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Review

Applications of the FIV Model to Study HIV Pathogenesis

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Abstract: Feline immunodeficiency virus (FIV) is a naturally-occurring retrovirus that infects domestic and non-domestic feline species, producing progressive immune depletion that results in an acquired immunodeficiency syndrome (AIDS). Much has been learned about FIV since it was first described in 1987, particularly in regard to its application as a model to study the closely related lentivirus, human immunodeficiency virus (HIV). In particular, FIV and HIV share remarkable structure and sequence organization, utilize parallel modes of receptor-mediated entry, and result in a similar spectrum of immunodeficiency-related diseases due to analogous modes of immune dysfunction. This review summarizes current knowledge of FIV infection kinetics and mechanisms of immune dysfunction in relation to opportunistic disease, specifically in regard to studying HIV pathogenesis. Furthermore, we present data which highlight changes in the oral microbiota and oral immune system during FIV infection, and outline the potential for the feline model of oral AIDS manifestations to elucidate pathogenic mechanisms of HIV-induced oral disease. Finally, we discuss advances in molecular biology, vaccine development, neurologic dysfunction, and the ability to apply pharmacologic interventions and sophisticated imaging technologies to study experimental and naturally occurring FIV, which provide an excellent, but often overlooked resource for advancing therapies and management of HIV/AIDS.

Keywords: Feline immunodeficiency virus; FIV; human Immunodeficiency virus; HIV; animal models, opportunistic disease, lentiviral pathogenesis; molecular biology

1. Feline immunodeficiency virus

Feline immunodeficiency virus (FIV) is a naturally-occurring retrovirus that infects domestic and non-domestic feline species. In domestic cats, FIV produces progressive immune depletion that eventually results in an acquired immunodeficiency syndrome (AIDS) [1-10]. As a consequence, FIV infection is associated with a variety of clinical syndromes, including cachexia, anterior uveitis, chronic rhinitis, gingivostomatitis and periodontitis, encephalitis and neurologic dysfunction, and lymphoma [1,4,9,11-21]. The acute phase of FIV infection, lasting approximately 4-8 weeks, is characterized by a sharp increase in CD4+ T lymphocytes that are accompanied by high levels of FIV viral RNA and proviral DNA in circulation [4,8,22]. These hematologic changes are typically accompanied by mild to moderate clinical signs which include pyrexia, lethargy, and peripheral lymphadenopathy [4,22,23]. Following a prolonged asymptomatic phase, during which the levels of circulating virus remains stable and integrated provirus establishes a reservoir of latently infected target cells, there is progressive decline of CD4+ T lymphocytes and other immunocytes, resulting in functional immunodeficiency and susceptibility to opportunistic infections [6,24-26].

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During FIV infection, loss of CD4+ T lymphocytes is directly attributable to a viral-induced cytopathic effect, in addition to an increase in FIV-specific CD8-mediated programmed cell death, lack of thymic regeneration, and spontaneous apoptosis in response to decreased cytokine support [10,25,27,28]. The most frequent clinical disease syndromes associated with FIV infection manifest as a consequence of immune dysfunction, such as oral opportunistic infection (gingivitis, stomatitis, and periodontitis), immune-mediated glomerulonephritis, chronic rhinitis, and dermatitis [15,16,19,20,29,30]. Oral opportunistic infections are prevalent in a high proportion of FIV-infected cats, and frequently present as erythematous, inflammatory lesions along the gingival margin (gingivitis), multifocal areas of necrotizing inflammation within the gingival sulcus or periodontal ligament (periodontitis), or ulcerative inflammatory lesions along the buccal mucosa, hard palate, or soft palate (stomatitis) [20,31-33]. Changes in the salivary/oral microbiota have been increasingly associated with FIV infection, and shifts in the proportion of opportunistic pathogens in saliva of FIV-infected cats have been associated with the development of oral inflammatory lesions [31,34]. Similarly, FIV-infected cats frequently present with severe, necrotizing and/or ulcerative inflammatory lesions (dermatitis) due to opportunistic infection with various bacterial, fungal, protozoal, and parasitic etiologies, including mycobacteriosis, leishmaniasis, toxoplasmosis, and dermatophytosis [16,29,35,36]. Upper respiratory disease is also a frequently finding in FIV-infected cats, and may occur in conjunction with concurrent viral, bacterial, or fungal infections [4,15,37,38].

Interestingly, FIV is also associated with the occurrence of neoplastic diseases, most frequently demonstrated by the development of lymphoma in a large proportion of infected cats [7,39]. This association has been described in both naturally and experimentally infected animals, and predominately manifests as high-grade B-cell neoplasms that are remarkably similar to HIV-associated diffuse large B-cell lymphoma (DLBCL) (Figure 1) [7,40-42]. Also similar to HIV, direct viral-mediated oncogenesis related to proviral integration within oncogenes is an uncommon feature of FIV infection, and neoplastic transformation has been attributed to indirect consequences of viral-induced immune dysfunction that arise in response to prolonged viral infection [7,42-44]. Specifically, recent studies have shown that clonal proviral integration sites are not typically detected during FIV infection and that proviral loads are lower in neoplastic tissues, indicating neoplastic growth of cells lacking provirus [7]. Conversely, FIV and other lentiviral infections are strongly associated with polyclonal B-cell expansion, immunoglobulin production, and cytokine expression of proliferative mediators in response to immune activation and dysregulation [45,46]. It is proposed that such infection kinetics provide opportunities for somatic rearrangements associated with generation of B-cell receptor diversity, or mutations in immunological cells during rapid expansion that disrupt or activate oncogenes; thus resulting in neoplastic transformation [7,42]. However, the causal relationship of FIV and lymphoma has not been fully elucidated, and further studies are necessary to evaluate the specific role that viral infection and immune function play during tumorigenesis.

