deaminase-independent inhibition of HIV-1 reverse transcription by APOBEC3G. Nucleic Acids Res. 2007; 35:7096–7108. [PubMed: 17942420]

Jarrett O, Laird HM, Hay D, Crighton GW. Replication of cat leukemia virus in cell cultures. Nature. 1968; 219:521–522. [PubMed: 5695164]

Jouvenet N, Neil SJ, Zhadina M, Zang T, Kratovac Z, Lee Y, McNatt M, Hatziioannou T, Bieniasz PD. Broad-spectrum inhibition of retroviral and filoviral particle release by tetherin. J. Virol. 2009; 83:1837–1844. [PubMed: 19036818]

Kaletsky RL, Francica JR, Agrawal-Gamse C, Bates P. Tetherin-mediated restriction of filovirus budding is antagonized by the Ebola glycoprotein. Proc. Natl. Acad. Sci. U S A. 2009; 106:2886–2891. [PubMed: 19179289]

Kamada K, Igarashi T, Martin MA, Khamsri B, Hatcho K, Yamashita T, Fujita M, Uchiyama T, Adachi A. Generation of HIV-1 derivatives that productively infect macaque monkey lymphoid cells. Proc. Natl. Acad. Sci. U S A. 2006; 103:16959–16964. [PubMed: 17065315]

Katzourakis A, Tristem M, Pybus OG, Gifford RJ. Discovery and analysis of the first endogenous lentivirus. Proc. Natl. Acad. Sci. U S A. 2007; 104:6261–6265. [PubMed: 17384150]

Keckesova Z, Ylinen LM, Towers GJ. The human and African green monkey TRIM5alpha genes encode Ref1 and Lv1 retroviral restriction factor activities. Proc. Natl. Acad. Sci. U S A. 2004; 101:10780–10785. [PubMed: 15249687]

Keckesova Z, Ylinen LM, Towers GJ, Gifford RJ, Katzourakis A. Identification of a RELIK orthologue in the European hare (Lepus europaeus) reveals a minimum age of 12 million years for the lagomorph lentiviruses. Virology. 2009; 384:7–11. [PubMed: 19070882]

Keppler OT, Welte FJ, Ngo TA, Chin PS, Patton KS, Tsou CL, Abbey NW, Sharkey ME, Grant RM, You Y, Scarborough JD, Ellmeier W, Littman DR, Stevenson M, Charo IF, Herndier BG, Speck RF, Goldsmith MA. Progress toward a human CD4/CCR5 transgenic rat model for de novo infection by human immunodeficiency virus type 1. J. Exp Med. 2002; 195:719–736. [PubMed: 11901198]

Keppler OT, Yonemoto W, Welte FJ, Patton KS, Iacovides D, Atchison RE, Ngo T, Hirschberg DL, Speck RF, Goldsmith MA. Susceptibility of rat-derived cells to replication by human immunodeficiency virus type 1. J. Virol. 2001; 75:8063–8073. [PubMed: 11483751]

Kestler H, Kodama T, Ringler D, Marthas M, Pedersen N, Lackner A, Regier D, Sehgal P, Daniel M, King N, et al. Induction of AIDS in rhesus monkeys by molecularly cloned simian immunodeficiency virus. Science. 1990; 248:1109–1112. [PubMed: 2160735]

Kestler, HWd; Ringler, DJ.; Mori, K.; Panicali, DL.; Sehgal, PK.; Daniel, MD.; Desrosiers, RC. Importance of the nef gene for maintenance of high virus loads and for development of AIDS. Cell. 1991; 65:651–662. [PubMed: 2032289]

Khan MA, Kao S, Miyagi E, Takeuchi H, Goila-Gaur R, Opi S, Gipson CL, Parslow TG, Ly H, Strebel K. Viral RNA is required for the association of APOBEC3G with human immunodeficiency virus type 1 nucleoprotein complexes. J.Virol. 2005; 79:5870–5874. [PubMed: 15827203]

Kirchhoff F. Is the high virulence of HIV-1 an unfortunate coincidence of primate lentiviral evolution? Nat. Rev Microbiol. 2009; 7:467–476. [PubMed: 19305418]

Kirmaier A, Wu F, Newman RM, Hall LR, Morgan JS, O'Connor S, Marx PA, Meythaler M, Goldstein S, Buckler-White A, Kaur A, Hirsch VM, Johnson WE. TRIM5 suppresses cross-

species transmission of a primate immunodeficiency virus and selects for emergence of resistant variants in the new species. PLoS Biol. 2010; 8

Koito A, Kameyama Y, Cheng-Mayer C, Matsushita S. Susceptibility of mink (Mustera vision)-derived cells to replication by human immunodeficiency virus type 1. J. Virol. 2003a; 77:5109–5117. [PubMed: 12692213]

