Published in final edited form as:

Vet Immunol Immunopathol. 2008 May 15; 123(1-2): 32–44. doi:10.1016/j.vetimm.2008.01.010.

Evolution of feline immunodeficiency virus in Felidae: Implications for human health and wildlife ecology

Jill Pecon-Slaterry^{a,*}, Jennifer L. Troyer^b, Warren E. Johnson^a, and Stephen J. O'Brien^a

^aLaboratory of Genomic Diversity, National Cancer Institute-Frederick, Frederick, MD 21702, United States

^bLaboratory of Genomic Diversity, SAIC-Frederick, Inc., NCI-Frederick, Frederick, MD 21702, United States

Abstract

Genetic analyses of feline immunodeficiency viruses provide significant insights on the worldwide distribution and evolutionary history of this emerging pathogen. Large-scale screening of over 3000 samples from all species of Felidae indicates that at least some individuals from most species possess antibodies that cross react to FIV. Phylogenetic analyses of genetic variation in the *pol-RT* gene demonstrate that FIV lineages are species-specific and suggest that there has been a prolonged period of viral-host co-evolution. The clinical effects of FIV specific to species other than domestic cat are controversial. Comparative genomic analyses of all full-length FIV genomes confirmed that FIV is host specific. Recently sequenced lion subtype E is marginally more similar to Pallas cat FIV though *env* is more similar to that of domestic cat FIV, indicating a possible recombination between two divergent strains in the wild. Here we review global patterns of FIV seroprevalence and endemnicity, assess genetic differences within and between species-specific FIV strains, and interpret these with patterns of felid speciation to propose an ancestral origin of FIV in Africa followed by interspecies transmission and global dissemination to Eurasia and the Americas. Continued comparative genomic analyses of full-length FIV from all seropositive animals, along with whole genome sequence of host species, will greatly advance our understanding of the role of recombination, selection and adaptation in retroviral emergence.

Keywords

FIV; Evolution; Lion; Felidae

1. Introduction

The emergence of infectious disease within new host species or naïve populations can greatly influence species survival and adaptation. Recent outbreaks of SARS (Guan et al., 2003; Li et al., 2004; Li et al., 2005; Lu et al., 2004; Zhong et al., 2003), avian flu (Butler, 2006; Ghedin et al., 2005), and the devastating effects of the human immunodeficiency virus (HIV) (http://www.unaids.org/en/HIV_data/epi2006/), provide examples of how viral pathogen emergence can pose grave threats to human health. Infectious disease outbreaks are not unique to humans, but opportunities to observe such effects in free-ranging species are rare.

*Corresponding author. Tel.: +1 301 846 5882; fax: +1 301 846 6327. slattery@ncifcrf.gov (J. Pecon-Slaterry).

Conflict of interest

None of the authors have financial or personal relationships with people or organizations that could inappropriately influence or bias the paper entitled "Evolution of feline immunodeficiency virus in Felidae: Implications for human health and wildlife ecology".

Comparative studies in nonhuman species are invaluable, especially when they incorporate diverse disciplines such as wildlife biology with biomedical and veterinary medicine and thereby stimulate advances in genetic and evolutionary research of both pathogen and host.

Molecular genetic tools are informative in evaluating emerging pathogens and provide essential information such as pathogen identification, association of particular or novel strains with disease outbreaks, mutational changes leading to increased or decreased pathogenesis, and geographic and/or evolutionary origins of the pathogen. These tools also provide increasingly valuable information for design of vaccines and drug therapies. Similarly, comparative genomic analyses of mammalian species that serve as reservoir host species, or represent new opportunities for emergent pathogens, are critical in estimating patterns of outbreak, transmission, and inferring adaptive evolution and natural selection. Endangered species are particularly vulnerable to reduction in effective population size due to disease. A better understanding of viral emergence in natural populations is possible by phylogeographic methods.

Feline immunodeficiency virus (FIV) offers an important comparative genomic model for the current pandemic of HIV-1, which leapt from chimpanzee (*Pan troglodytes*) to humans; likely through direct contact with hunters in the bush meat trade in western Africa (Korber et al., 2000; Peeters et al., 2002; Sharp et al., 2000; Sharp et al., 1999). In domestic cat (*Felis catus*), FIV infection results in disease progression and outcome similar to that of HIV in humans, and offers a natural model to AIDS (Bendinelli et al., 1995; Dunham, 2006; VandeWoude and Apetrei, 2006; Willett et al., 1997). However, other free-ranging felids are infected with FIV, but seemingly do not develop AIDS-like disease (Carpenter and O'Brien, 1995; Lutz et al., 1992; Packer et al., 1999). Immune suppression may still occur as indicated by recent analyses of both captive and wild FIV-infected lions (*Panthera leo*) and pumas (*Puma concolor*) that describe mild to severe CD4⁺ T-cell depletion (Bull et al., 2002; Bull et al., 2003; Roelke et al., 2006). These findings raise the prospect that FIV is not completely benign in these species, but rather suppresses host immune response and may increase the incidence of opportunistic infections or spontaneous cancers as AIDS does in humans.

