A conflict of interest: the evolutionary arms race between mammalian APOBEC3 and lentiviral Vif

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Abstract

Apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3 (APOBEC3) proteins are mammalian-specific cellular deaminases and have a robust ability to restrain lentivirus replication. To antagonize APOBEC3-mediated antiviral action, lentiviruses have acquired viral infectivity factor (Vif) as an accessory gene. Mammalian APOBEC3 proteins inhibit lentiviral replication by enzymatically inserting G-to-A hypermutations in the viral genome, whereas lentiviral Vif proteins degrade host APOBEC3 via the ubiquitin/proteasome-dependent pathway. Recent investigations provide evidence that lentiviral vif genes evolved to combat mammalian APOBEC3 proteins. In corollary, mammalian APOBEC3 genes are under Darwinian selective pressure to escape from antagonism by Vif. Based on these observations, it is widely accepted that lentiviral Vif and mammalian APOBEC3 have co-evolved and this concept is called an "evolutionary arms race." This review provides a comprehensive summary of current knowledge with respect to the evolutionary dynamics occurring at this pivotal host-virus interface.

Keywords: Vif, APOBEC3, Lentivirus, Mammal, Evolutionary arms race

Overview of lentiviruses and APOBEC3

Classification of lentiviruses

Lentiviruses belong to the family Retroviridae and cause a variety of disorders in several species of mammals [1, 2]. In principle, exogenous lentiviruses are classified into five categories based on the host species: (1) primate lentiviruses (PLVs) in primates, (2) feline immunodeficiency viruses (FIVs) in felids, (3) bovine immunodeficiency virus (BIV) and Jembrana disease virus (JDV) in bovids, (4) Maedi–Visna virus (MVV) and caprine arthritis encephalitis virus (CAEV) in ruminants, and (5) Equine infectious anemia virus (EIAV) in horses (Fig. 1) [1, 2]. Human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) are PLVs and are known as the causative agents of acquired immunodeficiency syndrome (AIDS) in humans (Homo sapiens) (Fig. 1) (http://www.unaids.org/globalreport/). In addition, simian immunodeficiency viruses (SIVs) infect non-human primates including chimpanzees (Pan troglodytes), gorillas (Gorilla gorilla) and more than 40 species of Old World monkeys (OWMs) (Fig. 1).

Characteristics of APOBEC3 genes

Apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3 (APOBEC3; A3) proteins are cellular cytidine deaminases and are specifically found in mammals but not in other vertebrates [3, 4]. The A3 proteins of mammals, particularly those of primates, are considered to be cell-intrinsic immune factors that combat viruses, including lentiviruses and retrotransposons. To limit the replication of lentiviruses, the A3 proteins expressed in virus-producing cells are packaged into virions released from the cell. Then, A3 proteins are brought into neighboring cells and halt viral replication via enzymatic hypermutation of the viral genome and by blocking...
Fig. 1 A phylogenetic tree of lentiviral Vif. The names of the viral families (e.g., SIVgor, FIVfca and CAEV) and their strains (shown after the bars; e.g., CP2135, TM219 and Roccaverano) are labeled on the tips. The hosts of the respective viruses are represented on the right of each branch with an illustration. The estimated CSTs and a recombination of PLVs are indicated with arrows. The circulations of FIVlru/FIVpco (in bobcats and puma) and CAEV/MVV (in goat and sheep as SRLV) in the wild are indicated with the double arrows. The scale bar indicates 0.4 amino acid substitutions per site.
reverse transcription directly (for more detail, see references [5, 6]). As a result, lentiviral virions produced in the presence of A3 proteins are dramatically less infectious.

The mammalian A3 genes are duplicated in a chromosomal locus flanked by CBX6 and CBX7 [4, 5, 7]. As summarized in Fig. 2, the number of A3 genes and the history of the A3 duplication process are different in each mammalian lineage (for more detail, see references [4, 5, 7, 8]. For instance, primates, including humans (Homo sapiens), have seven A3 genes, while rodents including mice (Mus musculus) have only one ortholog. Horse (Equus caballus), pig (Sus scrofa), and bovids encode six, two and three A3 genes, respectively (Fig. 2) [7, 8].