FIV-induced renal disease is also observed in both experimentally and naturally infected cats, and includes pathologic changes which include glomerulonephritis, proteinuria, protein tubular casts and tubular microcysts, as well as diffuse interstitial inflammatory infiltrates [30,47]. Mesangial widening with glomerular and interstitial amyloidosis is also observed in kidneys of FIV-infected cats, and when evaluated in the context of another frequent finding during FIV infection, hypergammaglobulinemia, indicate the potential for immune complex deposition to occur within the glomerulus as a result of chronic antigenic stimulation and immune activation [30,48,49].

Neurologic disease is an important manifestation of FIV infection, and affected cats may present with either central nervous system (CNS) or peripheral nervous system (PNS) involvement [14,17,18,50,51]. In the PNS, FIV induces significantly increased numbers of CD3+ T cells and macrophages in dorsal root ganglia, and infected cats exhibit pronounced changes in epidermal nerve fiber densities [50,52]. FIV enters the CNS during the acute stages of infection and is present within the brain and cerebral spinal fluid [14,17,53]. The primary neuropathogenic effect of FIV infection within the CNS manifests as infiltration and accumulation of perivascular lymphocytes and macrophages (encephalitis), activation of microglial cells and astrocytes (gliosis), and occasional neuronal loss with myelin degeneration [14,17,18,53,54]. This infiltration of inflammatory cells and

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consequences associated with immune activation within the CNS frequently results in clinically apparent neurologic deficits and gradual decline in CNS function, functionally manifesting as abnormal stereotypic motor behaviors, anisocoria, increased aggression, prolonged latencies in brainstem evoked potentials, delayed righting and pupillary reflexes, decreased nerve conduction velocities, and deficits in cognitive-motor functions [55-58].

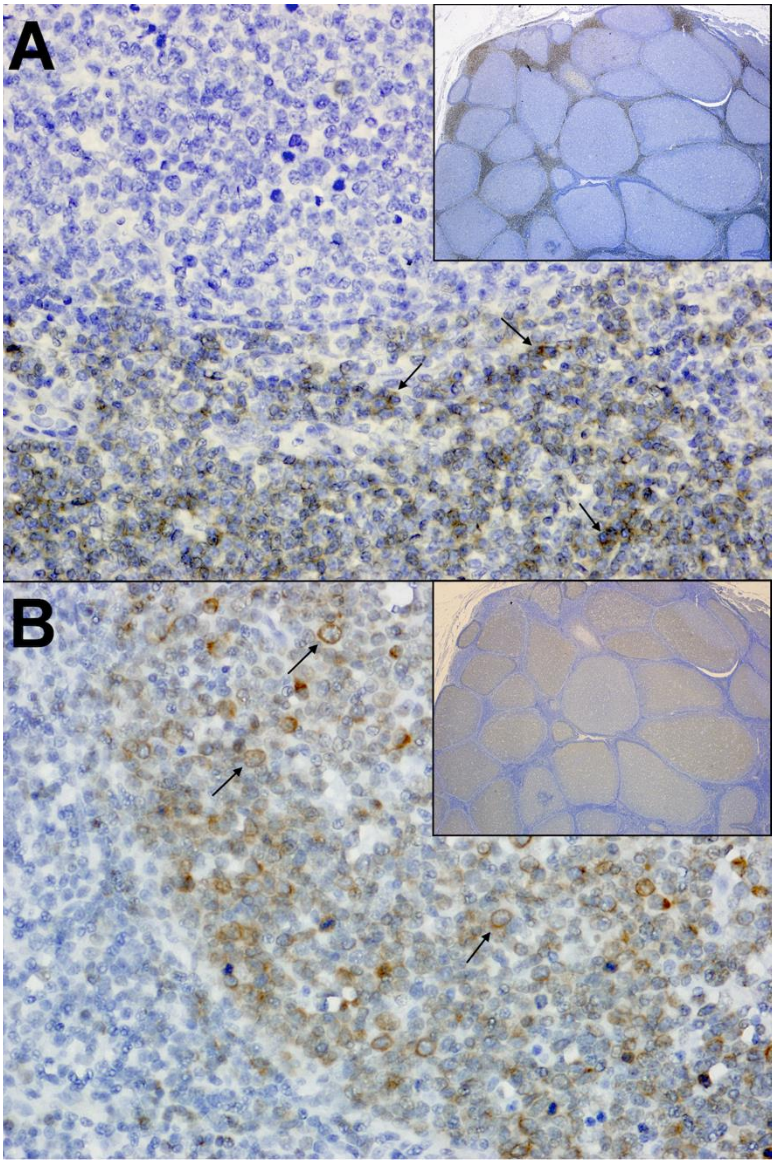

Figure 1. Immunohistochemistry from a FIV-infected cat with primary B cell lymphoma. **(A)** Mesenteric lymph Node; 40x and 4x (inset). Normal amounts of interlobular T lymphocytes (arrows) are present throughout the lymph node. Anti-CD3 (IHC) with DAB as chromogen and hematoxylin counterstain. **(B)** Mesenteric lymph Node; 40x and 4x (inset). Neoplastic B lymphocytes (arrows) multifocally expand the normal lymph node architecture. Anti-CD79a IHC with DAB as chromogen and hematoxylin counterstain.

2. FIV as a molecular analogue to HIV

FIV is a member of the Lentivirus genus within the Retroviridae family, and much has been learned about FIV since it was first described in 1987, particularly in regard to its application as a model to study the closely related lentivirus, human immunodeficiency virus (HIV) [8-10,59,60]. The FIV virion is approximately 100nm in diameter, spherical, and contains two identical strands of positive-sense RNA in its 9400-base genome, which is tightly associated with the nucleocapsid protein (NC, p7) and a t-RNA^{lys} bound to each RNA molecule, which serves as a primer for negative

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strand transcription [25,59-61]. This protein complex, along with viral enzymes involved with replication and maturation (protease, reverse transcriptase, integrase, and dUTPase), are enclosed within a core of capsid protein (CA, p24), and surrounded by a shell of matrix protein (MA, p14) [25,59,60]. Viral envelope glycoproteins (gp) are embedded within an outer lipid bilayer surrounding the matrix coat, and include the surface (SU, gp95) and transmembrane (TM, gp40) subunits, which are cleaved from a 130-150kDa membrane-bound precursor protein, glycosylated, and non-covalently anchored within the envelope in a trimeric form [25,59,60,62].

