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Vet Immunol Immunopathol. Author manuscript; available in PMC 2009 May 15.

Published in final edited form as:
Vet Immunol Immunopathol. 2008 May 15; 123(1-2): 3–13.

Molecular Mechanisms of FIV Infection

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Abstract

Feline immunodeficiency virus (FIV) is an important viral pathogen worldwide in the domestic cat, which is the smallest animal model for the study of natural lentivirus infection. Thus, understanding the molecular mechanisms by which FIV carries out its life cycle and causes an acquired immune deficiency syndrome (AIDS) in the cat is of high priority. FIV has an overall genome size similar to HIV, the causative agent of AIDS in man, and shares with the human virus genomic features that may serve as common targets for development of broad-based intervention strategies. Specific targets include enzymes encoded by the two lentiviruses, such as protease (PR), reverse transcriptase (RT), RNAse H, and integrase (IN). In addition, both FIV and HIV encode Vif and Rev elements essential for virus replication and also share the use of the chemokine receptor CXCR4 for entry into the host cell. The following review is a brief overview of the current state of characterization of the feline/FIV model and development of its use for generation and testing of anti-viral agents.

Keywords

feline immunodefiency virus; receptor; CD134; CXCR4

Introduction

FIV Pathology

FIV is a lentivirus associated with an AIDS-like syndrome in the domestic cat (Pedersen, 1993). Like HIV, FIV can be transmitted via mucosal exposure, blood transfer, and vertically via prenatal and postnatal routes (Pedersen, 1987; Rideout, 1992; O'Neil, 1995; O'Neil, 1996; Obert, 2000;). Progression of the disease follows a pattern typical of that observed with primate lentiviruses, starting with a relatively short (weeks) acute phase denoted by increasing viral loads, febrile episodes, weight loss, lymphadenopathy, and neutropenia. The acute phase

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Conflict of Interest Statement
None of the authors has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the paper entitled "Molecular Mechanisms of FIV Infection".

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is followed by an of t-protracted (years) asymptomatic phase denoted by relatively strong antiviral immune responses, lower viral titers, a gradual decline in $CD4^+$ cells, and minimal clinical symptoms. The terminal phase is marked by immunologic decompensation, exacerbation of plasma viral load, and clinical symptoms of immunodeficiency with opportunistic infections (Pedersen, 1993; English, 1994). Lymphoid tissue alterations are consistent with those in HIV and SIV infections and include thymic depletion, lymphoid hyperplasia, plasmacytosis, and terminal lymphoid depletion (Callanan, 1993; Bach, 1994; Beebe, 1994; English, 1994; Parodi, 1994; Woo, 1997; Rogers, 1998). Neurological manifestations are also evident (Lafrado, 1993; Phillips, 1994; Prospero-Garcia, 1994; Phillips, 1996) including delayed auditory evoked and visual evoked potential changes (Lafrado, 1993; Phillips, 1994) and marked alterations in sleep patterns (Prospero-Garcia, 1994a). Many of these early symptoms resolve as the animals proceed into the latent phase of the disease, although the neurological abnormalities persist. As the disease progresses, decline in the number of $CD4^+$ T cells continues, with ultimate increase in viral load in the later stages of the disease (O'Neil, 1996; Obert, 2000). Animals, if not euthanized, generally die of opportunistic infections.

Considerable advances have been made in understanding the molecular workings of FIV since its discovery 20 years ago, both from the standpoint of understanding the rudiments of the virus life cycle as well as in establishing the molecular basis for the observed pathogenic phenotypes outlined above. Although FIV is of direct concern to veterinary medicine, the majority of the work has involved comparison to HIV, with the hope that the cat model can contribute to the development of intervention strategies effective against both lentivirus infections. As will be shown below, many parallels exist in both the pathology and molecular structure of FIV and HIV and substantial progress has been made in use of the cat model for development of both drug and vaccine treatments.