Based on the sequence homology of zinc-coordinating (Z) catalytic domains, mammalian A3 proteins are classified into three subsets: Z1, Z2 or Z3. Each A3 protein is composed of single or double Z domains [4]. For

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**Fig. 2** Evolution of mammals and their A3 genes. Left A phylogenetic tree of mammals associated with lentiviruses with the geologic time (top) and age (bottom) scales is shown [14, 125]. In the phylogenetic tree, a subclass (Eutheria), a clade (Boreoeutheria), a superorder (Afrotheria), and some major orders (Primates, Rodents, Carnivora, Perissodactyla, Cetartiodactyla, Chiroptera, and Marsupialia) are labeled on each branch. Representative animals are illustrated with their common names and scientific names (in parentheses). Middle Schematics of the A3 genes in each mammal are shown. The A3 genes encoded in the CBX6-CBX7 loci of respective mammals are summarized. The name of each A3 gene is indicated on each open reading frame. Z1, Z2 and Z3 domains, which are classified by amino acid sequence, are shown in green, yellow, and blue, respectively [4]. Note that A3 genes are not encoded in the genome of opossum [115]. The '?' indicates that the number and composition of A3 genes in these mammals are currently unknown. Right The exogenous lentivirus in each mammal is shown. ND not detected (yet)
instance, human A3A, A3C and A3H encode single Z1, Z2 and Z3 domain proteins, respectively, whereas human A3B, A3D, A3F and A3G encode double Z domain proteins (Fig. 2) [4]. Previous molecular phylogenetic studies have indicated that the mammalian A3 genes are evolving under positive selection [9, 10] and the gene duplications themselves likely result from selection pressures imposed by virus infections [11].

An evolutionary arms race between mammals and lentiviruses

In the field of virology, revealing the co-evolutionary relationship between viruses and their hosts is intriguing and is crucial to understanding how viruses can impact the evolution of their hosts and vice versa. As summarized in Fig. 1, a hallmark of lentivirus ecology is the emergence of new lineages via cross-species transmission (CST) events. Additionally, viral recombination between lentivirus strains occurs frequently. As a result, reconstructing the dynamic relationship between lentiviruses and their hosts is complex.

To gain a better understanding of the evolutionary conflict between lentiviruses and their host species, cell-based virological experiments with a focus on the functional relationship between viral and host proteins have recently been conducted in combination with a molecular phylogenetic approach. This strategy stems from the concept known as the “Red Queen hypothesis [12],” which proposes that games of cat-and-mouse occur between viral and host proteins as they engage with one another over time [13–15]. Based on this concept, various experiments have been conducted using mammalian A3 proteins and a lentiviral protein, viral infectivity factor (Vif).

Vif-A3 interplay in terms of the CST events and the evolutionary arms race of lentiviruses and mammals

Vif is an accessory protein encoded by all lentiviruses with the exception of EIAV, a lentivirus found in horses [1, 2]. As described above, the replication of lentiviruses lacking a functional Vif protein is robustly impaired by certain A3 proteins in the host. In contrast, lentiviral Vif degrades the A3 proteins expressed in virus-producing cells in an ubiquitin/proteasome-dependent manner to antagonize the A3-mediated antiviral action [5, 6, 16]. As described in Fig. 3, knowledge regarding the functional interaction between Vif and A3 can inform the quest to elucidate the principle of CST events and the subsequent evolutionary arms race between lentiviruses and their hosts. In the following sections, we describe our current understanding of the evolutionary relationships between lentiviruses and their hosts, which has been informed by functional interactions between lentiviral Vif and host A3 proteins.

Fig. 3 CST and the evolutionary arms race between viruses and hosts. a A3 as a barrier restricting CST. The lentivirus X infects the host A, and the Vif protein of virus X antagonizes the anti-viral A3 protein of host A. Left: When the Vif of virus X antagonizes not only anti-viral A3 of host A but also that of host B, a candidate for the new host, virus X can be successfully transferred from host A to host B without anti-viral restriction mediated by A3 of host B. Right: On the other hand, if the Vif protein of virus X is unable to antagonize anti-viral A3 of host C, another candidate for the new host, the anti-viral A3 of host C plays a role in restricting the CST of virus X from host A to host C. For a successful CST, the virus X evolves to adapt to host C and its Vif acquires the ability to antagonize host C’s anti-viral A3 (“Adaptive evolution” in this panel). As a result, a nascent species virus, the virus Y, has emerged and infects host C. b The concept of an evolutionary arms race between lentiviruses (Vif) and hosts (A3). In the past, an ancestral host (the host Y) was infected with an ancestral pathogenic virus (the virus X) and an anti-viral A3 protein of host Y was antagonized by the Vif protein of virus X (1). To escape from the pathogenic infection of virus X, the host A3 acquires certain mutations to be resistant to the degradation mediated by the virus X Vif, resulting in the emergence of a novel host, the host Y (2). Although the anti-viral A3 of the host Y is resistant to the virus X Vif (3), the virus X Vif acquires mutations to adapt to the host Y (4). Then, a novel virus, the virus X’, emerges and its Vif is able to antagonize an anti-viral A3 of the host Y (5). Subsequently, similar to the process of (1) to (5), the selective pressure by the virus X’ produces the host Y’ of which A3 is resistant to the lentivirus X’ Vif (6 and 7), while the virus X’ evolves to antagonize the host Y’ A3 and becomes the virus X” (8 and 9). Such an “arms race” between lentiviruses and hosts has evolutionarily occurred over a long period of time (10). It is speculated that this process might trigger the duplication of A3 genes in mammals. After n-times arms races, in the present, the host Y” encodes multiple anti-viral A3 proteins, while the Vif of the virus X” antagonizes them (11).
A3 antagonism by lentiviral Vif proteins

