Host gene evolution traces the evolutionary history of ancient primate lentiviruses

Alex A. Compton¹,², Harmit S. Malik³,⁴ and Michael Emerman²,³

¹Molecular and Cellular Biology Graduate Program, University of Washington, Seattle, WA 98195, USA
²Division of Human Biology, ³Division of Basic Sciences, and ⁴Howard Hughes Medical Institute, Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA

Simian immunodeficiency viruses (SIVs) have infected primate species long before human immunodeficiency virus has infected humans. Dozens of species-specific lentiviruses are found in African primate species, including two strains that have repeatedly jumped into human populations within the past century. Traditional phylogenetic approaches have grossly underestimated the age of these primate lentiviruses. Instead, here we review how selective pressures imposed by these viruses have fundamentally altered the evolutionary trajectory of hosts genes and, even in cases where there now remains no trace of the viruses themselves, these evolutionary signatures can reveal the types of viruses that were once present. Examination of selection by ancient viruses on the adaptive evolution of host genes has been used to derive minimum age estimates for modern primate lentiviruses. This type of data suggests that ancestors of modern SIV existed in simian primates more than 10 Ma. Moreover, examples of host resistance and viral adaptation have implications not only for estimating the age and host range of ancient primate lentiviruses, but also the pathogenic potential of their modern counterparts.

1. Human lentivirus infections emerge from a brimming reservoir with unclear boundaries

Simian immunodeficiency virus (SIV) is the collective name for a diverse group of lentiviruses that naturally circulate among African non-human primate species. With over 40 species-specific strains characterized to date and high seroprevalence rates among reproductive adults, SIV amounts to an immense viral reservoir with zoonotic potential (figure 1; [1]). In the early twentieth century, two new lentivirus infections emerged in human populations. Human immunodeficiency virus type 1 (HIV-1) emerged via cross-species transmissions of SIVcpz from chimpanzees and gorillas; four independent transmission events gave rise to HIV-1 groups M, N, O and P. A separate lentiviral lineage, HIV-2, emerged in humans at least eight times via cross-species transmissions from SIVsmm, found in sooty mangabeys (figure 1) [3]. Therefore, spillover from the pool of non-human lentiviruses can be both recurrent and hazardous for human health. In fact, despite the species specificity attributed to each SIV strain, transmissions of SIV between non-human primates have been documented on numerous occasions and may lead to pathogenic outcomes in these hosts as well (figure 1).

HIV-1 causes a chronic infection in humans. Nearly all infected individuals progress to a state of life-threatening immunodeficiency (AIDS) if not treated with antiretroviral therapy. A recent study spanning nearly 10 years showed that chimpanzees infected with SIVcpz, the ancestor of HIV-1, also suffer from decreased lifespan and immunopathologies characteristic of AIDS [4–6]. SIVcpz is a recombinant lentivirus that arose following cross-species virus transmission(s) from other ‘natural host’ species that comprise the SIV reservoir [7]. By contrast to infected humans and chimps, the major predictors of disease progression (loss of the CD4⁺ T-cell compartment and chronic immune activation) are notably absent in natural hosts infected by SIV in the wild [8–11]. The mechanisms by which these
primates remain AIDS-free despite lifelong infection and high viremia have major implications for our understanding of HIV-1 pathogenesis [11]. Furthermore, the lack of disease progression is commonly attributed to coevolution between the host and the virus, but the time-scale appropriate to describe these relationships remains controversial.
In some instances, closely related primate species also harbour closely related, species-specific lentivirus strains. Such cases support a scenario of host–virus co-speciation, in which viral lineages diverge in parallel with diverging host populations. However, in other instances, lentivirus phylogeny is discordant with that of their respective hosts. These discordances reveal that host switching events (cross-species transmission) can also give rise to lentivirus–host relationships that must be younger by comparison [12,13]. Adding to the uncertain history of lentiviruses in primates is the fact that current phylogenetic approaches employing a molecular clock appear inadequate to reconstruct virus evolution in deep time [14,15]. For example, previous attempts at assigning a precise date of birth to the SIVsmm lineage have yielded an age estimate of just centuries, orders of magnitude less than what would be expected under conditions of host–virus coevolution [16]. Reasons for this discrepancy likely include the erosion of phylogenetic signal from viral sequences by purifying selection [17] and by convergence on similar viral genotypes (site saturation) over time [18].