FIV is endemic in Felidae species (Biek et al., 2003; Biek et al., 2006b; Brown et al., 1994; Carpenter et al., 1996; Carpenter et al., 1998; Carpenter and O'Brien, 1995; Driciru et al., 2006; Hofmann-Lehmann et al., 1996; Munson et al., 2004; Olmsted et al., 1992; Troyer et al., 2004; Troyer et al., 2005), many of which are considered endangered or threatened with extinction (<http://www.iucnredlist.org/>). Here we compare full-length proviral sequences from free-ranging lions (Pecon-Slattery et al., 2008) to FIV of domestic cat (Olmsted et al., 1989b), Pallas cat (*Otocolobus manul*) (Barr et al., 1997), and puma (Langley et al., 1994). Patterns of divergence describe substantial genetic differences among strains across the entire FIV genome and define monophyletic viral lineages unique to specific host species (Barr et al., 1997; Burkala and Poss, 2007; Carpenter and O'Brien, 1995; Langley et al., 1994; Olmsted et al., 1989a; Troyer et al., 2005). We interpret these findings in the context of felid phylogeographic history (Buckley-Beason et al., 2006; Culver et al., 2000; Eizirik et al., 2001; Gilbert et al., 1991; Johnson et al., 1998; Johnson and O'Brien, 1997; Johnson et al., 1999; Luo et al., 2004; Menotti-Raymond and O'Brien, 1993; O'Brien, 1994; O'Brien and Johnson, 2005; Slattery et al., 1994; Uphyrkina et al., 2001) and patterns of evolution and speciation within Felidae (Johnson et al., 2006; King et al., 2007; Masuda et al., 1996; Pecon Slattery and O'Brien, 1998; Pecon-Slattery et al., 2004) to assess FIV emergence in endangered cat species. Lastly, we offer a perspective on scientific advancements in retroviral emergence within humans and other mammalian species that has been made possible by the advent of the genomics era.

2. Complete genome analyses reveal differential patterns of evolution between FIV genes

Patterns of divergence within full-length genomes of emerging pathogens such as FIV define (1) changes linked with pathogenesis and virulence of each outbreak; (2) viral protein structure and function; and (3) estimates of mutation rates within viral genes. This approach, while promising, has been limited because only full-length FIV provirus from domestic cat FIV-Fca, pallas cat FIV-Oma, and puma FIV-Pco have been sequenced (Barr et al., 1997; Langley et al., 1994; Olmsted et al., 1989b). As part of our ongoing efforts to obtain complete proviral genome from all FIV seropositive species, we isolated and sequenced FIV-Ple subtype E from wild lions in Okavango Delta in Botswana (Pecon-Slaterry et al., 2008) for comparative genomic analysis. As postulated in our previous studies (Brown et al., 1994; Carpenter et al., 1998; Carpenter and O' Brien, 1995; Roelke et al., 2006), FIV-Ple may have acquired or maintained genetic motifs indicative of reduced virulence.

FIV-Ple subtype E shares similar genome organization with other FIV isolates and consists of LTR, *gag*, *pol*, *vif*, *orfA*, *env*, and additional small ORFs that may represent accessory genes including *rev* (Table 1). The LTR contains common transcription and regulatory elements of IR, AP-4, Aml-1 (EPB20), AP-1, TATA box, Poly A, and the cap transcription initiation site yet differs in the placement of NF-AT and CREBP-1/c-Jun (Pecon-Slaterry et al., 2008). FIV-Ple *gag* (sites 703-2199) encodes three structural proteins (matrix, capsid and nucleocapsid) shared by all FIV. *Pol* (sites 2004-5450) is highly conserved and encodes the key viral enzymes of protease, reverse transcriptase, RNAase, dUTPase and integrase. Similar to HIV-1 *vpr*, FIV-Ple *Vif* (sites 5447-6211) is thought to be an accessory protein essential for viral replication. *OrfA* (sites 6198-6452) in lion FIV-Ple likely corresponds to *tat* of HIV for targeting transcription factors in the LTR. *Env* (sites 6532-9222) has a leader region and also encodes the surface (SU) and transmembrane (TM) regions of the envelope glycoprotein essential in viral binding and entry into the host cell. Like other FIVs, FIV-Ple *rev* is thought to be essential in viral replication and is encoded by splicing two exons: the first in the leader region of *env*, the second in a ORF proximal to 3' region of *env* (Table 1).