Human A3 versus HIV

In 1983 and 1986, HIV-1 [17, 18] and HIV-2 [19] were isolated as the causative agents of AIDS, respectively. Both viruses likely emerged following independent CST events (Fig. 1), and molecular phylogenetic investigations have indicated that the origin of HIV-1 is SIVcpz (an SIV infecting chimpanzee [Pan troglodytes]) [20] or SIVgor (an SIV infecting gorilla [Gorilla gorilla]) [21], while the origin of HIV-2 is SIVsm (an SIV infecting sooty mangabey [Cercocebus atys]) [22]. Molecular clock analyses have estimated that the CST of SIVcpz (i.e., the birth of HIV-1) occurred ~100 years ago (around A.D. 1908–1933) [23], while the CST of SIVsm took place ~200 years ago (around A.D. 1729–1875) [24]. Moreover, HIV-1 is classified into 4 groups, M (main or major), N (new or non-M-non-O), O (outlier), and P. Each group has emerged following an individual CST event [20, 21, 25, 26] (Fig. 1). It should be noted that the virus causing the worldwide pandemic is HIV-1 group M [27]. The details of HIV pathogenesis and the clinical information through the study of infected individuals are well summarized elsewhere (e.g., see the following references: [2, 28, 29]).

In 2002, Sheehy et al. [30] identified A3G (this gene was originally designated CEM15) as a novel restriction factor against HIV-1 replication. Importantly, the A3G-mediated antiviral action is antagonized by HIV-1 Vif [30]. This report initiated research interest in Vif-A3 interactions and the impact of this interaction on HIV replication and pathogenesis (reviewed in references [5, 6, 16]). Now it is known that human (Homo sapiens) encodes seven A3 genes on chromosome 22 (Fig. 2). Specifically, endogenous A3D, A3F, and A3G expressed in human CD4+ T lymphocytes, a major target cell type for HIV infection, display robust anti-HIV activity in cell culture-based experiments (in vitro) and humanized mice (in vivo) [5, 6, 16, 31–34]. Although other human A3s, such as A3A and A3B, have exhibited anti-HIV-1 activity in overexpression experiments [35, 36], it seems controversial whether endogenously expressed A3A and A3B can elicit anti-HIV effects [37, 38]. Human A3C exhibits weak anti-HIV-1 activity [39, 40], but a recent paper has demonstrated that a single nucleotide polymorphism in human A3C (S188I substitution) results in enhanced HIV-1 inhibition in cell-based overexpression experiments [41].

Intriguingly, OhAinle et al. [42] have reported that A3H is polymorphic in human populations. A follow-up study showed that there are at least seven haplotypes and that three of them, called haplotype II, V, and VII, produce stably expressed proteins and exhibit anti-HIV-1 activity [43]. In contrast, the other four haplotypes (I, III, IV, and VI) do not exhibit stable protein expression [43]. Since chimpanzee A3H appears to be monomorphic, and the protein encoded is stable [42], it appears that the human A3H protein has developed reduced stability since the divergence from chimpanzee. Furthermore, the frequency of each haplotype is different among human populations, with a higher frequency of stable A3H in the African-descendant population and a lower frequency in other populations such as European, American and Asian populations [42, 43].

Although the ability of HIV-1 Vif to antagonize antiviral human A3s including A3D, A3F, and A3G is highly conserved [44], the ability of Vif to degrade stable A3H is not; the Vif proteins of some HIV-1 isolates (e.g., strains LAI, 93RW037 and 93BR029) are capable of degrading stable A3H (e.g., haplotype II), while other isolates (e.g., strains NL4-3, 92TH026, AD.MDR01 and 93TH305) are not [45]. Mutagenesis experiments determined that the Vif residues at positions 39 and 48 are closely associated with the ability to counteract stable human A3H [35, 46, 47]. These observations suggest that the extent of anti-HIV-1 ability elicited by endogenous A3H varies among humans, and the gain and loss of the function of HIV-1 Vif to counteract stable A3H has repeatedly occurred during viral spread in vivo and human population.

Non-human primate A3 versus SIV

The non-human primate hosts that are naturally infected with PLV in the wild can be divided into two groups: the OWMs in sub-Saharan Africa and the great apes, including chimpanzees (Pan troglodytes) and gorillas (Gorilla gorilla) (Fig. 1) [1]. Similar to humans, both OWMs and great apes encode seven A3 genes in their genomes.