The genomic structure of FIV consists of three primary open reading frames (ORFs), *gag*, *pol*, and *env*, which are flanked by two long-terminal repeats (LTR) and accompanied by numerous small ORFs containing regulatory and accessory genes such as *vif*, *rev*, and *orfA* (Figure 2). FIV *gag* encodes the Gag polyprotein, which is cleaved by the protease to form the three mature proteins (MA, CA, and NC) and is necessary to achieve formation of mature virus particles [59,63,64]. Pol polyprotein, the primary product of the FIV *pol* gene, contains 4 important enzymes involved in virus replication and maturation: protease, reverse transcriptase (RT), integrase (IN), and dUTPase (DU) [59]. Viral protease (PR) facilitates the cleavage of Gag and Pol polyproteins into functional enzymatic or structural proteins; DU catalyzes hydrolysis of dUTP to dUMP in effort to minimize misincorporation of potentially mutagenic dUTP into host DNA [59,65,66]; FIV RT is an RNA-dependent DNA polymerase involved in the reverse transcription of viral genomic RNA into a double-stranded copy of proviral DNA (cDNA). Once synthesized, cDNA is integrated into the host genome by a mature IN containing three functional domains: an N-terminal domain, a central catalytic core, and a C-terminal domain [67-69]. The FIV Env polyprotein, a 130-150 kDa product of the *env* gene, is glycosylated and trimmed within the Golgi apparatus, and proteolytically cleaved into two mature, glycosylated proteins prior to virion budding at the cell surface: SU (gp95) and TM (gp40), both of which play critical roles in virion attachment and entry into target cells [59,60].

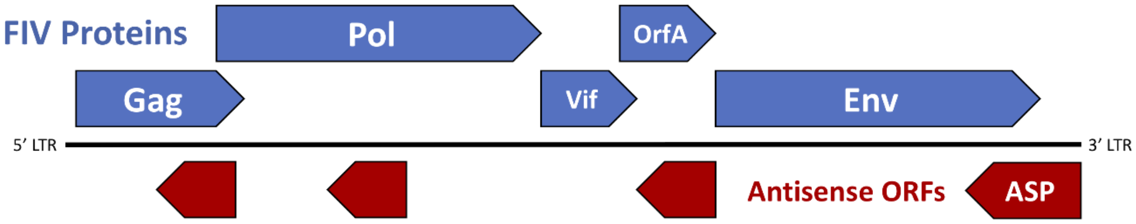

Figure 2. Genomic organization of FIV. The genomic structure of FIV consists of three primary open reading frames (ORFs), *gag, pol, and env*, which are flanked by two long-terminal repeats (LTR) and accompanied by numerous small ORFs containing regulatory and accessory genes such as *vif* and *orfA*. Potential short ORFs (antisense ORFs - shown in red) may be translated from a negative strand message.

FIV requires an initial interaction with a primary binding receptor for infection, and binds to host cells through a high-affinity interaction of the envelope SU protein (gp95) with the CD134 surface molecule present on CD4+ lymphocytes and monocytes/macrophages [70-74]. This interaction induces a conformational change in the SU protein, which then exposes a cryptic epitope in the V3 loop of Env; the binding site necessary for binding with the entry (co-) receptor CXCR4 [26,73,74]. Binding of the V3 loop exposes the serpentine region of TM (gp40), which results in the formation of a hairpin structure that allows fusion with the cell membrane and subsequent cell entry [26,74,75]. However, as infection progresses, the production of neutralizing antibodies by the host increases the need for FIV to escape selective pressures. New viral variants arise which exhibit a decreased dependence on CD134 and increased ability to infect cells that express CXCR4 with limited CD134 expression, such as naïve B cells and CD8+ T cells [2,3,60,76-79]. This expanded cell tropism results in an increase in the number of target cells susceptible to infection, which subsequently causes immunodepletion and clinical manifestations associated with AIDS-induced disease.

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The structural and sequence organization of FIV is very similar to HIV, which is also a member of the lentivirus genus [59]. HIV is morphologically characterized by a spherical virion that is roughly 120nm in diameter, and contains a diploid genome composed of two copies of single stranded, positive-sense RNA that is packaged with nucleocapsid (p7) and accessory proteins (protease, reverse transcriptase, integrase) [80]. Like FIV, the ribonucleoprotein complex at the heart of the HIV virion is contained within a dense core of Capsid protein (CA, p24) and surrounded by a spherical shell of Matrix protein (MA, p17)[80]. Mature Env glycoproteins, SU (gp120) and TM (gp 41), are anchored within the external lipid bilayer, and play significant role in cell entry through binding to host cell receptors. HIV also requires an initial interaction with a primary binding receptor for infection, and utilizes analogous modes of receptor-mediated entry as FIV utilizing chemokine co-receptors [81-83]. However, in lieu of CD134, HIV utilizes CD4 as primary binding receptor and CCR5 as its primary entry receptor, although HIV is also able to utilize CXCR4 [81,82]. Much like FIV, HIV binds to CD4+ target cells through a high-affinity interaction with the CD4 receptor that induces a conformational change in the envelope glycoprotein gp120, subsequently exposing the binding sites necessary for chemokine co-receptor binding (CXCR4 or CCR5) and subsequent fusion with the cell membrane.