Koito A, Shigekane H, Matsushita S. Ability of small animal cells to support the postintegration phase of human immunodeficiency virus type-1 replication. Virology. 2003b; 305:181–191. [PubMed: 12504551]

Kolchinsky P, Mirzabekov T, Farzan M, Kiprilov E, Cayabyab M, Mooney LJ, Choe H, Sodroski J. Adaptation of a CCR5-using, primary human immunodeficiency virus type 1 isolate for CD4-independent replication. J. Virol. 1999; 73:8120–8126. [PubMed: 10482561]

Koning FA, Newman EN, Kim EY, Kunstman KJ, Wolinsky SM, Malim MH. Defining APOBEC3 expression patterns in human tissues and hematopoietic cell subsets. J. Virol. 2009; 83:9474–9485. [PubMed: 19587057]

LaRue RS, Andresdottir V, Blanchard Y, Conticello SG, Derse D, Emerman M, Greene WC, Jonsson SR, Landau NR, Lochelt M, Malik HS, Malim MH, Munk C, O'Brien SJ, Pathak VK, Strebel K, Wain-Hobson S, Yu XF, Yuhki N, Harris RS. Guidelines for naming nonprimate APOBEC3 genes and proteins. J. Virol. 2009; 83:494–497. [PubMed: 18987154]

LaRue RS, Jonsson SR, Silverstein KA, Lajoie M, Bertrand D, El-Mabrouk N, Hotzel I, Andresdottir V, Smith TP, Harris RS. The artiodactyl APOBEC3 innate immune repertoire shows evidence for a multi-functional domain organization that existed in the ancestor of placental mammals. BMC Mol. Biol. 2008; 9:104. [PubMed: 19017397]

LaRue RS, Lengyel J, Jonsson SR, Andresdottir V, Harris RS. Lentiviral Vif degrades the APOBEC3Z3/APOBEC3H protein of its mammalian host and is capable of cross-species activity. J. Virol. 2010; 84:8193–8201. [PubMed: 20519393]

Le Tortorec A, Neil SJ. Antagonism to and intracellular sequestration of human tetherin by the human immunodeficiency virus type 2 envelope glycoprotein. J. Virol. 2009; 83:11966–11978. [PubMed: 19740980]

Letvin NL, Daniel MD, Sehgal PK, Desrosiers RC, Hunt RD, Waldron LM, MacKey JJ, Schmidt DK, Chalifoux LV, King NW. Induction of AIDS-like disease in macaque monkeys with T-cell tropic retrovirus STLV-III. Science. 1985; 230:71–73. [PubMed: 2412295]

Li XY, Guo F, Zhang L, Kleiman L, Cen S. APOBEC3G inhibits DNA strand transfer during HIV-1 reverse transcription. J. Biol. Chem. 2007; 282:32065–32074. [PubMed: 17855362]

Liao CH, Kuang YQ, Liu HL, Zheng YT, Su B. A novel fusion gene, TRIM5-Cyclophilin A in the pig-tailed macaque determines its susceptibility to HIV-1 infection. Aids. 2007; 21(Suppl 8):S19–S26. [PubMed: 18172386]

Lim ES, Emerman M. Simian immunodeficiency virus SIVagm from African green monkeys does not antagonize endogenous levels of African green monkey tetherin/BST-2. J. Virol. 2009; 83:11673–11681. [PubMed: 19726508]

Lim ES, Malik HS, Emerman M. Ancient adaptive evolution of tetherin shaped the functions of Vpu and Nef in human immunodeficiency virus and primate lentiviruses. J. Virol. 2010a; 84:7124–7134. [PubMed: 20444900]

Lim SY, Rogers T, Chan T, Whitney JB, Kim J, Sodroski J, Letvin NL. TRIM5alpha Modulates Immunodeficiency Virus Control in Rhesus Monkeys. PLoS Pathog. 2010b; 6:e1000738. [PubMed: 20107597]

Lochelt M, Romen F, Bastone P, Muckenfuss H, Kirchner N, Kim YB, Truyen U, Rosler U, Battenberg M, Saib A, Flory E, Cichutek K, Munk C. The antiretroviral activity of APOBEC3 is inhibited by the foamy virus accessory Bet protein. Proc. Natl. Acad. Sci. U S A. 2005; 102:7982–7987. [PubMed: 15911774]

Luban J. Cyclophilin A, TRIM5, and resistance to human immunodeficiency virus type 1 infection. J. Virol. 2007; 81:1054–1061. [PubMed: 16956947]

Luban J, Bossolt KL, Franke EK, Kalpana GV, Goff SP. Human immunodeficiency virus type 1 Gag protein binds to cyclophilins A and B. Cell. 1993; 73:1067–1078. [PubMed: 8513493]