Calibration of these time-scales is greatly aided by other temporal markers. For instance, the discovery of SIV strains in species endemic to Bioko, an island which became geographically isolated from the African mainland at least 10 000 years ago, provided a means to more accurately calibrate the molecular clock phylogenetic analysis [19]. This led to the minimum estimate of the time to most recent common ancestor of SIV to be pushed back to 32 000 years, although it is likely that this date still considerably underestimates the age of the SIV lineage [19]. Because phylogenetic methods based on viral sequences alone have failed to bridge the time gap between ancestral viruses and their modern counterparts, there is a keen interest in alternative approaches which estimate the evolutionary age of virus families. By unearthing both endogenous viral imprints in host genomes and instances of virus-driven evolution of the host genome, we focus our review on how such approaches have led to an appreciation for the true antiquity of lentiviruses and their impact on primate hosts.

2. Paleovirology: endogenous viruses and virus-driven evolution of host immunity

Roughly 5–8% of the human genome consists of endogenous retroviruses, the remnants of ancient, exogenous viruses that integrated into the germline (reviewed in [20]). The availability of sequenced genomes from a variety of organisms has led to the discovery of additional endogenous viral elements (EVEs), revealing that several virus families with relevance to human health have far more distant origins than previously appreciated [21,22]. Dating of these EVEs does not rely on using molecular clocks of virus evolution, but rather on well-established dates of host species divergence. One such endogenous lentiviral ‘fossil’ uncovered in the genomes of Malagasy prosimians (mouse and dwarf lemurs, figure 1) provided the first genetic evidence of an early association between primates and lentiviruses. This germline integration event called prosimian SIV (pSIV), establishes that lentiviruses were circulating among some primates at least 4 Ma [23,24]. pSIV is a transitional viral form, sharing some aspects of genomic architecture with non-primate lentiviruses (such as dLTRPase) while lacking genes typically found in extant primate lentiviruses (such as vpr) [23]. However, no trace of an endogenous lentivirus-like entity has been identified in the genomes of simian primates, which comprise the hosts for the known, extant primate lentiviruses. Thus, despite its utility for other viruses and for lentiviruses in other mammals [18,22], the ‘fossil’ record of viral imprints has been mostly uninformative of the lentiviruses harboured by modern simian primates.

On the other hand, even in the absence of direct evidence of past infections, ancient viruses can also be detected indirectly by examining how they have driven adaptive changes in antiviral immunity over time [25]. The discovery of an extremely diverse set of innate immune genes with lentivirus-blocking potential, known as host restriction factors, has provided a means to understand how lentiviruses impact host evolution [26]. The rate at which non-synonymous mutations accumulate between species is a classic measure of adaptive evolution. Many restriction factors are evolving under selection, and in fact it has been proposed that this is a criterion by which they should be defined [26]. Furthermore, because many of these cellular factors are directly antagonized by the lentiviruses they have evolved to restrict, adaptive evolution at the host–virus interface signals when lentivirus infections likely occurred in the past [25]. Selective pressure applied by virus-encoded antagonists will select adaptive ‘escape’ mutations in host factors at sites critical for the host–virus interaction (figure 2a). Adaptive evolution of the host is followed by virus counter-evolution in order to re-establish the interaction, inciting a perpetual ‘genetic conflict’ characterized by host–virus antagonistic coevolution (figure 2a). (See [27] for more comprehensive review of positive selection as a result of virus–host interactions.)

Analysis of amino acid changes in restriction factor genes isolated from a broad panel of extant primates, representing tens of millions of years of evolution, provides a temporal axis to determine when cases of virus-driven evolution occurred in the past (figure 2b). Within the framework of the host phylogeny, signatures of selection can be read like a genetic ledger, documenting when a given host population was exposed to a lentivirus threat. In order to gain specific insights into the age and provenance of primate lentiviruses, we focus only on restriction factors with antiviral specificity for lentiviruses, which is assumed to reflect selection by ancient lentiviral infections. Alternatively, even if the restriction factor acts generally on a wider class of viruses or retroelements, the positive selection of residues at known lentivirus-interacting surfaces (figure 2c) permits deconvolution of the multiple selective forces that may have acted on it and on the phylogeny (figure 2d). These criteria allow us to discern positive selection signatures that are likely to have been driven exclusively by lentiviruses.

As primate genomes encode a diverse arsenal of antiviral effectors with lentivirus-blocking potential, SIV has left its mark on the evolution of several host restriction factors that block the viral life cycle at different stages. We discuss restriction factors that serve as examples of lentivirus-driven evolution.