The HIV genome encodes three primary polyproteins, Gag, Pol, and Env, as well as the regulatory protein, Rev, and accessory protein, Vif – all of which exhibit similar functions to FIV [59,60,80]. However, in addition to these, HIV also contains genes that encode additional accessory proteins involved in viral maturation, replication, and survival [80]. These include: Tat (p16/p14), a viral transcriptional activator; Vpr (p10-15), a promoter of nuclear localization and inhibitor of cell division (cell cycle arrest at G2/M); Vpu (p16); a promotor of extracellular release of viral particles; Nef (p27-25), a downregulator of CD4 and MHC I expression; Vpx (p12-16), a Vpr homolog present in HIV-2 (absent in HIV-1); and Tev (p28), a tripartite tat-env-rev protein [80].

The FIV genome contains one regulatory gene (*rev*) and two accessory genes (*vif* and *orfA*). FIV *rev* encodes Rev, a nucleolar polyprotein that binds to the Rev Response Element (RRE) to allow export of partially spliced and unspliced viral RNA transcripts out of the nucleus with the help of the nuclear export protein, exportin-1 [59,60,84]. The FIV Vif protein, is crucial to FIV replication and is involved in counteraction of host defense mechanisms such as APOBEC3, a cellular protein that exerts an antiviral effect by deamination of cytosine to uracil during viral replication, resulting in degradation of synthesized minus-strand DNA [59,60,85]. FIV Vif counteracts APOBEC3 by targeting the host protein to the E3 ubiquitin ligase complex, which is subsequently degraded by the proteasome [59,60,85].

The FIV OrfA protein is encoded by the accessory gene *orfA* (Figure 2), and was originally considered a transactivator of transcription due to a role in increasing the net translation of proteins expressed from genes under transcriptional control of the FIV LTR. The localization of the *orfA* gene in the viral genome also roughly coincides with the location of the gene encoding the HIV transactivator, Tat [86]. However, studies have failed to show increase in transcription directed by OrfA and there is no trans-activation response (TAR) element, as acted on by HIV Tat. Thus, increase in net protein translation facilitated by OrfA must be by other means and may be involved in late steps of virion formation and the early steps of virus infectivity, although the precise role of OrfA is still undetermined [59,60,87-90]. OrfA localizes in the nucleus and causes cell cycle arrest at G2 in infected cells, reminiscent of effects caused by the Vpr protein in HIV-1. Also, OrfA has been shown to downregulate expression of the viral receptor for FIV (CD134) on the surface of cells, as well as E2 ubiquitin-conjugating enzymes and a ubiquitin-protein ligase [60,86,91], similar to effects ascribed to the Nef protein on CD4 downregulation during HIV-1 infection. These potential functions of OrfA may have implications which aid in viral dissemination by preventing surface interactions with budding virions, and limit degradation of viral proteins by host cell ubiquitin ligase mechanisms.

In 1988, Miller [92] made the observation that there was also potential to encode a peptide product from an RNA transcribed from the minus strand of the provirus. Since then, there have been a number of reports providing evidence for predicted RNA and protein products from the minus strand in HIV-1 [93-102], SIV [103], FIV [104], and in the deltaretrovirus, BLV [105]. In FIV, there are several potential short open reading frames that may be translated from a negative strand message

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(Figure 2). However, the major potential reading frame in the negative strand of both FIV and HIV coincides with the Env coding region in the plus strand RNA, in the region underlying the Rev Responsive Element (RRE) encoded on the plus strand. A recombinant protein transcribed and translated from the ASP open reading frame has been used to screen both naturally and experimentally FIV infected cats for antibodies to the protein and a small percentage (<10%) do show some level of positivity (manuscript in preparation) (Figure 2). Furthermore, knocking out the putative start codon for ASP resulted in a dramatic reduction in viral protein production, suggesting a critical role in the virus life cycle. Immunohistochemistry shows a non-nuclear localization of the protein, suggestive of some post-transcription event. Further studies will be required to define the role of ASP, but it may contribute to the ability of the virus to replicate by counteracting some innate anti-viral response in the cell.

3. FIV as a model to study HIV pathogenesis

3.1. Immune dysfunction

The primary immunodeficiency of FIV, a gradual and progressive decline in CD4+ T lymphocytes, is a hallmark feature of both natural and experimental infection, and the most obvious fundamental feature to parallel HIV infection. During both FIV and HIV infection, CD4+ lymphocyte numbers decline over an extended asymptomatic phase, and is associated with an increase in activated CD8+ lymphocytes that have antiviral activity [106-109]. The net effect of this event is a decrease in the ratio of CD4+ cells to CD8 + cells (CD4:CD8), and is used as a clinical indicator of immunosuppression in both FIV and HIV infected patients [108-110]. Additionally, several studies have shown that FIV induces defects in immune function similar to HIV, such as a decreased proliferation response of T lymphocytes in response to mitogens, a deficit in the humoral immune response, and dysregulation of cytokine expression [10,24,59].

Large granular lymphocytes (LGLs) are a lymphoid subset comprising 10-15% of peripheral mononuclear blood cells (PBMCs) (Figure 3), and consist of either CD3- NK cells or CD3+ T-cells that mediate antibody-dependent cytotoxicity [111-114]. Analysis of LGL populations during HIV infection have been hampered by the low percentage of these cells in circulation, and has typically only been reported in association with neoplasia [114-116]. However, recent studies have shown that LGLs are detectable and elevated during HIV infection in humans, and may represent viral-suppressive CD8+ T cells [114,117]. Interestingly, studies in FIV-infected cats have determined that similar elevations in LGL phenotypes may represent polyclonal T-cells with viral suppressive properties, indicated by increased interferon-γ (IFN-γ) expression and decreased PBMC proviral loads in correlation with LGL lymphocytosis [114,118].