Although sharing conserved genome organization, large genetic differences exist among species-specific FIV strains. Consequently, the necessary step of aligning FIV sequences for detecting evolutionary and adaptive differences between species-specific strains is problematic. Therefore, amino acid residues are used as a "scaffold" for alignment of nucleotides using RevTrans (Wernersson and Pedersen, 2003). Our results indicate *pol* is the most conserved gene across FIV, although it exhibits substantial average pair-wise genetic distances of 60% and 54% for nucleotide and amino acid data, respectively. Similarly, *gag* has an average pair-wise genetic distance of 72% for nucleotides, and 62% amino acids. In contrast, *vif*, *orfA*, *env* and *rev* all were more divergent, with average genetic distances of 100% for both nucleotide and amino acid data across all FIV, suggesting multiple hits and mutational saturation of variable sites across viral strains (Pecon-Slaterry et al., 2008).

Specific comparison of FIV-Ple subtype E with the other FIV proviral genomes confirms functional constraints for *gag* and *pol* (Burkala and Poss, 2007; Carpenter et al., 1996; Carpenter et al., 1998), and the rapid evolution of *vif*, *orfA*, and *env* (Table 2). FIV-Ple viral genes *gag* and *pol* are marginally more similar to Pallas cat FIV-Oma, followed by FIV-Fca, and highly divergent from FIV-Pco (Table 2). Lion *vif* and *orfA* show some homology to FIV-Oma, but virtually none with FIV from domestic cat and puma.

Phylogenetic analyses of concatenated sequences from coding regions excluding *env* (6435 bp) recapitulate that FIV strains are specific to their host species. Three subtypes of FIV-Fca in domestic cat exhibit the least, and puma subtypes A and B the most, within-species genetic

divergence among FIV subtypes (Fig. 1A). FIV-Ple and FIV-Oma are monophyletic and appear to have evolved from a common ancestral virus.

Inclusion of *env* sequences within the data (9393 bp) alters this association between FIV-Ple subtype E and FIV-Oma (Fig. 1B). In *env*, the SU and TM regions of FIV-Ple are more closely affiliated with domestic cat FIV-Fca, albeit with a large average genetic distance (67% nucleotide and 69% amino acid; Table 2). Only the leader region of FIV-Ple *env*, which also encodes the first exon of *rev* (Table 1), retains homology with FIV-Oma (Pecon-Slaterry et al., 2008). These *env* differences represent a novel feature that has evolved during the emergence of FIV-Ple subtype E in lions and appears to result from an ancestral episode of recombination. It is not clear if FIV-Ple recombined with FIV-Fca, since the divergence is quite large, or with *env* from another FIV that is not yet sequenced. Nonetheless, recombination in FIV-Ple *env* may be a genetic signature of viral pathogenicity in lions and is under further investigation (Pecon-Slaterry et al., 2008).

3. FIV evolution and adaptation linked with host species natural history and phylogeography

Conservation of gene structure and sequence in *gag* and *pol* make these genes useful markers of FIV diversification in Felidae. Phylogenetic analyses of the *pol-RT* region isolated from 72 diverse FIV strains derived from six felid species, plus spotted hyaena, *Crocuta crocuta*, affirm the high level of species-specificity worldwide (Fig. 2). However, three general phylogenetic patterns are present among lineages, suggesting FIV evolutionary differences that may be further resolved by our phylogeographic studies of cat species.

In natural populations of American puma (*P. concolor*), FIV-Pco consists of two highly divergent subtypes A and B (Fig. 1A and B) that appear to be paraphyletic within the *pol-RT* phylogeny (Fig. 2), perhaps a consequence of two separate introductions of FIV within puma populations (see Troyer, this issue). Long branch lengths uniting and defining strains within each puma subtype, and low geographic concordance between strains (Fig. 2), support our previous hypothesis of a long residence time within pumas (Carpenter et al., 1996). The puma species diverged approximately 4 million years ago (MYA) from a common ancestor shared with the jaguarundi (Johnson et al., 2006; Pecon-Slaterry et al., 2004). During the last ice age of the late Pleistocene, pumas were extirpated from North America, but re-emerged from Brazil 10-12,000 years ago (Culver et al., 2000). Except for a relic, inbred population dwelling in Florida (Roelke et al., 1993), North American pumas are panmictic and inhabit western continental regions (Biek et al., 2006a; Culver et al., 2000). Although studies of FIV-Pco B infecting pumas in the Rocky Mountains indicate that small local areas of closely related strains occurs in the wild (Biek et al., 2006a; Biek et al., 2003; Culver et al., 2000), the overall lack of broad geographic associations (Carpenter et al., 1996) is consistent with the virus freely circulating within one large population. Further, Central and South America FIV-Pco are more related to North American strains than to each other (Carpenter et al., 1996) (Fig. 2). The pattern of deeply divergent strains (consistent with long residence time within pumas) that do not cluster by geographic location within the New World, suggests that divergent FIV-Pco strains were already present in those South American pumas which re-colonized North America and supports a more ancient origin of the virus. The evolution of the more rare FIV-Pco subtype A remains inconclusive, and awaits further clarification from our ongoing FIV studies of Central and South American populations of puma.