Luo K, Liu B, Xiao Z, Yu Y, Yu X, Gorelick R, Yu XF. Amino-terminal region of the human immunodeficiency virus type 1 nucleocapsid is required for human APOBEC3G packaging. J. Virol. 2004; 78:11841–11852. [PubMed: 15479826]

Malim MH. APOBEC proteins and intrinsic resistance to HIV-1 infection. Philos Trans R Soc Lond B Biol. Sci. 2009; 364:675–687. [PubMed: 19038776]

Malim MH, Emerman M. HIV-1 accessory proteins--ensuring viral survival in a hostile environment. Cell Host Microbe. 2008; 3:388–398. [PubMed: 18541215]

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; 424:99–103. [PubMed: 12808466]

Mansouri M, Viswanathan K, Douglas JL, Hines J, Gustin J, Moses AV, Fruh K. Molecular mechanism of BST2/tetherin downregulation by K5/MIR2 of Kaposi's sarcoma-associated herpesvirus. J. Virol. 2009; 83:9672–9681. [PubMed: 19605472]

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; 114:21–31. [PubMed: 12859895]

Mariani R, Rasala BA, Rutter G, Wiegers K, Brandt SM, Krausslich HG, Landau NR. Mouse-human heterokaryons support efficient human immunodeficiency virus type 1 assembly. J. Virol. 2001; 75:3141–3151. [PubMed: 11238841]

Marin M, Rose KM, Kozak SL, Kabat D. HIV-1 Vif protein binds the editing enzyme APOBEC3G and induces its degradation. Nat. Med. 2003; 9:1398–1403. [PubMed: 14528301]

Mbisa JL, Barr R, Thomas JA, Vandegraaff N, Dorweiler IJ, Svarovskaia ES, Brown WL, Mansky LM, Gorelick RJ, Harris RS, Engelman A, Pathak VK. Human immunodeficiency virus type 1 cDNAs produced in the presence of APOBEC3G exhibit defects in plus-strand DNA transfer and integration. J. Virol. 2007; 81:7099–7110. [PubMed: 17428871]

McEwan WA, Schaller T, Ylinen LM, Hosie MJ, Towers GJ, Willett BJ. Truncation of TRIM5 in Feliformia explains the absence of retroviral restriction in cells of the domestic cat. J. Virol. 2009; 16:8270–8275. [PubMed: 19494015]

McKnight A, Clapham PR, Weiss RA. HIV-2 and SIV infection of nonprimate cell lines expressing human CD4: restrictions to replication at distinct stages. Virology. 1994; 201:8–18. [PubMed: 8178492]

Mehle A, Strack B, Ancuta P, Zhang C, McPike M, Gabuzda D. Vif overcomes the innate antiviral activity of APOBEC3G by promoting its degradation in the ubiquitin-proteasome pathway. J. Biol. Chem. 2004; 279:7792–7798. [PubMed: 14672928]

Michel N, Goffinet C, Ganter K, Allespach I, Kewalramani VN, Saifuddin M, Littman DR, Greene WC, Goldsmith MA, Keppler OT. Human cyclin T1 expression ameliorates a T-cell-specific transcriptional limitation for HIV in transgenic rats, but is not sufficient for a spreading infection of prototypic R5 HIV-1 strains ex vivo. Retrovirology. 2009; 6:2. [PubMed: 19144136]

Mische CC, Javanbakht H, Song B, Diaz-Griffero F, Stremlau M, Strack B, Si Z, Sodroski J. Retroviral restriction factor TRIM5alpha is a trimer. J. Virol. 2005; 79:14446–14450. [PubMed: 16254380]

Miyagi E, Opi S, Takeuchi H, Khan M, Goila-Gaur R, Kao S, Strebel K. Enzymatically active APOBEC3G is required for efficient inhibition of human immunodeficiency virus type 1. J. Virol. 2007; 81:13346–13353. [PubMed: 17928335]

Münk C, Beck T, Zielonka J, Hotz-Wagenblatt A, Chareza S, Battenberg M, Thielebein J, Cichutek K, Bravo IG, O'Brien SJ, Lochelt M, Yuhki N. Functions, structure, and read-through alternative splicing of feline APOBEC3 genes. Genome Biol. 2008; 9:R48. [PubMed: 18315870]

Munk C, Hechler T, Chareza S, Lochelt M. Restriction of feline retroviruses: lessons from cat APOBEC3 cytidine deaminases and TRIM5alpha proteins. Vet. Immunol. Immunopathol. 2009:14–24. [PubMed: 19896724]

Münk C, Zielonka J, Constabel H, Kloke BP, Rengstl B, Battenberg M, Bonci F, Pistello M, Lochelt M, Cichutek K. Multiple restrictions of human immunodeficiency virus type 1 in feline cells. J. Virol. 2007; 81:7048–7060. [PubMed: 17459941]