FIV Genomic Structure

The overall genomic structure of FIV is markedly similar to HIV, although there are important distinctions (Olmsted, 1989; Talbott, 1989; Phillips, 1990) (Figure 1). The length of the FIV genome is around 9400 nucleotides, approximating that of HIV and other lentiviruses. The integrated provirus is bordered by long terminal repeats (LTRs) and possesses *gag*, *pol*, and *en*v genes as all other retroviruses. As with other lentiviruses, FIV uses a $tRNA_{Lys}$ primer binding site to prime first strand synthesis by reverse transcriptase (RT). Transport of unspliced and singly spliced mRNAs is regulated by Rev interaction with the distinction that Rev Response Element (RRE) and second coding exon of Rev are located 3′ of *env* instead of overlapping it as in primate lentiviruses (Phillips, 1992). FIV lacks Vpr, Vpu, and Nef "accessory" genes that are present in HIV. FIV has an apparent transactivator, termed OrfA (or Orf2), which promotes a net increase in translation of gene products whose transcription is driven by the FIV LTR (Sparger, 1992; Waters, 1996; de Parseval, 1999). However, OrfA does not act via a TAR element, as is the case with HIV-1 Tat and promotes transcription/translation via mechanisms distinct from that of other lentiviruses (Chatterji, 2002). Sparger's laboratory has presented evidence that there is no wholesale increase in transcription in the presence of Orf A and thus, the increase in net translation may be the consequence of downstream action (Gemeniano, 2003, 2004). They also showed that OrfA may have relatedness to Vpr and present indications of involvement in virus release from the cell and influence on cell cycle, similar to HIV Vpr (Gemeniano, 2003). Overall, the findings suggest that OrfA may be a multi-functional protein, which would certainly be in keeping with the need for versatility of gene products encoded by a relatively small viral genome.

Typical of most other lentiviruses, the Gag polyprotein is expressed via ribosomal frame-shifting (Morikawa, 1992) and is comprised of a myristoylated matrix (MA) protein, a capsid

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(CA) protein, and a nucleocapsid (NC) protein that has two copies of the zinc finger motif (Elder, 1992) (Figure 1). FIV lacks a P6 protein between Gag and Pol, but contains instead a P2 protein (Elder, 1993) that has a P(S/T)AP domain necessary for virus budding (Manrique, 2004). Thus, it is likely that P2 serves the same purpose as HIV-1 P6. It is now recognized that the PTAP domain in HIV P6 recruits TSG 101, a cellular protein involved in the virus budding process (Garrus, 2001; Martin-Serrano, 2001; VerPlank, 2001; Demirov, 2002; Freed, 2002). As to whether similar interactions are critical for FIV budding remains to be determined, but this appears likely. The FIV Pol polyprotein is comprised of protease (PR), reverse transcriptase (RT), and integrase (IN) genes, but in addition contains a gene encoding deoxyuridine pyrophosphatase (DU) between RT and IN (Elder, 1993; Lerner, 1995) (Figure 1). FIVs lacking DU are incapable of successful propagation in cells that are not undergoing division, such as primary macrophages, whereas wild type FIV will productively infect such cells (Lerner, 1995). These findings are also true for equine infectious anemia virus (EIAV), which is also a DU^+ lentivirus (Threadgill, 1993; Steagall, 1995). DU is not necessary for replication in rapidly dividing cells, due to high endogenous levels of DU in the replicating cell (Lerner, 1995). The primary role of DU is to prevent mis-incorporation of uracil into DNA by limiting the concentration of dUTP through conversion to dUMP, a precursor for dTTP synthesis. DU^- FIV accumulates five- to eight-fold more base changes, primarily G->A transitions, than wild type FIV during replication in macrophages *in vivo*, consistent with the mis-incorporation of uracil into viral DNA through utilization by RT of undegraded dUTP during viral DNA synthesis. Importantly, when HIV-1 infects non-dividing cells, it must also deal with the problem of uracil misincorporation, although it does not encode DU. Findings of others suggest that Vpr may compensate for the lack of DU in HIV-1, both by its necessity for growth of macrophage-tropic isolates in primary macrophages and by an apparent association with uracil N-glycosylase (Ung), the enzyme responsible for excision of uracil mis-incorporated into DNA (Bouhamdan, 1996). Mutations of Vpr that knock out Ung association causes a phenotype remarkably similar to the DU^-phenotype noted in FIV and EIAV (Mansky, 2000).