As summarized in Fig. 1, a variety of OWM species reside in Africa, and most of them harbor a species-specific SIV that is not overtly pathogenic [48–51] suggesting that SIVs have co-existed with their OWM hosts for a very long time [52]. In contrast, there is also evidence for more recent CST events that give rise to new lentivirus infections. Bailes et al. [26] have reported that SIVcpz emerged through the recombination of two SIV lineages: SIVrcm (an SIV infecting red-capped mangabeys [Cercopithecus torquatus]) and SIVgsn/mn/mus (SIVs infecting greater spot-nosed monkeys [Cercopithecus nictitans], mona monkeys [Cercopithecus mona] and mustached monkeys [Cercopithecus cephus]) (Fig. 1), and this recombination event is assumed to have occurred ~500 years ago (around A.D. 1266–1685) [24]. SIVgor has appeared through the CST of SIVcpz [21]. In sharp contrast to SIV infection in OWMs in Africa, exogenous PLVs have not been found in the New World.

As briefly described in the introduction, Vif-A3 interactions can provide clues to elucidate virus-host (i.e., lentivirus-mammal) evolutionary relationships and history.
Here, we introduce three major examples suggesting that host A3 proteins may represent a barrier to inhibit CST: (1) rhesus macaque (*Macaca mulatta*) A3G is resistant to degradation mediated by HIV-1 Vif (strain NL4-3) [53, 54]; (2) rhesus macaque A3G is resistant to degradation mediated by SIVagm (an SIV infecting African green monkeys *Cercopithecus aethiops*); strain TAN-1) Vif [53]; and (3) gorilla A3G is resistant to degradation mediated by the Vif proteins of SIVcpz (e.g., strains LB715, MT145, EK505 and Gab2), the putative ancestor of SIVgor [25]. In contrast to example (3), SIVgor Vif is able to degrade and counteract gorilla A3G [25], suggesting that this virus has gained the ability to counteract gorilla A3G through adaptation to gorilla following CST from chimpanzee. Moreover, Compton and Emerman have recently demonstrated that the Vif proteins of SIVs naturally infecting OWMs, such as SIVagm, SIVmus, SIVsm, SIVdeb (an SIV infecting De brazza’s monkeys *Cercopithecus neglectus*) and SIVvolc (an SIV infecting colobus monkeys *Procolobus verus*) (Fig. 1), counteract A3G proteins in a species-specific manner [55]. The species specificity of Vif action arises because many species encode point mutations in the region of A3G recognized by Vif [55]. These findings suggest that each SIV Vif has evolutionarily acquired the ability to overcome the restriction imposed by A3G of their respective hosts. Furthermore, three codons have been inserted into the A3G gene of the *Colobinae* primate subfamily, rendering it resistant to most SIV Vif proteins. The recurrent mutation of A3G at sites important for sensitivity to Vif suggests that Vif or Vif-like viral proteins must have applied selective pressure in ancestral primates. This implies that these ancient lentiviruses caused lethal pathogenesis and/or reproductive defects that drove evolutionary change in primate hosts. By dating the appearance of adaptive mutations in primate A3G, it has been inferred that SIV has been infecting non-human primates for at least 12 million years.

Similar to the case of human A3H (described above), A3G polymorphism has been observed in OWMs and is believed to affect viral transmission within and between species [55–58]. Furthermore, the antiviral potency can be divergent between different A3 proteins in the same host. For example, human A3F exhibits higher antiviral activity than human A3D, while chimpanzee A3F exhibits lower antiviral activity than chimpanzee A3D [59]. Altogether, the following issues may unravel the functional interaction of PLV Vif and primate A3s and its consequence a challenge: the multiplicity of primate A3 genes, the difference in anti-viral activity among A3 genes and their hosts, inter- and intra-species heterogeneity of A3 gene sequences, and divergence in PLV *vif* genes. Therefore, future investigations addressing the Vif-A3 interaction using experimental and comprehensive approaches through the techniques of molecular phylogenetic, evolutionary biology and mathematic modeling will be important to elucidate detail of the evolutionary arms race between PLVs and mammals.