The analysis of the host restriction factor APOBEC3G (A3G) has provided the most precise details in calculating the age of ancient primate lentiviruses. A3G is an antiviral cytidine deaminase that incorporates itself into virions and mutates viral DNA produced during reverse transcription [28]. While many retroviruses have evolved mechanisms to evade or directly antagonize the activity of A3G [29–31], the primate lentiviruses devote an entire accessory gene, vif,
to this purpose [32]. Vif binds A3G directly and links it to a cellular E3 ubiquitin ligase to accelerate its turnover at the proteasome [33–36]. Vif originated early during lentivirus evolution and has been retained by every member of Lentiviridae except equine infectious anaemia virus [18,37]. Therefore, antagonism of primate A3G and its homologues in mammals may be crucial for long-term lentivirus persistence, making it an ideal candidate for studies of lentivirus-driven evolution. An initial analysis of A3G evolution in primates exposed signals of selection throughout its length, suggesting that many surfaces of the enzyme have been engaged by viral antagonists of unknown origin [38]. However, a subsequent study of A3G orthologues from a broad panel of Old World monkeys (OWMs), including African green monkey (AGM) and several other species comprising the SIV reservoir, revealed recurrent selection at residues involved in the interaction with the lentiviral Vif protein [39,40]. Single amino acid substitutions that allow evasion of Vif-mediated degradation independently emerged on several occasions during primate evolution, the oldest of which appeared at least 5 Ma in the common ancestor of the guenon species. An even older Vif-blocking adaptation in A3G, a multi-residue insertion event, arose at least 12 Ma in a subset of OWMs (Colobinae) [39]. These findings suggest that, millions of years ago, lentiviruses

Figure 2. Virus-driven evolution fuels a genetic conflict. (a) Depicted is a cycle of host–virus coevolution initiated when an antagonist encoded by a pathogenic virus counteracts a host restriction factor. Host factor variants are drawn in solid black, and viral antagonists are drawn in white. Selection of host factor variants that successfully evade antagonism is followed by counter-selection of viral variants that re-establish the host–virus interaction, applying selective pressure on the host once again, resulting in a cycle of coevolution. Note that the ‘direction’ of the arms race can be reversed, such that host antiviral effectors ‘chase’ their viral targets. (b) The age of host genetic adaptations, and consequently of the causal pathogenic viruses, can be estimated when superimposed onto the primate species phylogeny. For instance, the origins of positive selection on primate SAMHD1 appear to coincide with the birth of SAMHD1-degrading activity specific to some lentiviruses. (c) In cases where a particular restriction factor can be generally antagonized by a variety of different antagonists, information about binding sites can nevertheless delineate those amino acid changes that occurred on account of lentiviruses rather than due to antagonists encoded by other viruses (grey shading). (d) By tracing these lentiviral-specific changes on the primate phylogeny, one can infer whether one or several branches in primate phylogeny underwent selection on account of pathogenic lentiviruses. For instance, despite being antagonized by several viruses, changes in APOBEC3G required to evade lentiviral Vif can be used to calibrate Vif-escaping adaptive episodes in primate APOBEC3G. (Online version in colour.)
left footprints of selection stamped in the A3G locus of simian primates. Therefore, an examination of virus-driven evolution of host immunity enables the inference of past lentivirus infections in much deeper time-scales.

Similar inferences can be made from the evolution of the newly discovered restriction factor SAMHD1, which imposes a block to the viral reverse transcription in myeloid-derived blood cells and resting CD4+ T cells [41]. Evolutionary analysis of primate SAMHD1 revealed residues evolving under positive selection that underlie interaction with and sensitivity to the lentiviral-encoded antagonists Vpr and Vpx [42,43]. Interestingly, mapping these signatures onto the primate phylogeny found that the selection is most pronounced in members of the Cercopithecidae lineage (figure 1), the OWM subfamily that includes a large component of natural host species including AGMs and sooty mangabeys. Taken together with functional analyses demonstrating that SAMHD1-antagonizing activity first arose in Vpr/Vpx from lentiviruses that infect the Cercopithecidae lineage, these results suggest that lentiviral pressure led to both the origin and persistence of rapid evolution in primate SAMHD1. Dating this origin of positive selection using the host species tree suggests that lentiviruses with the ability to degrade SAMHD1 are at least 10 Myr old within primates.