A gene encoding viral infectivity factor (Vif) is present 3′ of *pol*, as in other lentiviruses except EIAV. Interestingly, findings indicate that HIV Vif also acts to reduce G->A transition mutations, but by preventing cytidine deamination by the cellular deaminase, APOBEC-3G (Mangeat, 2003; Zhang, 2003). The role of Vif in the FIV life cycle is currently being investigated to determine if parallels exist between Vif function in FIV and HIV.

The *env* gene encodes heavily glycosylated SU and TM proteins and exhibits considerable amino acid sequence variation, with 5 consensus major variable regions (V1–V5) in SU and 3 (V6–V8) in TM (Phillips, 1990; Pancino, 1993). The mechanism of virus entry dictated by interactions of the FIV envelope with binding and entry receptors closely parallels SU/receptor interactions noted with HIV. Characterization of receptor binding and entry of FIV has progressed markedly in the last few years and may offer an additionally target for development antiviral therapies in both cats and man (see below and also Willett, this issue). Four *env* subtypes (clades) plus numerous outliers have been defined via Env sequences (Bachmann, 1997). The genetic-clade variation of FIV is remarkably similar to that found in HIV (Delwart, 1997), although the bias towards non-synonymous site changes is not as great, especially for the B clade (Bachmann, 1997; Delwart, 1997). As with HIV, heteroduplex mobility assay has been used to define the diversity of FIV envelope sequence subtypes, as well as assist in the identification of numerous inter-subtype recombinants. Evolutionary trends, as assessed by rates of synonymous and non-synonymous base changes and level of mutational saturation, differ between the most commonly found FIV *env* clades, A and B (Sodora, 1994, 1995). FIV is tropic for T cells (Pedersen, 1987; Yamamoto, 1988; Sparger, 1989; Novotney, 1990; Brown, 1991; Beebe, 1994) macrophages (Brunner, 1989; Rideout, 1992; Callanan, 1993; Parodi, 1994), and central nervous system (CNS) cells. *In vivo* tissue tropism studies have demonstrated viral RNA in T cells, macrophages, and CNS cells. FIV RNA has also been

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demonstrated in association with follicular dendritic cells (FDC) (Toyosaki, 1993; Bach, 1994; Hurtrel, 1994). Although $CD4^+$ cell decline is a hallmark of FIV infection, FIV has a broader lymphocyte tropism than $CD4^+$ T cells, with infection also evident in at least a subset of $CD8^+$ T cells and B cells *in vitro* and *in vivo* (Brown, 1991; Willett, 1993; de Parseval, 2000).

In spite of the targeting of $CD4^+$ cells, CD4 is not used as a binding receptor for FIV. However, all domestic cat FIVs examined to date bind and utilize the chemokine receptor, CXCR4 as an entry receptor (Poeschla, 1998; Willett, 1998) similar to T celltropic HIVs. Recent studies (de Parseval, 2001; Joshi, 2005) have indicated that FIV infection of certain cells may occur solely mediated via CXCR4 if expression of the chemokine receptor is sufficiently high. However, feline $CD4^+$ T cells express a 43 kDa glycoprotein that past studies had demonstrated is a binding receptor for FIV SU (de Parseval, 1999). Studies of Shimojima et al (Shimojima, 2004) have now shown that this molecule is the activation marker, CD134, and we have now confirmed that the SU binding molecule previously reported was, indeed, CD134 (de Parseval, 1999; also see below). The demonstration that CD134 is up-regulated on activated $CD4^+$ T cells (de Parseval, 2004) explains how FIV targets this cell population *in vivo* in spite of failure to bind CD4. Furthermore, soluble CD134 can interact with the virus to facilitate productive infection of $CD134^-$ $CXCR4^+$ target cells (de Parseval, 2005), indicating that the binding receptor alters the conformation of SU to promote high affinity binding to CXCR4 (Figure 2). This parallels findings with CD4 binding to HIV SU and indicates that although different binding receptors are involved, both viruses use very similar mechanisms to infect target cells. Furthermore, neutralizing monoclonal antibodies have been identified that only neutralize the virus when soluble CD134 is present (de Parseval, 2006). Again, these findings parallel observations of such masked neutralizing epitopes on HIV that become available upon interaction of SU with the CD4 binding receptor (Kwong, 2002; Moulard, 2002; Labrijn, 2003; Lusso, 2005; Xiang, 2005). The striking similarity and conservation of entry mechanisms between the two divergent lentiviruses likely is the result of common immunological pressures in the two hosts. Thus, the feline lentivirus offers a valuable venue to study the mechanisms of lentivirus infection of T cells and for development of strategies to compromise the virus' ability to escape immune surveillance.