**Carnivore A3 versus FIV**

FIV was first isolated in 1987 from domestic cats (*Felis catus*) with chronic AIDS-like disorders [60]. Epidemiological studies by ELISA, immunoblotting, and/or PCR techniques have revealed that FIV is detectable in a broad range of wild animals in the family Felidae [61–63]. FIV has been detected in felids residing in the Old World, including lions (*Panthera leo*), cheetahs (*Acinonyx jubatus*) and leopards (*Panthera pardus*), and those in the New World, including pumas (*Puma concolor*), jaguars (*Panthera onca*), and ocelots (*Leopardus pardinus*) [61]. FIV appears to be distributed worldwide, since a felid species in Asia, Pallas’ cat (*Otocolobus manul*), has been shown to be positive for FIV by PCR [61, 64, 65]. Furthermore, one study has confirmed that a FIV-related virus is present in spotted hyenas (*Crocuta crocuta*), a related carnivore family belonging to *Hyaenidae* [61]. In contrast to the disorders seen in FIV-infected domestic cats, it appears that FIV infections in wild felids are relatively benign and apathogenic because of less divergence in the viral sequences and no obvious symptoms in the infected felids [66]. Therefore, it has been assumed that FIV has co-existed with felids for a long period of time, as in the case of SIV infection in OWMs (see above). The higher FIV pathogenicity in domestic cat is reminiscent of the observation of SIV infection in rhesus macaques (*Macaca mulatta*): SIVmac (an SIV infecting rhesus macaque [*Macaca mulatta*]) is highly pathogenic in this monkey and emerged from a CST of SIVsm from sooty mangabeys in 1985 (Fig. 1) [67]. Therefore, similar to the situation of SIVmac emergence, FIVfca might also have emerged from a relatively recent CST event from wild felids.

Because surveys designed to detect FIV have largely utilized serological methods (e.g., ELISA and immunoblot), FIV *vif* sequences are only available for the following viruses: FIVfca (an FIV infecting domestic cats [*Felis catus*]), FIVoma (an FIV infecting Pallas’ cats [*Otocolobus manul*]), FIVpco (an FIV infecting pumas [*Puma concolor*]), FITru (an FIV infecting bobcats [*Lynx rufus*]), and FIVpke (an FIV infecting lions [*Panthera leo*]) (Fig. 1). Although each FIV has adapted to a specific host felid, recent studies have suggested that FITru and a subclass of FIVpco co-circulate in both puma and lynx in North America (Fig. 1) [68, 69].

Felids, including domestic cats (*Felis catus*), pumas (*Puma concolor*), bobcats (*Lynx rufus*) and lions (*Panthera leo*), encode multiple A3 proteins: three A3Z2
proteins (A32a, A32b and A32c; the orthologs of pri-
mate A3C) and a single A3Z3 (the ortholog of primate
A3H) (Fig. 2) [70, 71]. In addition, a two-domain A3Z2Z3
hybrid protein is generated through alternative splicing
[70, 71]. Similar to the relationship between primate A3s
and PLVs (see above), previous studies revealed that the
feline A3Z3 and A3Z2Z3 proteins potently suppress the
infectivity of vif-deleted FIVfca [70–75] and that the Vif
proteins of FIVfca (strains Petaluma, C36 and Shizuoka)
counteract the antiviral action of domestic cat A3Z3 and
A3Z2Z3 [71, 74].

Interestingly, de Castro et al. [76] have reported that
there are at least seven A3Z3 haplotypes in domestic
cats (haplotypes I to VII) containing four nonsynony-
mous polymorphisms at codons 65, 68, 94, and 96, and
a synonymous substitution at codon 100. A follow-up
molecular phylogenetic analysis determined that codon
65 is under positive selection [74]. Intriguingly, cell-based
experiments revealed that domestic cat A3Z3 haplotype
V (A65I substitution compared to haplotype I) is resis-
tant to degradation mediated by the FIVfca Vif proteins
(strains Petaruma, C36 and Shizuoka) [74]. BEAST
(Bayesian evolutionary analysis by sampling trees) anal-
ysis further implied that domestic cat A3Z3 haplotype
V emerged approximately 60,000 years ago [74]. These
observations strongly suggest that domestic cat A3Z3
haplotype V has been naturally selected to escape from
an ancestral FIV and that an evolutionary arms race
between FIVfca (or its ancestor) and domestic cats has
taken place.