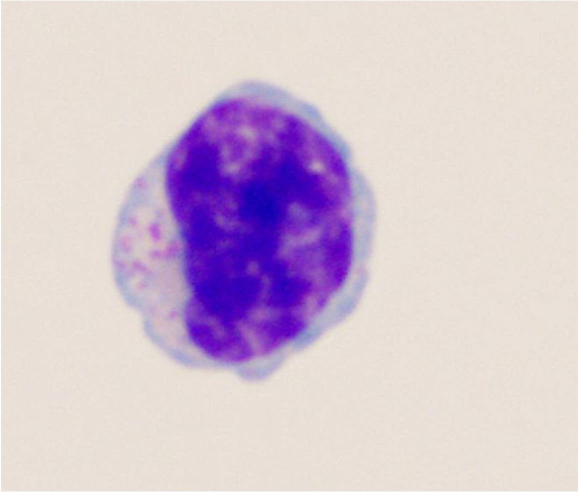

Figure 3. Cytological morphology of a large granular lymphocyte (LGL). Recent studies have determined that elevations in LGL phenotypes during both FIV and HIV infection may represent polyclonal T-cells with viral suppressive properties.

Conversely, recent studies have shown that CD4+ CD25+ T regulatory (Treg) cells are responsible for inhibition of CD8+ IFN-γ production during both FIV infection [119] and HIV infection [120], highlighting potential mechanisms by which these viruses exhibit an immunosuppressive effect on the CD8+ immune response. Furthermore, additional studies have shown that FIV directly infects and activates CD4+ CD25+ Treg cells, which are then able to suppress CD4+ CD25- T helper (Th) cells [121]. While this relationship and the potential mechanisms of Treg cell activation during HIV infection is still unclear, such comparative studies in FIV may offer potential to help our understanding of CD8+ T cell function in HIV infection.

3.2. Neurologic dysfunction

Previous studies have shown that both FIV and HIV enter the central nervous system (CNS) at acute stages of infection, either via trafficking of infected monocytes and lymphocytes, or by penetration of free virus across the blood-brain or blood-CSF barriers [17,122-127]. Once present in the CNS, both FIV and HIV infection spread to microglia and astrocytes, which then serve as a reservoir for latent viral persistence [13,17,126-128]. Although multinucleated giant cells are rarely observed in the CNS during FIV infection, the fundamental neuropathologic finding of encephalitis is well-documented in both HIV and FIV infected patients, and resultant proliferation and activation of these cells (gliosis) is associated with neurodegenerative processes such as myelin degradation and neuronal injury/loss [14,17,51,54,129]. Thus, the clinical manifestations associated with neuropathology of FIV are likewise observed in HIV infection, and because of this, FIV has been repeatedly used as a model to investigate the pathogenesis of dementia and cognitive-motor processing deficits in AIDS patients. *In vitro* models of FIV have been useful to expand our understanding of role of calcium dysregulation and neural dysfunction during lentiviral infection, and have provided a unique system for the development neuroprotective treatments such as neurotrophin ligands, which prevent the delayed accumulation of intracellular calcium and decreased cytoskeletal damage of neuronal dendrites [17,130]. Furthermore, because of the low natural prevalence and slow clinical course associated with lentiviral-induced neurologic dysfunction, experimental *in vivo* studies have been developed in the FIV model which accelerate neuropathogenesis (neonatal inoculation, inoculation with neurovirulent strains, direct intracranial inoculation), allowing increased opportunity to evaluate viral kinetics of CNS infection, neurovirulence determinants, and the potential for novel treatments designed to decrease neurocognitive defects during HIV infection [53,57,130,131].

The use of neurovirulent strains of FIV has also allowed for the investigation of neuropathogenic effects on the peripheral nervous system (PNS) as a model of HIV distal symmetric polyneuropathy (DSP), demonstrating rapid onset of peripheral neuropathy in FIV infected cats with axonal injury, macrophage activation, and detection of virus within the nerve [50,132]. Indeed, FIV infection results in pathological events in the PNS that are very similar to HIV, including increased numbers of CD3+ T lymphocytes and activated macrophages in skin and dorsal root ganglia (DRGs) that are associated with increased expression of the pro-inflammatory cytokines, as well as changes in epidermal nerve fiber densities, indicative of axonal and myelin degeneration [50,52]. FIV has also been useful in the evaluation of the neurotoxicity of antiretroviral toxic neuropathy (ATN), due to mitochondrial dysfunction associated with nucleoside analogue reverse transcriptase (NRTI) inhibitor treatment. Thus, FIV has the potential to expand our understanding of the role of the immunopathology and progression of neuropathy in FIV-infected cats.

SIV models of neuropathogenesis have been used to study HIV-associated neurologic dysfunction (HAND), and has resulted in elucidation of many mechanisms of neuroAIDS development, such as acute CNS infection and the importance of monocyte/macrophage activation in driving CNS lesions [133-136]. Recently, the SIV model of neuroAIDS has been adapted to study peripheral neuropathy, and significant advances have been made that have implicated macrophages within dorsal root and trigeminal ganglia as a source of viral maintenance, in addition to their role in neuronal loss and neuronophagia [137,138]. These findings are coupled with additional studies that have defined impaired mitochondrial function in distal axons which are more pronounced in ART-treated animals, indicating the potential for antiretroviral-mediated mitochondrial toxicity [139].

However, the SIV model of HAND is most commonly employed in rhesus macaques using SIV strains that arose via nosocomial infections or lab adaptation of African monkey strains [140]. SIV neurologic disease is therefore chiefly manifested as rapid progression to AIDS with hallmarks of CNS inflammation which amplify pathology compared to HIV-infected humans [135,136]. Furthermore, NHP studies are also limited by increased zoonotic risk to researchers, high cost associated with animal care and housing, the low number of animals available for research, and the potential for co-infection with a wide array of other pathogens, including rhesus rhadinovirus (RRV), lymphocryptovirus (LCV), simian cytomegalovirus (CMV), simian foamy virus (SFV), simian virus 40 (SV40), and rhesus papillomavirus (RhPV) [141,142].