FIV as a system for development of intervention strategies

As detailed above, there are many parallels between the outcomes of infection with FIV in the cat and infection of humans by HIV. Additionally, the target cell populations are similar and thus both viruses are confronted with similar obstacles for replication and perpetuation of species. These two lentiviruses have evolved along unique pathways that have led to development of alternative mechanisms to deal with certain aspects of replication, including transcriptional transactivation and uracil misincorporation. However, there are sufficient similarities to make the cat/FIV model a valuable tool for several lines of direct experimentation. The utilization of CXCR4 by FIV as one of the receptors used to enter target cells is an important similarity to HIV that can be explored in development of intervention strategies. The parallels in the role of the binding receptor in facilitating interaction with CXCR4 in the two systems are striking and imply a strong selection for similar mechanisms of entry and evasion of immune surveillance. The Gag and Pol gene products have common functions in the two viruses and in many cases, respond to the same inhibitors. Use of the cat for development of broad-based protease inhibitors has been successful (Lee, 1998, 1999; also see below). Nucleoside analogs that interact with the active site of reverse transcriptase have been found efficacious against both FIV and HIV (North, 1989). Given the high relatedness of integrase proteins in the two lentiviruses, it is likely that FIV will serve as a valuable system for development of anti-integrase drugs. The structural proteins of Gag may also provide broad-based targets, since all lentiviruses share common morphological features. Elements of the

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virus core are likely to maintain commonalities in their mechanisms of action and orientations in the particles. The matrix, capsid, and nucleocapsid proteins may thus present effective targets for broad-based intervention strategies. As pointed out above, the P2 protein of FIV (Elder, 1993) is an apparent functional homologue to the P6 protein of HIV and shares late domain homologies (Demirov, 2002; Freed, 2002). Both HIV and FIV encode Vif proteins, which may provide an additional target for intervention strategies to be used in both lentivirus systems. Importantly, the cat offers an economical, low biohazard, and readily manipulated venue for *in vivo* testing of potential therapeutic modalities that cannot be economically tested in primate models. Thus, anti-viral approaches, both drug and vaccine treatments (see Yamamoto, this issue), can be carried forward directly into the natural host species.

PR as a target for antiviral therapies

Much of our laboratory's efforts to develop broad-based antivirals using the cat model have centered around use of PR as a target for drug development and testing. The aspartic protease has the critical responsibility for the processing of viral Gag and Gag-Pol polyproteins into individual structural and enzymatic proteins during assembly and maturation (Pettit, 1991; Elder, 1993; Dunn, 1994; Katz, 1994; Tozser, 1997; Palella, 1998). This proteolytic step is highly specific, ordered, and essential for producing mature and infectious retrovirus particles (Pettit, 1994; Tomasselli, 1994; Swanstrom, 1997; Pettit, 1998). Therefore, PR has been a very important target for antiviral therapies (Vacca, 1997; Swanstrom, 2000). There are several approved protease inhibitors available that are effective for treating HIV-1 infection (Vacca, 1997; Swanstrom, 2000; Richman, 2004; Johnson, 2005). Combination drug therapies have been used successfully in the treatment of AIDS brought on by infection of individuals with HIV-1. In particular, the use of highly specific inhibitors of PR in combination with RT inhibitors, referred to as highly active anti-retroviral therapy (HAART), has proven to suppress HIV-1 replication to undetectable levels in patients (Collier, 1996; Gulick, 1997; Kirk, 1999; Richman, 2004; Johnson, 2005). However, HIV-1 variants frequently evolve that are resistant to these inhibitors (Condra, 1995; Jacobsen, 1996; Molla, 1996; Zhang, 1997; Palella, 1998; Young, 1998; Lawrence, 1999; Kutilek, 2003; Kozal, 2004). As many as 40% of the patients receiving HAART have a viral rebound within the first 3 years and this number is likely to be higher outside of controlled studies (Cohen, 1998). In addition, transmission of resistant HIV has been observed and is likely to increase with the increase of patients on combination therapy (Cohen, 1998). Also, poor tolerance to current protease inhibitors by a significant number of patients may lead to increased non-compliance, which may be the leading reason for cases of failure of HAART therapy. Side effects resulting from long-term drug treatment have also been observed. Both of the latter problems might be allayed by development of drugs with better bioavailability and length of efficacy per dosage, which would reduce the drug regimen. Thus, there is a need to develop novel inhibitors with activities against drug-resistant isolates that exhibit delayed resistance development and show a high degree of specificity (Kutilek, 2003). Defining the determinants of substrate specificity of the lentiviral PRs is a logical first step in the development of such broad-based inhibitors.