In addition to the interaction between FIVfca and
domestic cat A3s, a previous paper has revealed that
FIVfca (strain Petaluma) Vif is able to antagonize A3Z3
and A3Z2Z3 of other felids, including pumas, lions and
tigers [71, 75]. In contrast, FIVpco (strain PLV-1695)
Vif is unable to degrade domestic cat A3Z3 [75]. Most
intriguingly, FIVpco (strain PLV-1695) Vif is incapable of
counteracting A3Z3 of pumas, which are its natural host
[75]. This is the first report demonstrating that a non-pri-
mate lentiviral Vif protein is incapable of degrading an anti-
viral A3 protein of its natural host. Then, how is it possible
that FIVpco Vif does not counteract A3 of its natural host?
One possibility is that this may result in the elimi-
nation of this virus from circulation. However, a recent
study by Lee et al. [77] have demonstrated an on-going
cross-species circulation of FIVpco in puma and bobcat
in North America. Additionally, as a higher viremia has
been detected in the pumas infected with FIVpco [77],
these observations argue against this possibility. Another
possibility is that puma A3Z3 may provide only partial
protection. Since the expression levels of endogenous
A3 genes in puma remain unassessed, it may be plausi-
ble to speculate that the anti-viral effect of endogenous
puma A3Z3 is negligible. However, endogenous anti-viral
A3 proteins are expressed in domestic cats and exhibit
robust activity against FIVfca [78], Yoshikawa et al. [79]
have recently demonstrated that the Vif proteins of a sub-
type of FIVfca (subotype B) lose their ability to antagonize
domestic cat A3-mediated anti-viral effect despite the
worldwide spread of this subtype. These findings imply
that the Vif-A3 interaction is more complicated than
expected, at least in the interplay between FIV Vif and
feline A3. Therefore, future investigations should focus
on elucidating the role of feline A3 in controlling feline
lentiviruses and their cross-species circulation in the
wild.

As described above, several FIV lineages have been iso-
lated from various felids; however, the molecular inter-
action between their Vif proteins and the A3 proteins of
their hosts remains unclear. Also, the importance of Vif
antagonism of A3 proteins may depend on the host-virus
context, and may suggest differences in lentivirus repli-
cation and pathogenesis in vivo. Therefore, investigation
of the interplay of FIV Vif and the A3 proteins of Felidae
will lead to a better understanding of an intriguing virus-
host co-evolutionary episode.

**Artiodactyla A3 versus their lentiviruses**

To evaluate the antiviral activity of A3 proteins of Artio-
dactyla such as cattle and sheep, cell-based experiments
have been performed using a viral vector system based
on HIV-1 and murine leukemia virus and expression
plasmids for the A3Z3 and A3Z2Z3 proteins derived
from cattle (Bos taurus) and sheep (Ovis aries) [80–82].
These studies revealed that the A3Z3 and A3Z2Z3 pro-
tiens of both cattle and sheep have the ability to suppress
the infectivity of vif-deleted HIV-1 and murine leukemia
virus (a prototype retrovirus in mice) [80–82]. Cattle
A3Z3 is degraded by the Vif proteins of BIV (strain
BIM127), MVV (strain Iceland), and SIVmac (strain 239)
but not by those of HIV-1 (strain LAI) and FIV (strain
NCSU) [80, 81]. On the other hand, sheep A3Z3 is
degraded by the Vif proteins of MVV (strain Iceland) and
HIV-1 (strain LAI) but not by those of SIVmac (strain
239), BIV (strain BIM127) and FIV (strain NCSU) [80,
81]. These findings imply that the Vif-A3Z3 interaction
can be promiscuous and that each lentiviral Vif protein
is optimized to antagonize the A3Z3 protein of its mam-
malian host.

**Bovine A3 versus BIV and JDV**

At least 2 lineages of lentivirus have been isolated in
bovids: BIV and JDV. BIV was isolated in 1972 in the
United States from cattle (Bos taurus) displaying persis-
tent lymphocytosis [83]. However, subsequent studies
reported that the disorders caused by BIV infection in
cattle seem relatively mild compared to those that occur in humans as a result of HIV-1 infection [1, 84, 85]. In contrast, sporadic outbreaks of JDV infection that result in severe disorders and high mortality have occurred in Bali cattle and domesticated banteng (Bos javanicus), in certain islands of Indonesia since 1964 [86]. JDV was subsequently identified as the causative agent of severe disorders in Bali cattle in 1993 [87]. Serosurveillance studies reported that BIV infection appears worldwide in cattle [88–94], while JDV infection is endemic in Bali cattle, banteng, and cattle of the islands of Southeast Asia including Indonesia and Malaysia [86, 87, 95, 96].

To address the co-evolutionary dynamics of bovine A3 and the two bovine lentiviruses, BIV and JDV, a recent study determined the sequences of three A3 genes (i.e., A3Z1, A3Z2, and A3Z3) of various bovids belonging to the tribe Bovini, which includes the genera Bos and Bison: cattle (Bos taurus), zebu (Bos indicus), banteng (Bos javanicus), gaur (Bos gaurus), yak (Bos grunniens), European bison (Bison bonasus) and American bison (Bison bison), as well as the genus Bubalus (water buffalo [Bubalus bubalis]) [97]. Molecular phylogenetic analyses inferred that bovine A3Z3 is under strong positive selection and that the amino acids at positions 32, 62, and 92 have been positively selected [97]. Intriguingly, cell-based assays using a vif-deleted HIV-1-based reporter system, BIV Vif (strain R27) and JDV Vif (strain Tabanan/87) expression plasmids and respective bovine A3Z3 proteins revealed that gaur A3Z3 is specifically resistant to JDV-mediated degradation [97]. The resistance of gaur A3Z3 to JDV Vif is attributed to 3 codons at position 32, 62, and 92, all of which show evidence of positive selection [97]. As the A3Z3 protein of the MRCA (most recent common ancestor) of cattle, banteng, zebu and gaur, which has been estimated using a molecular phylogenetic method, is sensitive to JDV Vif-mediated degradation [97], the resistance of gaur A3Z3 to JDV Vif is attributed to 3 codons at position 32, 62, and 92, all of which show evidence of positive selection [97].