In African lions, FIV-Ple has diverged into 6 subtypes A-F, each with distinct geographic areas of endemnicity (Brown et al., 1994; O'Brien et al., 2006; Troyer et al., 2004). Fossil records indicate the African lion (*P. leo*) arose approximately 2 MYA, and spread throughout Africa, Asia and the Americas (Johnson et al., 2006). However, modern lions are confined to the

African continent except for a small relic population in the Gir forest of India. Genetic studies indicate modern African lion populations trace back to a founders event around 325,000 years ago in East Africa (Antunes et al., submitted). The pattern of FIV-Ple gene evolution shows division of Southern and Eastern clades, with somewhat greater diversity seen in East Africa, and evidence for spread of one Southern strain (FIV-Ple A) into the Eastern population of the Serengeti National Reserve (Fig. 2; Antunes et al., submitted; Troyer et al., 2004). The high level of phylogeographic integrity of FIV-Ple compared to FIV-Pco may reflect behavioral differences; lions are social with frequent opportunities for viral transmission within and between prides whereas puma are solitary, and interact infrequently. Given the relative genetic uniformity of African lions, the absence of FIV-Ple in populations east of the Kalahari is puzzling, but may be explained by the low density of lions in this area (Antunes et al., submitted).

Evolution of FIV-Fca in domestic cat is characterized a relatively long monophyletic branch diverging into three FIV-Fca subtypes A, B and C. Intra-subtype genetic differences are minimal, denoted by short branch lengths for each FIV-Fca subtype strain (Fig. 2). The domestic cat evolved as a unique felid lineage only around 10,000 year ago (Vigne et al., 2004) from subspecies of wildcat *Felis silvestris* inhabiting Near East Asia (Driscoll et al., 2007). With the exception of some populations of European wild cat, *F. silvestris* (Fromont et al., 2000). FIV appears to be absent from nearly all of the close relatives of domestic cat (Troyer et al., 2005). Thus, the pattern of FIV-Fca divergence may represent recent emergence combined with rapid viral diversification within the domestic cat worldwide.

FIV genome sequences have been recovered from wild populations of leopard (*Panthera pardus*), cheetah (*Acinonyx jubatus*), Pallas cat (*O. manul*) and spotted hyaena (*C. crocuta*). In these species, FIV exhibits sequence diversity comparable to that observed for the domestic cat FIV-Fca suggesting rather recent (compared to lion or puma) acquisition of FIV (Fig. 2). Two species that evolved in distinctly different felid lineages (Fig. 3), leopard and cheetah, co-exist in the Serengeti National Park in Tanzania, and are infected with closely related viruses (FIV-Ppa and FIV-Aju, respectively) suggesting recent inter-species transmission (Fig. 2). The cheetah once had a global distribution and was extirpated from North America 10,000 years ago, but has since rapidly expanded throughout Africa (Menotti-Raymond and O'Brien, 1993). Thus, FIV-Aju emergence may have occurred within the last 10,000 years, perhaps acquired from leopards. Alternatively, FIV-Aju may have been already present in pre-bottleneck cheetahs, and re-emerged and spread within extant populations, with a subsequent inter-species transmission into leopards. Lastly, FIV-Ccr occurs in spotted hyena, a species from the Hyaenidae family within Carnivores that co-exist in the same habitats as most African species of cat, affording opportunities for cross-species transmission. However, with few exceptions (see Troyer, this issue) the strong monophyletic origin of each species-specific strain suggests that FIV has rarely undergone effective transmission between species.

4. The origin and global dissemination of FIV during Felidae evolution

The pattern of prevalence of FIV, considered with the habitat range of each host species, depicts FIV as a global pathogen. Recently, 3055 specimens from 35 felid species and three hyaena species (family Hyaenidae) were screened with both western blot and PCR amplification of *gag* and *pol* (Troyer et al., 2005). The findings demonstrated that 19 free-ranging species were sero-reactive to FIV (Fig. 3). Studies of felid populations in the wild indicate FIV occurs in majority of New World species, including the ocelot (*Leopardus pardalis*), puma (*P. concolor*), jaguar (*Panthera onca*), margay (*Leopardus wiedii*), and tigrina (*Leopardus tigrina*) as well as several large African cats of lion (*P. leo*), cheetah (*A. jubatus*) and leopard (*P. pardus*), and spotted hyena (*C. crocuta*) from the related carnivore family of Hyaenidae. Only one species of Asian cat, Pallas cat (*O. manul*), has been confirmed by PCR to harbor

FIV. Thus, these findings suggest FIV distribution worldwide is not uniform, being endemic in most exotic cat species in Africa and the Americas but infrequent in Eurasia.