FIV protease, like HIV-1 protease, is a homodimeric aspartic proteinase and the two enzymes are strikingly similar at the crystallographic level, particularly within the substrate binding region (Wlodawer, 1995; Laco, 1997) (Figure 3). However, FIV is distinct in that each monomer is comprised of 116 amino acids, as opposed to 99 amino acids for HIV-1 protease, with only 27 conserved amino acids between FIV and HIV-1 PRs. Like HIV protease, FIV PR is responsible for processing Gag and Gag-Pol polyproteins (Elder, 1993). Similar to SIV and HIV-1 PRs, autoproteolysis of FIV protease is observed *in vitro* (Laco, 1997). Despite these similarities, FIV PR is specific to its respective substrates and inhibitors of HIV-1 protease currently employed in clinic do not inhibit FIV protease (Slee, 1995; Schnolzer, 1996; Dunn, 1999). FIV protease cleaves the FIV MA/CA cleavage junction efficiently. However, it does

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not appreciably cut the HIV-1 MA/CA cleavage junction, despite the presence of four identical residues in the P3-P3′ position. HIV-1 protease prefers its own substrates as well, but can cleave FIV MA/CA cleavage junction to some degree. Important to the present discussion, there are at least 6 mutations found in HIV-1 proteases associated with drug resistances that are identical to structurally equivalent residues of wild type FIV protease (Slee, 1995). Two particularly interesting resistance mutations of HIV-1 protease, Val32→Ile (FIV Ile37) and Ile50→Val (FIV Val59), are located in the substrate binding pockets of the protease (Figure 3), which suggests they may play an important role in the inhibitor and substrate selectivity of retroviral protease. Recent studies (Lee, 1998; Lee, 1999) have shown that a major structural distinction between FIV and HIV-1 PRs is that the combined S1/S3 substrate binding pocket is restricted in size relative to the same site in HIV-1 PR. This finding offers a structural explanation for the failure of the current HIV-1 PR inhibitors, which possess bulky P3 groups, to inhibit FIV PR (Lee, 1998, 939–44). Importantly, many drug-resistant HIV-1 PRs appear to have more restricted *S*1/S3 subsites as well (Lee, 1999, 1145–1155), reducing inhibitor binding affinities in a manner similar to the feline enzyme. In addition, the nature of S2/S2′ amino acids is particularly critical in directing PR substrate specificity as well as certain inhibitor efficacies. Thus, studies directed at understanding the structural basis for inhibitor and substrate specificity in the feline and human systems may lead to development of broad-based inhibitors with efficacy for a range of HIV variants.