Naidu YM, Kestler HW 3rd, Li Y, Butler CV, Silva DP, Schmidt DK, Troup CD, Sehgal PK, Sonigo P, Daniel MD, et al. Characterization of infectious molecular clones of simian immunodeficiency virus (SIVmac) and human immunodeficiency virus type 2: persistent infection of rhesus monkeys with molecularly cloned SIVmac. J. Virol. 1988; 62:4691–4696. [PubMed: 2846880]

Navarro F, Bollman B, Chen H, Konig R, Yu Q, Chiles K, Landau NR. Complementary function of the two catalytic domains of APOBEC3G. Virology. 2005; 333:374–386. [PubMed: 15721369]

Neagu MR, Ziegler P, Pertel T, Strambio-De-Castillia C, Grutter C, Martinetti G, Mazzucchelli L, Grutter M, Manz MG, Luban J. Potent inhibition of HIV-1 by TRIM5-cyclophilin fusion proteins engineered from human components. J. Clin Invest. 2009; 119:3035–3047. [PubMed: 19741300]

Neil SJ, Sandrin V, Sundquist WI, Bieniasz PD. An interferon-alpha-induced tethering mechanism inhibits HIV-1 and Ebola virus particle release but is counteracted by the HIV-1 Vpu protein. Cell Host Microbe. 2007; 2:193–203. [PubMed: 18005734]

Neil SJ, Zang T, Bieniasz PD. Tetherin inhibits retrovirus release and is antagonized by HIV-1 Vpu. Nature. 2008; 451:425–430. [PubMed: 18200009]

Newman EN, Holmes RK, Craig HM, Klein KC, Lingappa JR, Malim MH, Sheehy AM. Antiviral function of APOBEC3G can be dissociated from cytidine deaminase activity. Curr. Biol. 2005; 15:166–170. [PubMed: 15668174]

Newman RM, Hall L, Kirmaier A, Pozzi LA, Pery E, Farzan M, O'Neil SP, Johnson W. Evolution of a TRIM5-CypA splice isoform in old world monkeys. PLoS Pathog. 2008; 4:e1000003. [PubMed: 18389077]

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; 101:13324–13328. [PubMed: 15326303]

Nisole S, Stoye JP, Saib A. TRIM family proteins: retroviral restriction and antiviral defence. Nat. Rev Microbiol. 2005; 3:799–808. [PubMed: 16175175]

OhAinle M, Kerns JA, Malik HS, Emerman M. Adaptive evolution and antiviral activity of the conserved mammalian cytidine deaminase APOBEC3H. J. Virol. 2006; 80:3853–3862. [PubMed: 16571802]

Pacheco B, Basmaciogullari S, Labonte JA, Xiang SH, Sodroski J. Adaptation of the human immunodeficiency virus type 1 envelope glycoproteins to new world monkey receptors. J. Virol. 2008; 82:346–357. [PubMed: 17959679]

Pecon-Slattery J, Troyer JL, Johnson WE, O'Brien SJ. Evolution of feline immunodeficiency virus in Felidae: implications for human health and wildlife ecology. Vet. Immunol. Immunopathol. 2008; 123:32–44. [PubMed: 18359092]

Pedersen NC, Ho EW, Brown ML, Yamamoto JK. Isolation of a T-lymphotropic virus from domestic cats with an immunodeficiency-like syndrome. Science. 1987; 235:790–793. [PubMed: 3643650]

Perez-Caballero D, Hatziioannou T, Zhang F, Cowan S, Bieniasz PD. Restriction of human immunodeficiency virus type 1 by TRIM-CypA occurs with rapid kinetics and independently of cytoplasmic bodies, ubiquitin, and proteasome activity. J. Virol. 2005; 79:15567–15572. [PubMed: 16306627]

Perez-Caballero D, Zang T, Ebrahimi A, McNatt MW, Gregory DA, Johnson MC, Bieniasz PD. Tetherin inhibits HIV-1 release by directly tethering virions to cells. Cell. 2009; 139:499–511. [PubMed: 19879838]

Perkovic M, Schmidt S, Marino D, Russell RA, Stauch B, Hofmann H, Kopietz F, Kloke BP, Zielonka J, Strover H, Hermle J, Lindemann D, Pathak VK, Schneider G, Lochelt M, Cichutek K, Munk C. Species-specific inhibition of APOBEC3C by the prototype foamy virus protein bet. J. Biol. Chem. 2009; 284:5819–5826. [PubMed: 19074429]

Perron MJ, Stremlau M, Lee M, Javanbakht H, Song B, Sodroski J. The human TRIM5alpha restriction factor mediates accelerated uncoating of the N-tropic murine leukemia virus capsid. J. Virol. 2007; 81:2138–2148. [PubMed: 17135314]