The precise origin of FIV emergence into Felidae is not easily discerned by viral phylogenetic analyses. FIV *pol-RT* phylogenetic trees have a “star-burst” phylogenetic pattern typically associated with recent, rapid evolution, in which hierarchical internal nodes are short, and fail to resolve the relative order of lineage divergence (Fig. 2). Yet, the distinct differences in topology and branch lengths observed between FIV lineages (Fig. 2) plus extreme genetic divergence among FIV strains, suggest a more ancient introduction of FIV to the Felidae.

We also have examined patterns of speciation within Felidae in the context of FIV dissemination. Modern felids are highly adapted, widely distributed species that have a fairly well-represented fossil record that has been integrated with extensive molecular genetic data sets (Johnson et al., 2006). These analyses show that extant felids arose from a common ancestor in Asia 10.8 MYA during the Miocene. The 38 felid species form eight distinct evolutionary lineages that have successfully inhabited all continents except Antarctica through a series of migrations likely facilitated by sea-level oscillations (Fig. 3) (Johnson et al., 2006).

The widespread occurrence of FIV combined with large interspecies divergence in Africa would suggest that FIV arose in Africa rather than Asia. Lentiviruses are endemic in Africa, infecting over 36 species of primates (Hahn et al., 2000; Hirsch et al., 1995; Sharp et al., 2005) and at least four of five African species of cat surveyed in the wild (Fig. 3). Considered together with the presence of CAEV, BIV, and visna in African ungulate species (Achour et al., 1994; Adams et al., 1984; Ayelet et al., 2001; Payne et al., 1986; Quérat et al., 1987; Tibbo et al., 2001; Woldemeskel et al., 2002), an African origin of all lentiviruses may be posited. Second, the substantial genetic difference observed among FIV lineages in Africa is consistent with a long residence time within these species, and does not support recent dissemination from Asia into Africa (Figs. 1A and B and 2). Third, the position of hyena FIV-Ccr within felid FIV suggests increased opportunities for inter-species transmission due to a greater elapsed time since the virus entered and disseminated in African felids.

As an alternative to an African origin, FIV might have arisen in Asia along with the progenitor of modern felids 10.8 MYA. In this scenario, we might expect a more ubiquitous viral presence in all cat species worldwide, high endemnicity of FIV residing in Asian felids, and substantial genetic diversity in Asian FIV strains accumulating over a prolonged period of time. The near absence of FIV in Asian species (except for the Mongolian Pallas cats), supported by ongoing surveillance, does not preclude an ancient Asian origin. Nonetheless, the most parsimonious interpretation, considering the rarity of FIV in Asian felids along with the complete absence of SIV in Asian primates, and combined with the dynamic biogeographic changes in sea level limiting species migrations into and out of this region during felid evolution, is that the virus did not originate along with ancestral felids of Asia.

Global dissemination of FIV from Africa might have been possible during two periods of felid transcontinental migrations into Eurasia and the Americas. The earliest felid migration across the Bering Strait to North America was approximately 4.5 MYA, during a short geologic interval of relatively low sea levels (Johnson et al., 2006). These early migrants into North America radiated into seven species of the ocelot lineage; cheetah, puma and jaguarundi of the puma lineage; and the four modern species within the lynx lineage (Fig. 3). A second opportunity for FIV transmission from Eurasia into the New World would not occur again until Asian lions and jaguars moved into North America and subsequently into South America in the late Pliocene/early Pleistocene (Johnson et al., 2006). This more recent migration appears to be the most parsimonious interpretation, but this issue should be clarified further once FIV

from the remaining seropositive felid species are sequenced. Further, the potential role of extinct felids, such as the saber-tooth species, which co-existed with modern felids until around the end of the Pleistocene (Turner, 1997), in FIV dissemination may never be known but is intriguing nonetheless. In conclusion, our consensus scenario describes FIV originating in Africa, successfully infecting all related species within the *Panthera* lineage no earlier than the late Pliocene, migrating with ancestral populations of species such as African lion and jaguar across Eurasia into North America during the Pleistocene with subsequent dissemination into New World cat species.