Both FIV and HIV-1 PRs recognize, approximately, the P4-P4′ residues of peptide substrates via a long cavity in the middle of the protease, as analyzed by biochemical experiments (Moore, 1989; Weber, 1989; Tozser, 1991; Tozser, 1992; Silva, 1996; Tozser, 1997) and crystallographic analyses (Miller, 1989; Erickson, 1990; Swain, 1990). Both homodimeric PRs utilize an acid-base hydrolysis mechanism in which aspartic acids 25 and 25′ (of HIV-1 PR; 30 and 30′ for FIV PR) activate a water molecule to perform a nucleophilic attack on the amide carbonyl between the P1 and P1′ positions in various peptide substrates (Silva, 1996). Like most aspartic proteases, optimal substrate cleavage occurs at approximately pH 4–5 (Tozser, 1992; Polgar, 1994; Kutilek, 2003). There are three major structurally conserved regions that make up the substrate binding pockets of PR: 1) the active core region (residues 30–38 for FIV; 25–33 for HIV); 2) the flap (residues 54–60 for FIV; 45–51 for HIV); and 3) C-terminal “90’s loop” region (residues 98–101 for FIV; “80’s loop” for HIV, residues 80–84) (Figure 3). Within these regions, there are 11 amino acids that differ between FIV and HIV-1 proteases. These residues have proved to be good candidate targets for mutational studies of substrate selectivity. The 11 different amino acid residues in the S4 - S4′ subsites of FIV protease; Ile35, Ile37, Gln54, Asn55, Met56, Ile57, Val59, Ile98, Gln99, Pro100 and Leu101, most likely account for the specificity of the substrate/inhibitor binding. The corresponding residues in HIV-1 protease are Asp30, Val32, Lys45, Met46, Ile47, Gly48, Ile50, Pro81, Val82, Asn83 and Ile84, respectively. All the aforementioned residues have now been documented to mutate in response to protease inhibitor treatment (Schinazi, 1997, 129–142; Rhee, 2003, 298–303). We have prepared a series of mutant FIV PRs in which HIV-1 amino acid residues have been substituted into the FIV PR background at equivalent positions (highlighted in Figure 3). Confirmation of the involvement of several of these residues in both substrate and inhibitor specificities has been obtained (Lee, 1998; Lin, 2000, 2003, 2006). These wild type and mutant FIV PRs have, and will continue to serve, as a structural library for further defining substrate specificity and for inhibitor refinement in the proposed research.

Role of Gag-Pol polyprotein structure in processing

An increasing body of evidence points to a pivotal role of the polyprotein folding/conformation in the temporal cleavage of the Gag- and Gag-Pol proteins that is necessary for generation of infectious virus (Pettit, 1994; Vogt, 1996; Swanstrom, 1997; Wiegers, 1998; Gross, 2000). The studies of Petit et al. (Pettit, 1994; Swanstrom, 1997; Pettit, 1998, 2004, 2005, 2005) pointed

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out that polyprotein cleavage occurs in a specific order and that alteration of the order by site-directed mutagenesis of certain sites resulted in production of non-infectious HIV. In particular, cleavage at the N-terminus of NC appeared to be the earliest cleavage event, at least *in vitro*, and subsequent studies have shown early cleavage on either side of NC (Pettit, 2005; also see below). Differences in the rate of cleavage of synthetic substrates encompassing the cleavage sites suggested that the order of cleavage was in part, dictated by the relative cleavage efficacy of each junction. However, more recent studies have indicated that the availability of sites around NC, based on folding of the polyprotein relative to the "embedded" protease, is likely the critical trigger to the initiation of ordered processing. Interesting studies of Kaplan, Dunn, and colleagues have shown that subtle changes at the N-terminus of the embedded protease can markedly influence polyprotein processing in *cis* with no apparent influence on the ability of free protease to cleave the polyprotein in *trans* (Pettit, 2004, 2005). This finding underscores the role of polyprotein conformation in processing and the importance of the temporal cleavage of Gag-Pol in the generation of infectious virus. As recently reported (Lin, 2006), similar events occur during processing of FIV Gag-Pol polyprotein and the data again reinforce the requirements for early cleavage around NC to generate infectious virus. Additional studies are in progress to investigate factors that dictate ordered polyprotein cleavage. Given the critical nature of the proper temporal cleavage of Gag/Pol in generating infectious virus, that process offers yet another venue to disrupt the virus life cycle, independent of direct inhibition of PR.

Conclusion

In summary, great strides have been made in dissecting the inner workings of the FIV genome and in defining the parallels and distinctions between the feline lentivirus and HIV. FIV is sufficiently diverse from HIV so as to allow extensive *ex vivo* and *in vivo* work with low biohazard and the cost of maintaining this small animal model is a fraction of that required for non-human primate models. Of particular importance, FIV and HIV share many features in their life cycles, host cell targets, and protein functions so as to make the cat a particularly valuable system for developing antiviral therapies at several levels.