In mechanistic studies of HIV-associated neurologic dysfunction, interaction of CXCR4 with viral envelope has been shown to enhance neuronal apoptosis via Ca^{2+}-regulating systems and NMDA receptors (NMDARs) in the synaptic membrane [143-149]. This neurotoxic pathway is known to involve Ca^{2+} influx through NMDARs, nitric oxide (NO) production, and subsequent activation cGMP-dependent protein kinase II, however, the precise cellular mechanisms by which this occurs are unknown and difficult to assess in chronically infected human patients [150-155]. Because FIV binds to CXCR4 on the neuronal membrane in a similar non-infectious interaction as HIV, the feline model may provide answers particularly in regard to the viral envelope-receptor interaction and synaptic activity-mediated neurotoxicity in HAND [156,157]. Given these similarities (and limitations of the SIV model), FIV represents an adjunct lentiviral model that can accurately recapitulate neuroAIDS progression in HIV-infected humans for applications such as evaluation of ART-induced neurotoxicity, neurofibrillary tangle development, and calcium homeostasis during viral infection [14,17].

3.3. Vaccine development

Considerable effort has been directed at the development of an anti-HIV vaccine strategy that can produce protective immunity in humans, and this effort has been paralleled in regard to FIV. A commercially available, whole inactivated virus vaccine containing two FIV subtypes (Fel-O-Vax FIV®) is currently licensed for use in the United States, and various reports have described virus neutralization and cellular immunity in a significant proportion of study animals [158-160]. However, the efficacy of this vaccine is still under debate, as recent studies and field evaluations have reported that the vaccine does not confer immunity against certain FIV strains (ie: FIV_{GL8}), and that the neutralizing antibody response and protective rate may be low in certain cat populations (i.e. protection is not conferred to certain virulent recombinant strains of FIV) [161-164]. Other attempts at FIV vaccine development have either failed to induce protective immunity against FIV infection, or have resulted in increased susceptibility to infection via antibody-dependent enhancement or general immune activation [165-170].

The development of an anti-HIV vaccine has been impeded by a wide variety of similar complications, such as lack of efficacy or unanticipated side effects, as well as increased susceptibility to infection via analogous mechanisms of FIV vaccine enhancement (antibody-dependent viral enhancement or general immune activation) [171-177]. Indeed, vaccine-induced enhancement of viral infection has been previously reported in a large number of HIV studies [178-181], and has been shown to occur via antibody-dependent or antibody-independent mechanisms of complement activation [182-189], as well as an increase in general immune activation and/or expansion of lymphoid target cells [190-194]; features that have also been observed in FIV studies [165-170]. However, despite these setbacks in lentiviral vaccine development, there are many similarities in the disease course of HIV and FIV infection, and the use of the FIV model to circumvent these roadblocks may have great potential to provide a translational model for the development of novel immunotherapies to protect from HIV infection in humans.

Traditionally, non-human primate (NHP) models have been at the forefront of anti-HIV vaccine development due to the similarities of SIV and HIV, and have revealed several promising vaccine targets such as *nef*-deleted SIV (which protects from wild-type SIV infection) and broad neutralizing antibodies utilizing chimeric SHIVs that express the HIV-1 envelope glycoprotein [195-198]. However, the successful outcome of these methods to prevent HIV infection in humans has been significantly impeded by various causes, such as restrictions on the use of live-attenuated HIV-1 in humans, as well as difficulty in producing a sufficiently efficacious neutralizing antibody response by vaccination [196]. Alternatively, various humanized mouse models have played a vital role in elucidating key aspects of the immune response to HIV, primarily through use of generally immunocompromised mice engrafted with reconstituted human immune system tissues such as human fetal thymus and liver (scid-*hu-Thy/Liv*) or peripheral blood lymphocytes (scid-*hu-PBL*) [199]. These models have been used for key studies in HIV immunopathogenesis, including mechanisms of CD4+ T-cells loss, antiretroviral therapy response, and passive immunization with monoclonal antibodies to HIV envelope protein (and testing of *Env*-based vaccines) [142,199-203]. However, because only certain parts of the human immune system can be reconstituted in humanized mouse models, interactions between the introduced human cells and the murine immune system cannot be evaluated in these hosts, nor the effects of HIV infection in non-hematopoietic tissues [199]. Although FIV lacks certain molecular similarities to HIV, it induces similar immunopathologies in its natural host, and therefore represents an important yet underutilized animal model for full evaluate the immune response during natural lentiviral infection. Furthermore, the availability of a commercially-available vaccine in cats with efficacy against at least a subset of FIV may provide important clues to improving the efficacy of anti-HIV vaccines, and the elucidation of the mechanisms associated with vaccination failure in analogous FIV and HIV models of immunotherapy may provide key insights into improving the efficacy of lentiviral vaccines.

3.4. HIV-induced oral disease

Oral manifestations of HIV are exhibited through various disease syndromes such as Oral Candidiasis (OC, “thrush”), Linear Gingival Erythema (LGE), Necrotizing Ulcerative Gingivitis (NUG), and Necrotizing Ulcerative Periodontitis (NUP) [204-206]. Despite the success of combinational antiretroviral therapy (cART) in diminishing HIV viral replication and prolonging immune function, lesions associated with systemic and local immune activation and opportunistic oral infections persist in HIV-infected patients [204,207-209]. Previous studies have demonstrated that CD4+ T-cells are rapidly and severely depleted from the intestinal mucosa following HIV infection due to direct effects of targeted virus infection and virus-induced Fas-mediated apoptosis, resulting in loss of mucosal integrity and a reduced capacity to control potential pathogens at mucosal surfaces - thereby triggering local and systemic pro-inflammatory responses [210-213]. Based upon the analogous microenvironments of the oral and gastrointestinal mucosa, the same effects of viral-induced immunosuppression is predicted to occur in the oral cavity, resulting in a chronic cycle of immune stimulation, leukocyte recruitment, and target cell infection that produces HIV-induced oral disease lesions [204,214].