Poeschla E, Looney D. CXCR4 is required by a non-primate lentivirus: heterologous expression of feline immunodeficiency virus in human, rodent and feline cells. Journal of Virology. 1998; 72:6858–6866. [PubMed: 9658135]

Polani S, Roca AL, Rosensteel BB, Kolokotronis SO, Bar-Gal GK. Evolutionary dynamics of endogenous feline leukemia virus proliferation among species of the domestic cat lineage. Virology. 2010; 405:397–407. [PubMed: 20615520]

Refsland EW, Stenglein MD, Shindo K, Albin JS, Brown WL, Harris RS. Quantitative profiling of the full APOBEC3 mRNA repertoire in lymphocytes and tissues: implications for HIV-1 restriction. Nucleic Acids Res. 2010; 38:4274–4284. [PubMed: 20308164]

Roca AL, Pecon-Slattery J, O'Brien SJ. Genomically intact endogenous feline leukemia viruses of recent origin. J. Virol. 2004; 78:4370–4375. [PubMed: 15047851]

Roelke ME, Brown MA, Troyer JL, Winterbach H, Winterbach C, Hemson G, Smith D, Johnson RC, Pecon-Slattery J, Roca AL, Alexander KA, Klein L, Martelli P, Krishnasamy K, O'Brien SJ. Pathological manifestations of feline immunodeficiency virus (FIV) infection in wild African lions. Virology. 2009; 390:1–12. [PubMed: 19464039]

Roelke ME, Pecon-Slattery J, Taylor S, Citino S, Brown E, Packer C, Vandewoude S, O'Brien SJ. T-lymphocyte profiles in FIV-infected wild lions and pumas reveal CD4 depletion. J.Wildl Dis. 2006; 42:234–248. [PubMed: 16870846]

Saenz DT, Teo W, Olsen JC, Poeschla E. Restriction of Feline Immunodeficiency Virus by Ref1, LV1 and Primate TRIM5a Proteins. Journal of Virology. 2005; 79:15175–15188. [PubMed: 16306589]

Sakuma R, Mael AA, Ikeda Y. Alpha interferon enhances TRIM5alpha-mediated antiviral activities in human and rhesus monkey cells. J. Virol. 2007; 81:10201–10206. [PubMed: 17609277]

Sakuma T, Noda T, Urata S, Kawaoka Y, Yasuda J. Inhibition of Lassa and Marburg virus production by tetherin. J. Virol. 2009; 83:2382–2385. [PubMed: 19091864]

Sarma PS, Tseng J, Lee YK, Gilden RV. Virus similar to RD114 virus in cat cells. Nat. New Biol. 1973; 244:56–59. [PubMed: 4124386]

Sauter D, Schindler M, Specht A, Landford WN, Munch J, Kim KA, Votteler J, Schubert U, Bibollet-Ruche F, Keele BF, Takehisa J, Ogando Y, Ochsenbauer C, Kappes JC, Ayouba A, Peeters M, Learn GH, Shaw G, Sharp PM, Bieniasz P, Hahn BH, Hatziioannou T, Kirchhoff F. Tetherin-driven adaptation of Vpu and Nef function and the evolution of pandemic and nonpandemic HIV-1 strains. Cell Host Microbe. 2009; 6:409–421. [PubMed: 19917496]

Sawyer SL, Emerman M, Malik HS. Ancient adaptive evolution of the primate antiviral DNA-editing enzyme APOBEC3G. PLoS Biol. 2004; 2:E275. [PubMed: 15269786]

Sawyer SL, Emerman M, Malik HS. Discordant evolution of the adjacent antiretroviral genes TRIM22 and TRIM5 in mammals. PLoS Pathog. 2007; 3:e197. [PubMed: 18159944]

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. U S A. 2005; 102:2832–2837. [PubMed: 15689398]

Sayah DM, Sokolskaja E, Berthoux L, Luban J. Cyclophilin A retrotransposition into TRIM5 explains owl monkey resistance to HIV-1. Nature. 2004; 430:569–573. [PubMed: 15243629]

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; 328:163–168. [PubMed: 15464836]

Schaller T, Hue S, Towers GJ. An active TRIM5 protein in rabbits indicates a common antiviral ancestor for mammalian TRIM5 proteins. J. Virol. 2007; 81:11713–11721. [PubMed: 17728224]

Schumacher AJ, Hache G, Macduff DA, Brown WL, Harris RS. The DNA deaminase activity of human APOBEC3G is required for Ty1, MusD, and human immunodeficiency virus type 1 restriction. J. Virol. 2008; 82:2652–2660. [PubMed: 18184715]

Sebastian S, Luban J. TRIM5alpha selectively binds a restriction-sensitive retroviral capsid. Retrovirology. 2005; 2:40. [PubMed: 15967037]