Acknowledgements

Work summarized in this review was supported from grants R01AI025825 and R01AI040882 of the National Institute of Allergy and Infectious Diseases of the National Institutes of Health. We thank Ms. Karen Tam for technical assistance and Ms. Nancy Dorman for manuscript preparation.

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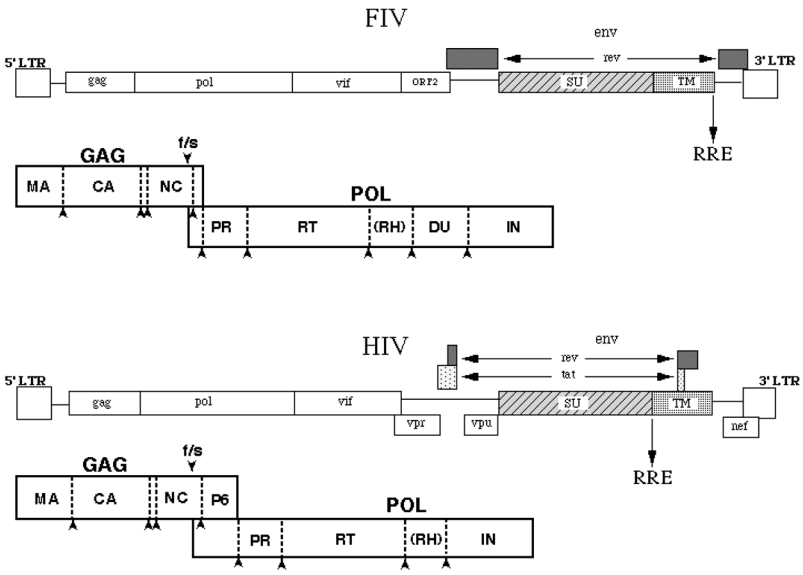

Figure 1.

Comparison of the genomic structures of Feline Immunodeficiency Virus (FIV) and Human Immunodeficiency Virus (HIV). Diagrams are shown for each virus genome as present in the integrated provirus, with organization of each respective Gag-Pol polyprotein shown below. LTR, long terminal repeat; f/s, frameshift; RRE, rev response element; Orf2, open reading frame 2; Vif, viral infectivity factor.

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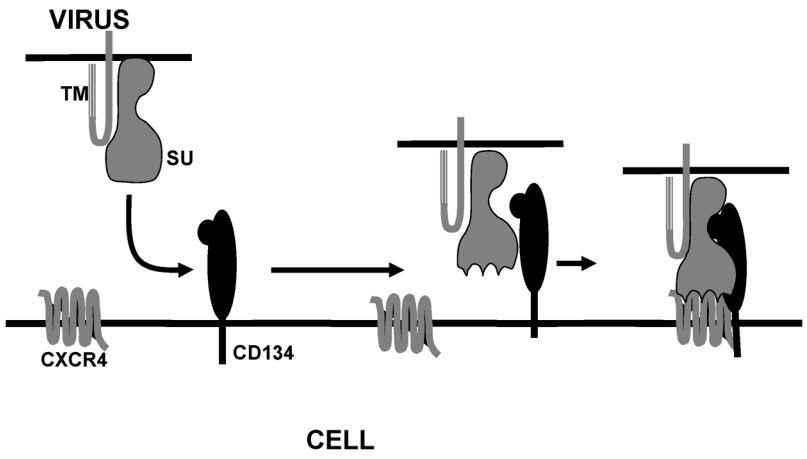

Figure 2.

Illustration depicting receptor binding events during FIV infection. Primary binding to CD134 causes a conformational change in the FIV surface glycoprotein (SU), which facilitates higher affinity binding to the chemokine receptor, CXCR4. Subsequent fusion events involving the host cell membrane and the viral transmembrane protein, TM, occur to facilitate virus entry (not shown).