The FIV model is particularly well suited for studies of HIV-associated oral disease, as it not only parallels HIV in its structural, biochemical, and immunological properties, but it is also the only naturally occurring lentivirus to predictably induce oral lesions in its natural host, the domestic cat [1,4,9,10,31,32]. Non-human primate (NHP) models of HIV do not reliably cause oral disease and are limited by zoonotic risk to researchers, high cost associated with animal care and housing, the low number of animals available for research, while humanized mouse models of HIV lack both the prevalence of oral lesions and the presence of tonsillar structures similar to humans [142,215-217]. In contrast, FIV oral manifestations are common in naturally and experimentally-infected cats [20,31,32], and the range of lesions seen include gingivitis, periodontitis, and feline chronic gingivostomatitis [32], with striking similarities to LGE, NUG, and NUP lesions noted in untreated HIV patients [1,4,107,204,218-221]. Furthermore, opportunistic infections detected in HIV-positive individuals are paralleled in feline oral disease syndromes [35,222-231], and feline tonsillar tissues (palatine, pharyngeal, and lingual tonsils) are analogous to those in humans [216]. Coupled with recent advances in new generation cART protocols available for use in cats [232-235], the domestic cat model of FIV presents an easily manipulated animal model to evaluate drivers of immune dysfunction and microbial dyscrasias during HIV infection using a controlled *in vivo* study design.

Thus, in order to assess *in vivo* mechanisms contributing to oral disease during lentiviral infection, we collected saliva from the sublingual area and ventral cheek pouches from juvenile SPF

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cats (12-14 month-old) and examined samples by 16S rRNA metagenomics analysis to detect differences in the oral microbiota of naïve and age-matched cats infected with FIV (PPR strain) of 8 months duration (n=5/group). FIV$_{\text{PPR}}$ is a relatively apathogenic strain of FIV that typically results in mild self-limiting gingivitis and/or periodontitis during acute infection [236], and animals did not have overt, visual signs of clinical periodontitis at the time of sampling. FIV-infected and naïve SPF animals were maintained on a similar diet, and similar anatomic regions were swabbed from all animals at the same time of day. DNA was extracted [237], and amplicon sequencing was performed using illumina MiSeq to generate paired-end 2x250bp sequences of the hyper-variable region 4 (V4) of the 16S rDNA. Data were normalized using cumulative sum scaling [238], and used to construct a nonmetric multidimensional scaling 3D plot (Figure 4A).