Tetherin (also called BST-2) is a broadly acting antiviral effector that ‘tethers’ virions to the cell surface to disallow their release and spread. The non-specific antiviral mechanism employed by Tetherin allows it to restrict a wide array of enveloped virus families, including retroviruses, flaviviruses, herpesviruses and paramyxoviruses [26]. Despite this apparent lack of specificity, a lentiviral-driven conflict of function appears to have played a prominent role during the evolutionary history of Tetherin in primates. Sequencing the Tetherin locus from representatives of major primate clades revealed that it is undergoing positive selection (adaptive evolution) [44,45]. In particular, the most rapidly evolving Tetherin residue in an analysis of OWM species maps precisely to one of the amino acids in the cytoplasmic tail of Tetherin which confers species specificity to antagonism by SIV Nef [45–48]. Nef downregulates Tetherin from the cell surface [46], and presumably binds directly to these amino acids in the cytoplasmic tail of Tetherin. This suggests that the repeated amino acid substitutions at this single residue were driven to allow escape from Nef antagonism [45]. However, because other viruses also encode Tetherin antagonists, it is possible that another antagonist with the same specificity as Nef was responsible for this host gene selection. Thus, a caveat of using the host gene evolution to date paleoviruses is that it may not be possible to determine which virus family drove the ancient selection. However, when selection converges on several antiviral factors inside the cell, as is the case for the paleo-lentiviruses in primates, it increases the confidence that an ancient virus that encoded Vif, Vpx/ Vpr and Nef was responsible for selection on multiple host genes in a similar time period.

Finally, the analysis of the ‘birth’ of an antiviral gene formed between the restriction factor TRIM5 and CypA, called TRIM-CypA, supports the existence of an even older lentivirus within primates [49]. Rhesus macaques (Macaca mulatta) encode a TRIM-CypA fusion protein that emerged in the ancestor of macaque species 5–6 Ma [50–52]. While rhesus TRIM5α potently blocks HIV-1 replication, TRIM-CypA exhibits specificity towards HIV-2 and SIVagm, suggesting that it was selected millions of years ago in response to a lentivirus with similar characteristics [53,54]. In a remarkable demonstration of convergent evolution, a TRIM-CypA fusion has evolved independently in owl monkeys (Aotus), a genus endemic to South America, establishing that the species of the New World may have been subjected to lentiviruses as well [55,56]. More recent analyses uncovered an even older TRIM-CypA fusion protein, which was present in the ancestor of all simian primates 43 Ma, and appears to have been active for 10 Myr before undergoing decay and loss of function [49]. If ‘birth’ of this older TRIM-CypA gene was also driven by selective pressure by a lentivirus, then this implies that lentiviruses have episodically infected simian primates for most of their evolutionary history. Thus, although each method of detecting paleoviruses has its advantages and shortcomings (reviewed in [15,21,25,57]), the use of host gene evolution to infer ancient viral infections has the potential to identify past pathogenic challenges, where any direct traces of the virus are long gone.

3. Host polymorphism as a readout for recent virus-driven evolution

Most examples of lentivirus-driven selection we have discussed so far examine interspecies divergence, presumably fixed mutations that distinguish the antiviral gene of one species from another. However, the selection can also manifest as variation (known as polymorphism) within a species or within very closely related species, which provides a powerful means to assess ongoing or very recent selective pressures. When applied to the evolution of antiviral immunity, polymorphism may result from relatively recent instances of virus-driven evolution because the variation has not yet been purged or fixed within the host population.

Analyses of gene diversity within AGMs (genus Chlorocebus), a highly abundant natural host species of lentiviral infections, have turned up polymorphisms in genes that have relevance to ongoing and ancient virus–host evolution. AGMs comprise four major subspecies known commonly as vervet, talantus, grivet and sabaexus monkeys, each occupying distinct geographies in sub-Saharan Africa. Each AGM subspecies harbours a distinct HIV strain (collectively referred to as SIVagm). In two of those subspecies, single amino acid changes in A3G emerged independently to allow evasion of the lentiviral antagonist, Vif. Specifically, these adaptive mutations prevent degradation by Vif from heterologous SIVagm isolates (those found in the other populations), suggesting that they are selected as a result of Vif-mediated selective pressure [40].