Sharp PM, Hahn BH. The evolution of HIV-1 and the origin of AIDS. Philos Trans R Soc Lond B Biol. Sci. 2010; 365:2487–2494. [PubMed: 20643738]

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; 418:646–650. [PubMed: 12167863]

Sheehy AM, Gaddis NC, Malim MH. The antiretroviral enzyme APOBEC3G is degraded by the proteasome in response to HIV-1 Vif. Nat. Med. 2003; 9:1404–1407. [PubMed: 14528300]

Shibata R, Kawamura M, Sakai H, Hayami M, Ishimoto A, Adachi A. Generation of a chimeric human and simian immunodeficiency virus infectious to monkey peripheral blood mononuclear cells. J. Virol. 1991; 65:3514–3520. [PubMed: 2041078]

Shimojima M, Miyazawa T, Ikeda Y, McMonagle EL, Haining H, Akashi H, Takeuchi Y, Hosie MJ, Willett BJ. Use of CD134 as a primary receptor by the feline immunodeficiency virus. Science. 2004; 303:1192–1195. [PubMed: 14976315]

Si Z, Vandegraaff N, O'Huigin C, Song B, Yuan W, Xu C, Perron M, Li X, Marasco WA, Engelman A, Dean M, Sodroski J. Evolution of a cytoplasmic tripartite motif (TRIM) protein in cows that restricts retroviral infection. Proc. Natl. Acad. Sci. U S A. 2006; 103:7454–7459. [PubMed: 16648259]

Sigurdsson B, Palsson PA, Grimsson H. Visna: a demyelinating transmissbile disease of sheep. J. Neuropathol. Exp. Neurol. 1957; 16:389–403. [PubMed: 13439402]

Sokolskaja E, Luban J. Cyclophilin, TRIM5, and innate immunity to HIV-1. Curr. Opin. Microbiol. 2006; 9:404–408. [PubMed: 16815734]

Stern MA, Hu C, Saenz DT, Fadel HJ, Sims O, Peretz M, Poeschla EM. Productive replication of Vif-chimeric HIV-1 in feline cells. J. Virol. 2010; 84:7378–7395. [PubMed: 20463079]

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; 12:591–601. [PubMed: 14527406]

Stoye JP, Yap MW. Chance favors a prepared genome. Proc. Natl. Acad. Sci. U S A. 2008; 105:3177–3178. [PubMed: 18299570]

Strebel K, Luban J, Jeang KT. Human cellular restriction factors that target HIV-1 replication. BMC Med. 2009; 7:48. [PubMed: 19758442]

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; 427:848–853. [PubMed: 14985764]

Stremlau M, Perron M, Lee M, Li Y, Song B, Javanbakht H, Diaz-Griffero F, Anderson DJ, Sundquist WI, Sodroski J. Specific recognition and accelerated uncoating of retroviral capsids by the TRIM5alpha restriction factor. Proc. Natl. Acad. Sci. U S A. 2006a; 103:5514–5519. [PubMed: 16540544]

Stremlau M, Song B, Javanbakht H, Perron M, Sodroski J. Cyclophilin A: an auxiliary but not necessary cofactor for TRIM5alpha restriction of HIV-1. Virology. 2006b; 351:112–120. [PubMed: 16643975]

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; 279:35822–35828. [PubMed: 15210704]

Swanson CM, Puffer BA, Ahmad KM, Doms RW, Malim MH. Retroviral mRNA nuclear export elements regulate protein function and virion assembly. Embo. J. 2004; 23:2632–2640. [PubMed: 15201866]

Tervo HM, Goffinet C, Keppler OT. Mouse T-cells restrict replication of human immunodeficiency virus at the level of integration. Retrovirology. 2008; 5:58. [PubMed: 18611257]

Tervo HM, Keppler OT. High natural permissivity of primary rabbit cells for HIV-1, with a virion infectivity defect in macrophages as the final replication barrier. J. Virol. 2010; 84:12300–12314. [PubMed: 20861260]

Tokarev A, Skasko M, Fitzpatrick K, Guatelli J. Antiviral activity of the interferon-induced cellular protein BST-2/tetherin. AIDS Res Hum. Retroviruses. 2009; 25:1197–1210.

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; 97:12295–12299. [PubMed: 11027299]

Towers GJ. The control of viral infection by tripartite motif proteins and cyclophilin A. Retrovirology. 2007; 4:40. [PubMed: 17565686]

Towers GJ, Hatziioannou T, Cowan S, Goff SP, Luban J, Bieniasz PD. Cyclophilin A modulates the sensitivity of HIV-1 to host restriction factors. Nat. Med. 2003; 9:1138–1143. [PubMed: 12897779]

Troyer JL, Vandewoude S, Pecon-Slattery J, McIntosh C, Franklin S, Antunes A, Johnson W, O'Brien SJ. FIV cross-species transmission: an evolutionary prospective. Vet. Immunol. Immunopathol. 2008; 123:159–166. [PubMed: 18299153]

Van Damme N, Goff D, Katsura C, Jorgenson RL, Mitchell R, Johnson MC, Stephens EB, Guatelli J. The interferon-induced protein BST-2 restricts HIV-1 release and is downregulated from the cell surface by the viral Vpu protein. Cell Host Microbe. 2008; 3:245–252. [PubMed: 18342597]

van Valen L. A new evolutionary law. Evol. Theory. 1973; 1:1–30.