Ovine and caprine A3 versus SRLV

During the 1930s through the 1950s, a pathogenic agent was identified in sheep (Ovis aries) in Iceland [100], and subsequent investigations in the early 1970s led to the isolation of MVV as the first lentivirus [101, 102]. CAEV was isolated from goats (Capra hircus) [1, 103, 104]. Despite their initial classification as distinct viruses subsequent genetic analyses of MVV and CAEV indicated that these viruses cluster closely [1, 105–107]. Therefore, MVV and CAEV have recently been classified into a single group called SRLV.

Sheep A3Z3 and A3Z2Z3 have the ability to impair vif-deleted HIV-1 infection, and these proteins are degraded by MVV Vif (Icelandic strain 1514) [80, 81]. In addition, both the sheep and goat A3Z2Z3 proteins are degraded by the Vif proteins of MVV (strain 1514) and CAEV (strains Cork, 1GA, and Roccaverano) [108]. Both sheep and goats are ruminants that belong to the subfamily Caprinae, and current evidence indicates that sheep split from goats approximately 4 million years ago [109]. Therefore, in contrast to felids and bovids, SRLV may have co-evolved with ruminants.

Vif co-factors

Throughout lentiviral lineages, the vif gene serves the same functional purpose of degrading antiviral A3 proteins. However, there is only ~25% conservation of its genetic sequence [81]. Despite the significant divergence of this genetic sequence, all lentiviral Vifs are capable of hijacking the cullin-RING ubiquitin ligase (CRL) complex, which consists of cullin E3 ubiquitin ligase (CUL; CUL2 or CUL5), ring box protein 2 (RBX2) and elongin B/C (ELOB/C) [81, 110, 111]. Although the vif sequence is highly divergent, the S/TLQ motif is highly conserved in all lentiviral Vif proteins, and Vif interacts with the CRL complex in an S/TLQ motif-dependent manner [81].

In 2012, two groups identified core binding factor sub-unit β (CBFB) as the co-factor necessary for PLV Vif to degrade host A3 proteins [110, 111]. PLV Vif, CBFB and ELOB/C form a substrate adaptor for CUL5 and RBX2, which allows the Vif interaction with suitable and susceptible A3 proteins [110]. Vif is the adaptor between the A3 proteins and the CRL complex [111]. CBFB is required for PLV Vif to degrade host A3s but is dispensable for other lentiviral Vif proteins [81, 110–112].

A comparative approach combining proteomic, biochemical, structural, and virological techniques conducted by Kane et al. [81] identified cyclophilin A (CYP A; also known as peptidylprolyl isomerase A) as the co-factor for MVV Vif. The requirement of CYP A is specific for MVV Vif (strain Iceland) [81], and a subsequent study has recently revealed that CAEV (strains Cork, 1GA, and Roccaverano), in addition to MVV Vif (strain 1514), also bind to CYP A [108]. These observations indicate that the CYP A requirement for host A3 degradation is a common feature of SRLV Vif proteins, although PLV Vif does not appear to need CYP A. Moreover, a combination approach of molecular phylogenetic and structural
techniques has suggested that mammalian CBFB and CYPAs are evolutionarily and structurally conserved [108]. Therefore, lentiviral Vif may have evolved to utilize evolutionarily and structurally stable proteins to degrade host A3 proteins [108]. In contrast to PLV and SRLV, it is intriguing that BIV Vif activity does not appear to be reliant on any co-factors, and no co-factors have yet been identified for FIV Vif activity [81]. These insights further suggest that each lentiviral Vif has evolved an individual strategy to adapt to each host mammal.

**Future perspective: when and how did the A3 and vif genes emerge?**

Here, we described the co-evolutionary relationship between mammalian A3 genes and exogenous lentiviruses. However, many intriguing questions remain: when and how was the A3 gene acquired in mammals? When and how did lentiviruses acquire the vif gene? Was vif gene acquired for the purpose of combating host A3s? Or did Vif perform other functions in lentivirus replication that were supplanted? Why is vif gene lacking in EIAV?