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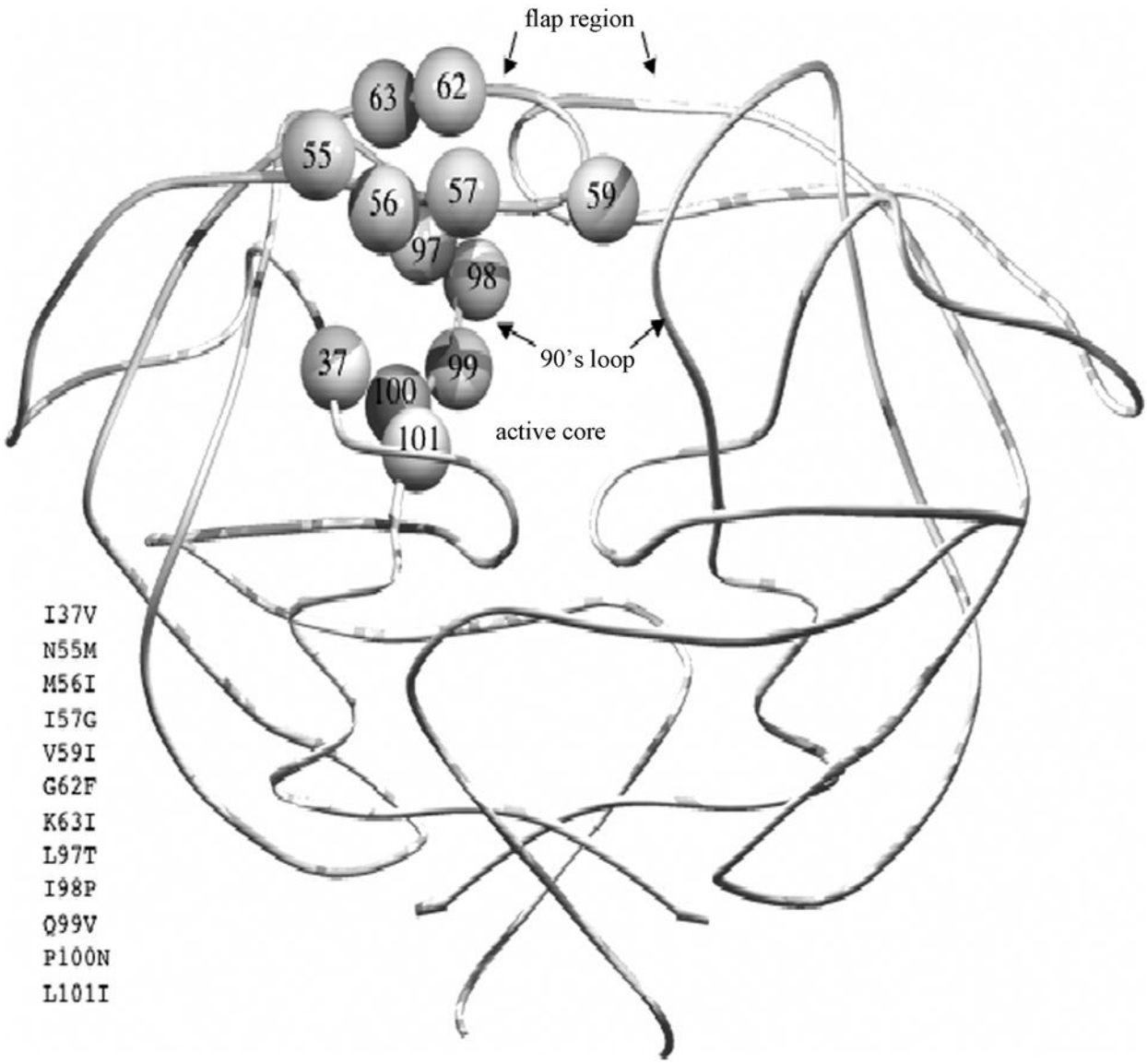

Figure 3.

Structural locations of substituted residues in FIV PR for defining both substrate and inhibitor specificities. Residues substituted in FIV/HIV chimeric PRs are shown on only one chain of the homodimeric FIV PR. Substitutions for equivalent residues of HIV-1 PR (FIV numbering with HIV-1 numbering in superscript) include $I37^{32}V$ in the active core, $N55^{46}M$, $M56^{47}I$, $I57^{48}G$, $V59^{50}I$, $G62^{53}F$, and $K63^{54}I$ in the flap, $L97^{80}T$, $I98^{81}P$, $Q99^{82}V$, $P100^{83}N$, and $L101^{84}I$ in 90's loop.