Virgen CA, Kratovac Z, Bieniasz PD, Hatziioannou T. Independent genesis of chimeric TRIM5-cyclophilin proteins in two primate species. Proc. Natl. Acad. Sci. U S A. 2008; 105:3563–3568. [PubMed: 18287034]

Wei P, Garber ME, Fang SM, Fischer WH, Jones KA. A novel CDK9-associated C-type cyclin interacts directly with HIV-1 Tat and mediates its high-affinity, loop-specific binding to TAR RNA. Cell. 1998; 92:451–462. [PubMed: 9491887]

Willett BJ, Hosie MJ, Neil JC, Turner JD, Hoxie JA. Common mechanism of infection by lentiviruses. Nature. 1997a; 385:587. [PubMed: 9024654]

Willett BJ, McMonagle EL, Ridha S, Hosie MJ. Differential utilization of CD134 as a functional receptor by diverse strains of feline immunodeficiency virus. J. Virol. 2006; 80:3386–3394. [PubMed: 16537606]

Willett BJ, Picard L, Hosie MJ, Turner JD, Adema K, Clapham PR. Shared usage of the chemokine receptor CXCR4 by the feline and human immunodeficiency viruses. Journal of Virology. 1997b; 71:6407–6415. [PubMed: 9261358]

Wilson SJ, Webb BL, Ylinen LM, Verschoor E, Heeney JL, Towers GJ. Independent evolution of an antiviral TRIMCyp in rhesus macaques. Proc. Natl. Acad. Sci. U S A. 2008; 105:3557–3562. [PubMed: 18287035]

Winkler I, Bodem J, Haas L, Zemba M, Delius H, Flower R, Flugel RM, Lochelt M. Characterization of the genome of feline foamy virus and its proteins shows distinct features different from those of primate spumaviruses. J. Virol. 1997; 71:6727–6741. [PubMed: 9261397]

Wu X, Anderson JL, Campbell EM, Joseph AM, Hope TJ. Proteasome inhibitors uncouple rhesus TRIM5alpha restriction of HIV-1 reverse transcription and infection. Proc. Natl. Acad. Sci. U S A. 2006; 103:7465–7470. [PubMed: 16648264]

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; 101:5652–5657. [PubMed: 15054139]

Yang SJ, Lopez LA, Hauser H, Exline CM, Haworth KG, Cannon PM. Anti-tetherin activities in Vpu-expressing primate lentiviruses. Retrovirology. 2010; 7:13. [PubMed: 20167081]

Ylinen LM, Keckesova Z, Webb BL, Gifford RJ, Smith TP, Towers GJ. Isolation of an active Lv1 gene from cattle indicates that tripartite motif protein-mediated innate immunity to retroviral infection is widespread among mammals. J. Virol. 2006; 80:7332–7338. [PubMed: 16840314]

Yu X, Yu Y, Liu B, Luo K, Kong W, Mao P, Yu XF. Induction of APOBEC3G ubiquitination and degradation by an HIV-1 Vif-Cul5-SCF complex. Science. 2003; 302:1056–1060. [PubMed: 14564014]

Zennou V, Perez-Caballero D, Gottlinger H, Bieniasz PD. APOBEC3G incorporation into human immunodeficiency virus type 1 particles. J. Virol. 2004; 78:12058–12061. [PubMed: 15479846]

Zhang F, Wilson SJ, Landford WC, Virgen B, Gregory D, Johnson MC, Munch J, Kirchhoff F, Bieniasz PD, Hatziioannou T. Nef proteins from simian immunodeficiency viruses are tetherin antagonists. Cell Host Microbe. 2009; 6:54–67. [PubMed: 19501037]

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; 424:94–98. [PubMed: 12808465]

Zielonka J, Marino D, Hofmann H, Yuhki N, Lochelt M, Munk C. Vif of feline immunodeficiency virus from domestic cats protects against APOBEC3 restriction factors from many felids. J. Virol. 2010; 84:7312–7324. [PubMed: 20444897]