Regarding the origin of A3 genes; A3 is known as a component of AID/APOBEC family. AID (activation-induced cytidine deaminase) is a nucleotide mutator contributing to the somatic hypermutation of immunoglobulin genes in B cells, while APOBEC1 edits the mRNA encoding apolipoprotein B that is expressed in small intestine (reviewed in [113, 114]). Since both AID and APOBEC1 are commonly encoded in all mammals as well as birds and reptiles [5], it is plausible to speculate that these genes can be the origin of A3 genes in mammals. On the other hand, it is known that A3 genes are not present in opossums (Fig. 2) [115], suggesting that A3 genes were acquired after (in which family/order of mammals?) divergence with Marsupialia. However, it is unclear whether A3 gene acquisition occurred in the common ancestor of Eutheria or Boreoeutheria (see Fig. 2). Moreover, we still do not know how many A3 genes are encoded in the other mammals such as bats and elephants (Fig. 2). Particularly, the mammals belonging to the order Chiroptera (e.g., microbats and megabats) are highly divergent [116]. Therefore, it is plausible to assume that Chiroptera A3 genes exhibit a high level of diversity. This information will be useful for considering the evolutionary scenario of A3 acquisition/duplication, which is likely to depend on the evolutionary relationship between lentiviruses and these hosts. Furthermore, Ikeda et al. [117] have recently demonstrated that opossum A1 possesses the activity to impair the replication of lentiviruses and retroelements, suggesting that certain marsupial AID/APOBEC family proteins potently exhibit compensatory activity to limit lentiviral replication instead of A3. Nevertheless, it is still intriguing that the duplications of AID and A1 genes have not been found and that the gene duplication of AID/APOBEC family in mammals is specifically occurred in A3 genes.

The driving force and moment of A3 duplication are still both unclear. In contrast to the Z1 and Z2 domains, it is intriguing that the duplication of Z3 domain has not been observed in any mammals (Fig. 2). This is reminiscent of the “Kondrashov hypothesis” (also known as “deterministic mutation hypothesis”), which assumes that the majority of deleterious mutations are of small effect and that each subsequent mutation has an increasingly large effect on host fitness [118]. According to this concept, duplication of the A3Z3 gene may be evolutionarily constrained due to deleterious effects for the host organism. The possibility of host A3Z3 toxicity is further supported by findings related to the A3H (the ortholog to A3Z3 in primates) gene of human and chimpanzee. Human has seven A3H haplotypes, but four are not expressed at the protein level [42]. In contrast, chimpanzee A3H is monomorphic, and this protein is expressed [42], suggesting that there is a cost to maintain multiple copies of functional A3H. In fact, a recent paper has revealed that human A3H likely contributes to cancer mutagenesis [119]. Therefore, functional A3H has been evolutionarily lost in humans after the divergence from chimpanzees due to its toxicity.

Similar to mammalian A3 genes, the origin of lentiviral vif genes is also unclear. In this regard, endogenous lentiviruses have been detected in the genomes of various mammals, including European rabbits (Oryctolagus cuniculus) [120], lemurs belonging to two different genera (Microcebus and Cheirogaleus) [121, 122], and ferrets (Mustela putorius furo) [123, 124]. More intriguingly, all endogenous lentviruses ever detected appear to encode putative vif sequences [121–123]. Considering that all exogenous lentiviruses, with the exception of EIAV in horses, also possess this accessory gene, vif gene is an ancient lentiviral component with crucial importance to maintaining lentivirus infections worldwide.

**Authors’ contributions**

YN, HA, AS, EY, MM, GJ-F, YK and KS wrote the paper. All authors read and approved the final manuscript.

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**Acknowledgements**

We would like to thank Robert Gifford (University of Glasgow, United Kingdom), Alex Compton (National Cancer Institute, USA) and Terumasa Ikeda (University of Minnesota, USA) for providing crucial comments, and Ms. Naoko Misawa and Kotubu Misawa for their dedicated support.
Competing interests
The authors declare that they have no competing interests.

Funding
This study was supported in part by CREST, JST (to KS), Takeda Science Foundation (to KS), Mochida Memorial Foundation for Medical and Pharmaceutical Research (to KS), Salt Science Research Foundation (to KS), Smoking Research Foundation (to KS), Grants-in-Aid for Scientific Research C 15K01766 (to KS), Scientific Research B (Generative Research Fields) 16K01111 (to KS), and Scientific Research on Innovative Areas 17H05813 (to KS) and 24115008 (to YK) from JSPS, the Platform Project for Supporting in Drug Discovery and Life Science Research (Platform for Dynamic Approaches to Living System) from AMED (to YK), and the JSPS Core-to-Core program, A. Advanced Research Networks (to YK), and Research on HIV/AIDS 16K0410203h0002 from AMED (to YK).

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Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 3 March 2017   Accepted: 27 April 2017

Published online: 08 May 2017

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