Earlier findings of polymorphism in the chemokine receptor gene CCR5 of AGM provide further evidence of lentivirus-driven selection in this natural host species. The CCR5 is used by HIV/SIV as a co-receptor to enter host cells. Non-synonymous mutations in CCR5 of AGM subspecies cluster in regions targeted by the viral envelope glycoprotein; this variation inhibits SIVagm infection in vitro [58]. Interestingly, the primary receptor for lentivirus entry, CD4, is also polymorphic in AGM [13] and is undergoing adaptive evolution in primates at positions that govern virus entry [59]. Together, signatures of recent selection in AGM suggest that both host factors with antiviral functions and host factors that are essential for virus replication are subjected to ongoing evolutionary change during the course of host–virus coevolution.
Whereas the variation between species allows us to infer the presence of ancient, pathogenic lentiviruses among primate ancestors, selection resolved to the population level hints that contemporary lentiviruses other than SIVcpz may also impact the fitness of their respective hosts. Indeed, cases of AIDS, while rare, have been documented in SIV-infected AGMs and sooty mangabeys in captivity [60,61]. Furthermore, cross-species transmission of apparently non-pathogenic SIV strains, both in the laboratory and in the wild, can induce disease in the non-natural host [62,63]. Even in the absence of full-blown AIDS, SIV infections may have subtler, unrecognized consequences that, nevertheless, seriously impact host fitness. For example, infection may affect either reproductive rate, as observed in SIV-infected chimpanzees [4], or social behaviours such as mate choice. Long-term field studies of SIV-infected natural hosts are needed to better understand the impact of wild lentivirus infections on these and other parameters of host fitness.

4. Protective polymorphism: tripping up a viral opponent that cannot be outrun

The lentivirus genome has a mutation rate that is one million times faster than that of its host [64]; so, primate species must overcome a severe handicap in order to survive. Nonetheless, it has been suggested that the presence of multiple host genotypes may insulate populations from invading viruses by slowing the rate of viral adaptation [65]. In fact, immune polymorphism will not only benefit populations but also individuals [66]. A potential protective role for heterozygosity at the A3G gene is made possible by examining SIV evolution following experimental infection of AGMs with differing A3G genotypes.

As described earlier, the sabaeus population of AGM encodes a unique, derived allele of A3G (D130H) that is resistant to Vif from SIVagm strains infecting other AGM populations. Using plasma samples isolated from three sabaeus monkeys experimentally infected with SIVagm.Ver (a virus naturally found in vervets) [67], we monitored the sequence evolution in vif. Vif readily counteracted A3G in individuals homozygous for the ancestral A3G allele. In animals that were homozygous for the A3G (D130H) allele that was resistant to Vif from the initial virus inoculum, the vif gene evolved within the animal in order to counter this A3G polymorphism [40]. However, in a sabaeus monkey that was heterozygous, encoding an ancestral A3G allele and a derived A3G (D130H) allele, SIVagm.Ver vif failed to evolve the capacity to antagonize both variants in vivo (figure 3a) [40]. These findings suggest that the virus adaptation is dramatically impeded when two variants of a host factor are present inside the cell.

Upon closer examination, the mechanism of constraint imposed by A3G heterozygosity becomes clear. Adaptive mutations selected in vivo enabled Vif to antagonize derived A3G, but as a result, Vif lost activity against the ancestral form (figure 3b, compare parental Vif with adapted Vif). Reversion of just one amino acid selected in Vif (Y84C) resulted in a protein with the opposite specificity (figure 3b, compare adapted Vif with adapted Vif + C84Y), demonstrates that this residue toggles the substrate specificity of Vif. Therefore, virus adaptation to A3G is an evolutionary trade-off, because evolving to target a variant of the host factor compromises its ability to target the other. These data support the idea that heterozygosity can provide an adaptive advantage to the host and shift the balance of power in a host–virus genetic conflict, at least temporarily. We find that the Vif protein from SIVagm.sab, the lentivirus naturally circulating among sabaeus monkeys in the wild, has overcome this challenge and learned to counteract both derived and ancestral variants of A3G [40]. However, this likely required repeated transmission cycles and more extensive bouts of virus adaptation, because SIVagm.sab Vif shares less than 40% amino acid identity with Vif from other SIVagm strains. Thus, heterozygosity in restriction factors may have the capacity to severely limit the ability of viruses to successfully counter- adapt during the early stages of virus emergence.

5. Ebb and flow of the lentivirus reservoir: virus extinction and re-emergence

In addition to describing the immune adaptations of natural host species that have resulted from, and possibly enabled, long-term coexistence with lentiviruses, some features of primate immunity suggest that lentiviruses may have been more widespread in the past than they are today. Species-specific SIV strains have been defined in dozens of African non-human primates, yet the relationship between lentiviruses and some species is more ambiguous. Surveys of SIV in the wild have identified ‘dead-end’ or ‘ incidental’ hosts that are not infected with unique versions of SIV but instead harbour transient infections normally found in other species. Examples include the yellow baboon, the chacma baboon and the white- crowned mangabey, three species that, at low prevalence, carry an SIVagm subtype usually confined to the autologous host [68–70]. While clearly exposed to lentiviruses today, it is uncertain whether such species were hosts to species-specific strains in the past, although analyses of the genetics of their restriction factors similar to that which has been done in AGMs [40] may be able to discern between these two hypotheses.