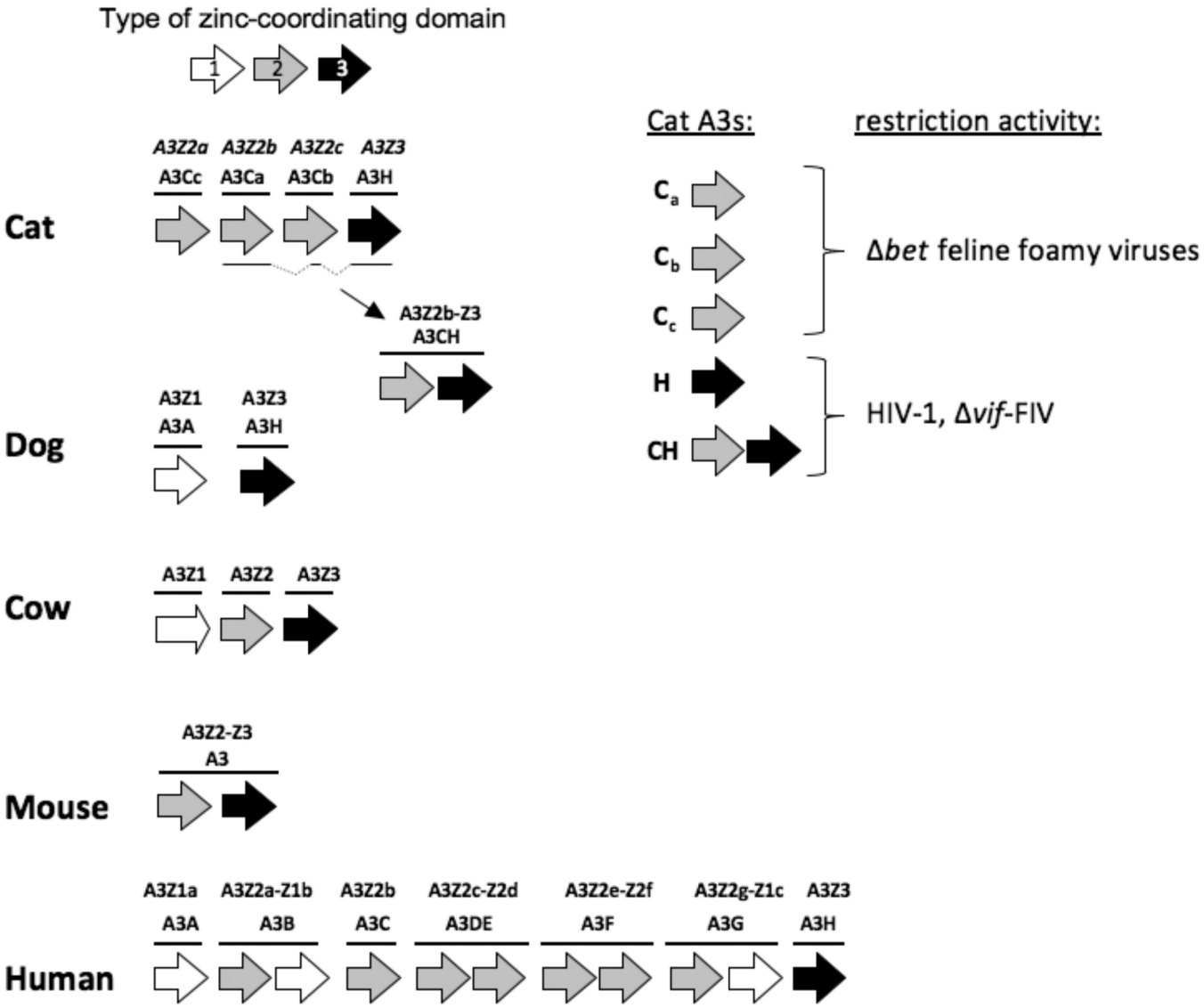

Figure 1. Carnivoran, artiodactyl, mouse and human A3 repertoires

Z domain names are shown above A–H names. Schematically, the figure follows those in LaRue et al. (LaRue et al., 2009; LaRue et al., 2008) and synthesizes findings from there and elsewhere (Münk et al., 2008; Munk et al., 2009; Münk et al., 2007; Stern et al., 2010; Zielonka et al., 2010). Dogs but not cats have a Z1 protein, suggesting that this gene was lost in cats after Caniformia and Feliformia diverged. The dog genomic locus has not been fully characterized but cDNAs for Z1 and Z3 proteins were cloned and relatively low-level activities against FIV were observed (Münk et al., 2008). The canine Z3 protein (A3H) restricted SIVagm approximately 10-fold in a single round assay (Münk et al., 2008). Antiretroviral activities of fA3H (Z3) and fA3CH (Z2–Z3) are inhibited by FIV Vif (Münk et al., 2008; Stern et al., 2010) and also by SIVmac Vif (Stern et al., 2010), while those of the fA3C (Z2) proteins are inhibited by the foamy virus accessory protein Bet (Lochelt et al., 2005; Münk et al., 2008; Perkovic et al., 2009)