5. Prospective aspects of retroviral emergence in both humans and wildlife species

Whole genome sequences of mammals, starting with human, mouse *Mus spp*, rat *Rattus spp*, and chimpanzee *P. troglodytes*, but now extended to dog *Canis familiaris*, cat *F. catus* (see Pontius, this issue), elephant *Loxodonata africana* and other mammals that capture phylogenetic divergence across all the orders of placental mammals (see NHGRI website: www.genome.gov/), are now available to provide a powerful new basis for genetic and pathogen studies.

Whole genome studies indicate mammalian genomes evolve at different rates (Cooper et al., 2004) and categories of genes experience different regimes of selection to either diversify or maintain function among species. Human and chimpanzee, separated by only 5-7 MY of evolution (Enard and Paabo, 2004), exhibit profound differences in chromosome recombination (Winckler et al., 2005), gene expression (Hill and Walsh, 2005) and differential selection for biological function (Clark et al., 2003). These are but a few of the growing number of studies using molecular genomic technologies in nonhuman animal species that will advance our ability to identify regulatory/virulence genes in pathogens as well as host genes that regulate transmission, incubation, latency, virulence, morbidity, mortality and the immune response.

Advances in human genomics and evolutionary history have led to a comprehensive depiction of retroviral strategies in global dissemination that can, in turn, aid in wildlife research. The emergence of HIV represents the extreme of an explosive pandemic, infecting within a single generation 40 million people worldwide, and causing devastating mortality. Biomedical research motivated by the search for vaccines and a cure, has led to exquisite detail on HIV genomics, epidemiology, virology and pathogenicity represented by over 200,000 publications listed within NCBI database alone (as of February 2007). Along with research on primate SIV, this information has been essential to research of FIV genomics, pathogenesis and prevalence in endangered species.

FIV evolution is analogous to human and simian T-cell leukemia virus (HTLV/STLV). HTLV-1, infects approximately 20 million people throughout the world and causes adult T-cell leukemia/lymphoma (Poiesz et al., 1980) and the neurologic disease tropical spastic paraparesis/HTLV-1-associated myelopathy (Gessain et al., 1985). Phylogenetic studies of HTLV-1 and STLV from over 20 species of non-human primates indicate HTLV-1 arose in humans at least six times from STLV strains (Slaterry et al., 1999). The extent of molecular divergence within strains from central Africa, high levels of endemnicity within isolated ethnic groups, and the recent discovery of additional HTLV/STLV types in that region (Switzer et al., 2006; Wolfe et al., 2005), suggest an ancient African origin of HTLV/STLV. Current patterns of distribution among ethnic peoples worldwide suggest the virus spread out of Africa via human migrations over the past 100,000 years (Cavalli-Sforza and Feldman, 2003; Slaterry et al., 1999; Switzer et al., 2006). Compared with HIV, HTLV/STLV exhibits relatively long-term co-evolution between host and pathogen (Overbaugh and Bangham, 2001). Thus, HTLV/

STLV in primates and FIV from species such as puma, jaguar, cheetah and lion, illustrate how naturally occurring retroviral infections have achieved modern-day global distributions.

6. Conclusions

Infectious disease epidemics are not unique to humans, but opportunities to observe such effects in free-ranging species are rare. Comparative studies in nonhuman species are invaluable and incorporate diverse disciplines such as genomics and wildlife biology with biomedical and veterinary science. Cumulative research on the 38 species within the cat family Felidae integrates host and pathogen genomics to provide a novel perspective of retroviral emergence in a successful, highly adapted Carnivore family.

FIV seroprevalence and genetic studies suggest the virus is global in distribution, with local regions of endemnicity in the wild. Evolutionary studies suggest FIV arose in Africa and has existed within Felidae since the late Pliocene. There is strong evidence that FIV evolves in different ways within each species. Rates of mutation vary among FIV genes. *Gag* and *pol*, genes that encode critical structural proteins and enzymes, are more conserved relative to *vif*, *orfA* and *env*, suggesting the latter genes are under greater host selection pressure and can withstand greater variation in structure without crippling viral replication.

Cumulative research on felid natural history, evolution and phylogeography provides important context for FIV emergence. The phylogeny of FIV resembles a “star-burst” pattern typically associated with recent, rapid evolution and is not concordant with host species evolution. However, integration of Felidae evolution and species phylogeography with FIV patterns of distribution describes an evolutionary scenario for a more ancient origin of FIV in Africa followed by global dissemination into Eurasia and the Americas.