Similarly, the first report of lentivirus infection in patas monkeys, a species that is closely related to and sympatric with sabaeus monkeys (AGM) in Senegal, showed that approximately 5% of animals were cross infected with the SIVagm.Sab subtype [71]. A later study showed that patas monkeys share the immunophenotypic features of canonical natural host species, namely the downregulation of the CD4 receptor from helper T cells, suggesting that a hypothetical patas-specific SIV may have once existed [72]. This observation raises the possibility that adaptation of host immunity (such as downregulation of lentivirus receptors or co-receptors) may in fact mediate resistance to infection, thereby driving the extinction of certain lentivirus strains. A similar conclusion may be drawn for the white-crowned mangabey, which exhibits a relatively low frequency of CD4+ T cells, a property shared by other mangabey species that are known natural hosts [73]. The prospect that genetic adaptations present in these species may provide resistance to lentivirus infections in the wild provides encouragement to gene therapeutic approaches being developed to control the spread of HIV-1 in humans.

While it may be reasonable to suspect that most (if not all) primate species in Africa have been infected by lentiviruses at one time or another, primate habitats span the globe from the New World to the Far East. Current surveillance efforts limit
the range of SIV infections to the African continent, but a trail of genetic evidence allows one to follow the spread of lentiviruses out of Africa. For example, the Asian macaque species housed in American primate centres recently acquired lentivirus infections via artificial cross-species transmission of SIV from sooty mangabeys [74]. On the other hand, more recent hallmarks of selection imprinted in other host factors strongly suggest the possibility of a ‘natural’ rhesus-specific SIV strain in the recent past. A high-frequency single nucleotide polymorphism (SNP) in $A3G$ of Indian-origin rhesus macaques, like those identified in other members of the Cercopithecinae subfamily of OWMs, encodes a unique charge-altering amino acid change that affects susceptibility to the viral antagonist Vif (figure 4) [39]. Likewise, there is an evidence of polymorphisms in the TRIM5 gene in rhesus macaques [75], as well as the presence of the TRIM5-CypA fusion gene in rhesus macaques [50–52] that would provide protection against some lentiviruses. These polymorphisms may represent a vestigial footprint of an extinct lentivirus that once circulated among these primates. Thus, innovation in the innate immune repertoire of the rhesus macaque may have been inspired by encounters with lentiviruses in wild habitats.

Perhaps most striking of all, human evolutionary genetics may allude to a lentiviral presence that preceded HIV-1. A unique five amino acid deletion is fixed in the human orthologue of Tetherin. As a broad acting antiviral effector, a deletion in $Tetherin$ could have been selected in response to any number of enveloped viruses. However, this deletion spans residues necessary for antagonism by the lentiviral Nef protein used by many SIV strains, suggesting that it may have been selected by a pathogenic, Nef-encoding lentivirus approximately 800 000 years ago (figure 4) [44,45,76]. Therefore, changes in innate immune genes of humans may have been triggered by previous lentivirus infections in our recent ancestors.

6. Looking backwards to move forward
The evidence presented in this review for ancient lentiviral infections of primate based on selections of host genes is
summarized in figure 4. An understanding of these virus origins may allow us to better understand the host–virus interactions that are pivotal to virus infection, transmission and long-term persistence. While selected by virus infections of the past, the strategies that primes have deployed to cope with lentiviruses, and an understanding of how such adaptations constrain virus fitness, may be exploited as novel therapeutic strategies to stem modern pandemics in humans. For example, the introduction of HIV-specific restriction factors into human cells is a burgeoning avenue for antiviral gene therapy [77–79]. However, the vast potential for viruses to counter-evolve in the face of genetic innovations of their hosts means that a combinatorial approach to gene therapy may prove most successful. That is, an enduring blockade of host–virus interactions might only be achieved by introducing multiple genetic changes in one or more antiviral genes, like those naturally selected in hosts of SIV. Finally, an appreciation for the size of the lentivirus reservoir, both past and present, and for the pathogenic prowess of the many species-specific virus strains contained therein, will help to identify the human populations most at risk of zoonotic infection and virus emergence.

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