Similarities in the natural history and evolution of FIV and primate retroviruses indicate Africa as a common nexus. Molecular genetic analyses of viral strains from African primates and felids show high levels of divergence consistent with long residence times. In Asia, FIV is rare in felids and SIV is absent in primates, suggesting lentiviruses did not originate in this region. Although HTLV/STLV are present in Melanesia, the greatest diversity among all known strains so far described occurs in Africa. The role of ancestral migrations of host species in retroviral dissemination from Africa throughout the world is supported both by the concordance between HTLV/STLV and HIV/SIV evolution and human history. These patterns are similar with FIV and the natural history of each felid host species and points to the intriguing role of ancestral patterns of migration in the global distribution of FIV in Felidae observed today.

Whole genome sequence is essential for the next generation of studies of host and pathogen. Emerging pathogens utilize diverse strategies for genome adaptation and re-organization to successfully infect new host species that are only discernable through full genome scans. Our depiction of changes with *env* of FIV-Ple subtype E in wild lions validates this approach, and argues for continued surveillance of wild populations and application of biomedical advances for both humans and wildlife.

Acknowledgments

All tissue samples were collected in full compliance with specific Federal Fish and Wildlife permits and Convention of International Trade in Endangered Species of Wild Flora and Fauna (CITES) permits issued to the National Cancer Institute-National Institutes of Health (SJ O'Brien, principal officer) by the US Fish and Wildlife Services of the Department of the Interior. This publication has been funded in whole or in part with Federal funds from the National Cancer Institute, National Institutes of Health, under contract number #N01-CO-12400. This research was supported [in part] by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research.

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Fig. 1.

Phylogenetic tree of full-length provirus with FIV-Ple subtype E isolated from wild lions. (A) Shown is the maximum likelihood tree based on concatenated coding regions (6435 bp), excluding *env*, using PAUP version 4.0b10 for UNIX (Swofford, 2002) with GTR + I + G substitution model based on AIC results of Modeltest ver 3.7 (Posada and Crandall, 1998): base frequencies of $A = 0.40270$, $C = 0.13540$, $G = 0.21190$, and $T = 0.25000$; shape parameter (α) = 0.9685; assumed proportion of invariable sites = 0.125; and rate matrix, $AC = 2.8202$, $AG = 4.9936$, $AT = 2.3389$, $GC = 2.9515$, $CT = 7.7709$, and $GT = 1.0$. (B) Shown is the maximum likelihood tree based on concatenated coding regions (9393 bp) including *env* using PAUP 4.0b10 and a GTR + I + G model of substitution based on AIC results of Modeltest: base frequencies $A = 0.39740$, $C = 0.13440$, $G = 0.21110$, and $T = 0.25710$; assumed proportion of invariable sites = 0.136; shape parameter (α) = 1.4128 and rate matrix, $AC = 2.2789$, $AG = 3.8102$, $AT = 1.9466$, $GC = 2.648$, $CT = 5.6925$, and $GT = 1.0$. Numbers in italics represent bootstrap proportions for adjacent node in the following order: minimum evolution (ME)/maximum parsimony (MP)/maximum likelihood (ML) based on 1000, 1000, and 100 iterations, respectively.

Fig. 2.

Phylogenetic tree of 72 nonidentical FIV from 7 carnivore species based on a region of *pol-RT* (420 bp), published previously [see (Troyer et al., 2005)] using PAUP ver4.0b10 for UNIX. Shown is the maximum likelihood tree using the following GTR + I + G model of substitution based on the AIC results of Modeltest: base frequencies of A = 0.4553, C = 0.1062, G = 0.1219, and T = 0.2500; rate matrix, AC = 1.9858, AG = 9.6455, AT = 0.7794, GC = 2.8590, CT = 15.8896, and GT = 1.0; shape parameter (alpha) = 0.8139; and assumed proportion of invariant sites = 0.3836. A nearly identical tree topology was obtained by both minimum evolution: neighbor-joining and maximum parsimony optimality criteria. Heuristic searches included starting tree obtained by neighbor-joining and tree-bisection-reconnection branch swapping. Circles indicate subtypes within FIV-Ple, FIV-Pco and FIV-Fca lineages.

Fig. 3. FIV seroprevalence plotted against the phylogenetic tree of the cat family Felidae. Shown is the maximum likelihood tree from 18,853 bp of nucleotide sequence data amplified from 38 species of cat [see Johnson et al., 2006 for details]. Underlined species are those infected with FIV in the wild [see Troyer et al., 2005 for details]. *Indicates seroprevalence data confirmed by PCR of FIV genome. **Indicates seroprevalence data from Western blot surveys. Δ Indicates FIV absent in these species. Numbers next to nodes define estimated time of divergence for each of the eight felid lineages.

Table 1

Gene size and location within FIV-Ple subtype E compared with previously published FIV-Fca, FIV-Oma and FIV-Pco

	5'LTR	5'UTR	Gag	Pol	Vif	OrfA	Env	PPT	3'LTR
FIV-Ple subtype E (Botswana)									
Gene position	1-397	398-702	703-2199	2004-5450	5447-6211	6198-6452	6532-9222	9478-9492	9495-9891
Gene length (bp)	397	306	1497	3447	765	255	2691	15	397
Translated protein size (# aa)			498	1149	255	85	897		
FIV-Fca Petaluma (subtype A)									
Gene position	1-355	356-627	628-1980	1868-5243	5236-5991	5992-6228	6266-8836	9098-9117	9120-9474
Gene length (bp)	355	272	1353	3375	756	237	2571	19	
Translated protein size (# aa)			451	1125	252	79	857		
FIV-Fca USIL (subtype B)									
Gene position	1-361	362-633	634-1983	1875-5248	5239-5994	5995-6231	6269-8830	9092-9110	9102-9462
Gene length (bp)	361	272	1350	3374	756	237	2562	17	361
Translated protein size (# aa)			451	1124	252	79	854		
FIV-Fca subtype C									
Gene position	1-354	355-632	633-1985	1874-5248	5241-5996	5997-6233	6271-8835	9092-9100	9113-9466
Gene length (bp)	354	278	1353	3375	756	237	2565	19	354
Translated protein size (# aa)			451	1125	252	79	855		
FIV-Oma									
Gene position	1-376	377-684	685-2181	1980-5432	5429-6187	6188-6448	6512-9103	9360-9375	9378-9751
Gene length (bp)	376	308	1497	3453	759	261	2592	16	374
Translated protein size (# aa)			499	1161	253	87	864		
FIV-Pco PLV-14 subtype A (Florida)									
Gene position	1-311	312-615	616-2055	2199-5459	5419-6249	5759-5938	6250-8772	8771-8787	8790-9100
Gene length (bp)	311	304	1440	3261	831	180	2523	17	311
Translated protein size (# aa)			480	1087	277	59	841		
FIV-Pco PLV-1695 subtype B (British Columbia)									
Gene position	1-306	307-638	639-2024	1886-5323	5298-6008	5972-6310	6283-8715	8772-8784	8787-9092
Gene length (bp)	306	332	1386	3438	711	339	2433	13	305
Translated protein size (# aa)			462	1146	237	113	811		

Genome coordinates refer to first base of starting codon and 3rd base of terminal stop codon. Gene locations for subtypes with FIV-Fca were verified through pairwise comparisons with subtypes A, B and C provirus and references (de Rozieres et al., 2004; Olmsted et al., 1989a,b; Sodora et al., 1995; Talbott et al., 1989). Gene locations among FIV-Pco subtypes were verified through pairwise comparisons of accession # DQ192583 with reference (Langley et al., 1994). PPT location inferred from (Whitnam et al., 2001). *Rev* position assessed by homology with FIV-Fca (Phillips et al., 1992) and accession # AAB22932 to identify *rev* exon 1 sites 6532-6888 and *rev* exon 2 sites 9345-9479 for FIV-Ple subtype E.

Table 2

Genetic divergence of FIV-Ple subtype E

Strain	Gene region	FIV GENE				
		Gag 703-2199	Pol 2004-5450	Vif 5447-6211	OrfA 6198-6452	Env 6532-9222
Nucleotide % genetic distance (GTR and BLAST) FIV-Oma	Total gene region	33	28	44	57	100
	Subset of gene region ^a					6532-6806/275/24
	Total gene region	63	51	100	100	67
	Subset of gene region ^a					7117-7617/51/39
FIV-Fca	Total gene region					8286-8336/442/16
	Subset of gene region ^a					8438-8878/360/38
	Total gene region	94	79	100	100	100
	Subset of gene region ^a					
FIV-Pco	Total gene region					
	Subset of gene region ^a					
	Total gene region	25	20	31	45	100
	Subset of gene region ^b					6532-6576/15/20
Amino acid % genetic distance (Pam-Dayhoff and BLAST) FIV-Oma	Total gene region					6592-6828/79/25
	Subset of gene region ^a					6838-7032/65/51
	Total gene region					9055-9210/52/58
	Subset of gene region ^b					6628-9087/819/47
FIV-Fca	Total gene region	50	42	56	88	69
	Subset of gene region ^b					
	Total gene region	83	73	93	100	100
	Subset of gene region ^b					6625-6702/26/51
FIV-Pco	Total gene region					7411-7596/61/27
	Subset of gene region ^b					8326-8445/40/36
	Total gene region					
	Subset of gene region ^b					

^a Nucleotide site position in FIV-Ple/# nucleotide sites/% genetic distance.^b Nucleotide site position in FIV-Ple/# amino acid residues/% genetic distance.