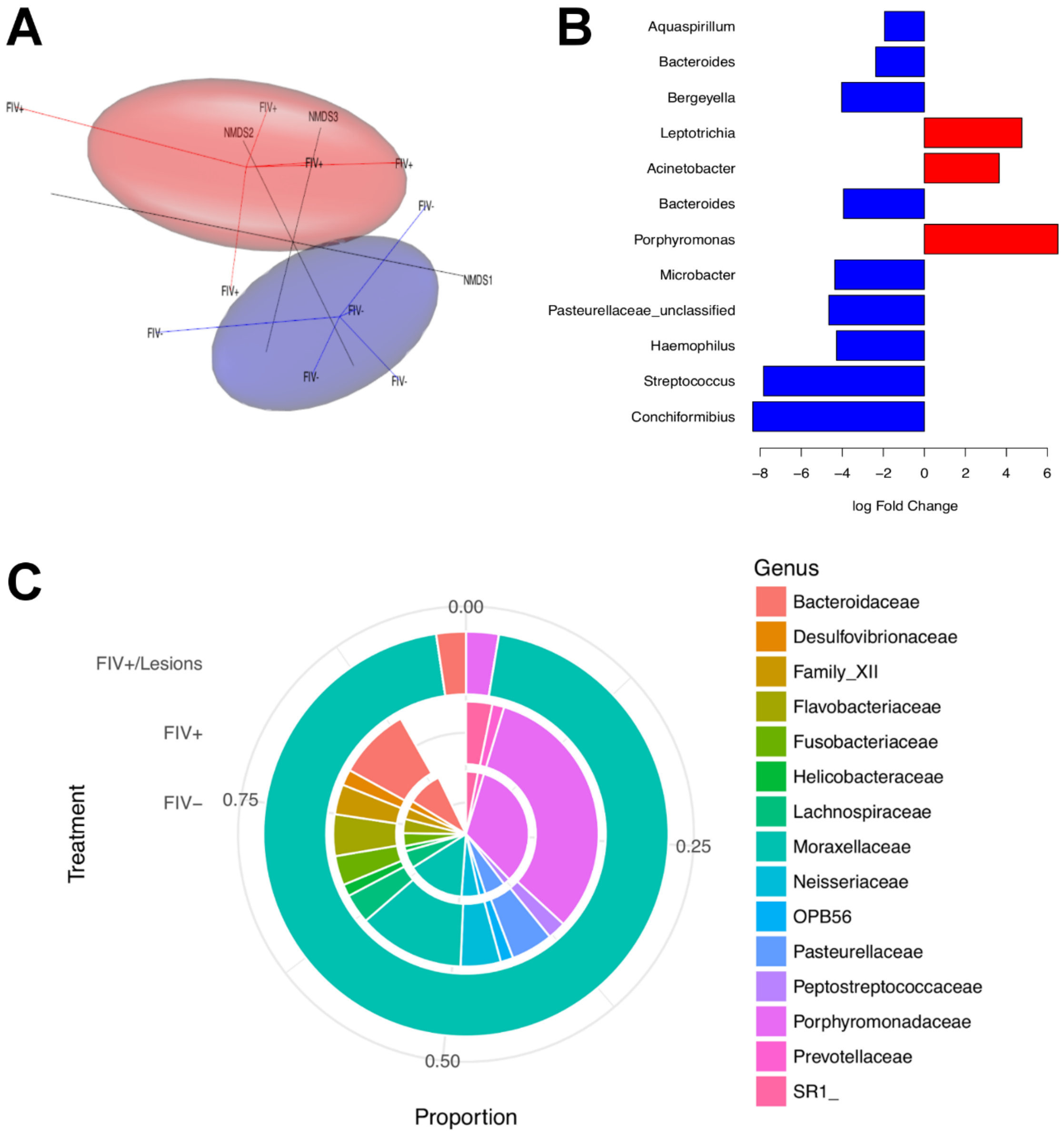

Figure 4. Salivary microbiome alterations during FIV infection. (A) 3D Nonmetric Multidimensional Scaling (NMDS) separates clusters of FIV- and FIV+ cat microbiome samples**.** Ovals represent the 90% confidence ellipsoids around the centroid of the clusters (FIV+ = red; FIV- = blue). **(B)** OTUs with significant log-fold change in abundance between FIV+ and FIV- cats at the 0.1 level of significance (after correcting for multiple testing). The list on the left shows the genera of each of these OTUs. Red indicates over representation of that OTU in the FIV+ cats. **(C)** FIV+ cat with clinical gingivitis/periodontitis with near monoculture of *Moraxellaceae* (outer circle) compared to the mean microbial community structure of cats that are FIV + (middle circle) and cats that are FIV negative (inner circle).

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Significant differences were detected in the oral microbiota composition of FIV-infected cats relative to naïve animals (Figure 4A). Normalized data were tested using the Zero Inflated Gaussian model implemented in the R package metagenomeSeq [239] to identify the putative OTUs driving differences between FIV+ and FIV- cats. Significant log-fold change in abundance in 12 genera were noted between groups at the 0.1 level of significance after correction for multiple testing (Figure 4B). One FIV-positive cat developed moderate to severe erythematous gingivitis during the course of infection and saliva was collected and analyzed as described above. Upon analysis of saliva, this individual demonstrated a dramatically altered microbiome population with >95% operational taxonomic units (OTUs) corresponding to the genus *Moraxellaceae* as compared to the FIV+ cats with no lesions and the FIV- cats (Figure 4C).

Collectively, these results demonstrate that similar to HIV, FIV infection of domestic cats is associated with oral microbiota dysbiosis and marked loss of microbial diversity during lentiviral-associated periodontitis. The persistence of HIV infection and periodontitis in patients on cART indicates that ancillary treatments specifically directed at restoring the normal oral microbiota in conjunction with cART may improve HIV periodontal progression and decrease systemic immune activation [225,240-242]. Feline dental disease is currently managed by comprehensive dental treatment consisting of hand and ultrasonic scaling, identical to techniques used in humans [243,244]. Probiotic supplementation has been successful in early studies as an adjuvant for treating periodontitis in people, and similar commercial oral probiotics products are available for management of feline oral conditions [245-247]. Thus, the application of comprehensive dental cleaning with probiotic treatments in the feline model has the potential to assess the impact of local therapy for restoring oral homeostasis during lentiviral infection, and may increase our understanding of the progression and/or resolution of FIV-induced oral lesions and oral microbiome in the presence and absence of cART.

4. Conclusions

Our understanding of FIV infection of cats has progressed remarkably over the last 3 decades, yet much remains to be learned from this widespread lentiviral infection. Correspondingly, many aspects of HIV pathogenesis and mechanisms of immune dysfunction are still poorly understood. Most notably, complete elimination of HIV from the host and restoration of immune function has not yet been achieved, nor has the means to provide protective immunity from infection. In regard to the future of HIV research, a precise understanding of the mechanisms for immunodeficiency, especially in the face of co-infections, viral-associated disease, and in the presence and absence of antiretroviral therapy will be necessary for the development of restorative or immuno-protective therapies and prophylaxis.

While genetically divergent, FIV shares remarkable overlap with HIV in regard to molecular biology and function. Coupled with the flexibility of working with a small animal model, FIV represents a useful system to assess *in vivo* aspects of lentiviral pathogenesis. As noted above, comparative pathogenesis of lentiviral immune dysfunction, neurologic and oral disease in the feline model could aid understanding of HIV AIDS. Further, the successful deployment of an FIV vaccine provides great opportunities for evaluation of lentiviral prophylaxis leading to sterilizing immunity.

The application of investigations in the molecular biology and function of genetic elements is another area which affords great potential to understand mechanisms of lentiviral infection via the FIV model. For example, contemporary studies in FIV have recently used the 3D structure of FIV reverse transcriptase to uncover the mechanistic basis of viral resistance to non-nucleoside inhibitor drugs [248]. These studies are now uncovering crucial elements in RT structure that can be used as a template for the development of novel compounds that target conventional sites of drugs resistance, providing increased efficacy against drug-resistant strains of HIV [248].

Finally, the FIV model holds significant potential as a tractable vehicle to assess efficacy of novel anti-retroviral therapies. Recent studies employing progressive cART regimen composed of nucleoside reverse transcriptase inhibitors (emtricitabine, tenofovir) and integrase inhibitors (dolutegravir) have demonstrated significant efficacy in both *in vitro* and *in vivo* FIV studies [232-

235]. Additionally, immuno-restorative therapies employing recombinant feline interferon omega (rFeIFN-ω) have resulted in improvement of clinical symptoms in FIV-associated oral disease and feline chronic gingivostomatitis [249-251]. IFN-ω has also been reported to be a potent inhibitor of HIV infection *in vitro*, but *in vivo* therapeutic potential in human patients has not been evaluated [252]. Because IFN-ω exerts strong immunomodulatory effects by stimulating Natural Killer cell activity, enhancing expression of MHC-I, and inhibiting lymphocyte proliferation, testing outcomes of IFN-ω therapy on FIV-associated disease may therefore elucidate anti-inflammatory mechanisms and offer significant potential for adoption as an agent to treat HIV-associated diseases [253].

Improvements in molecular technology and available diagnostic analyses for domestic cats, as well as the ability to apply pharmacologic interventions and sophisticated imaging technologies to the study of experimental and naturally occurring FIV provide an excellent, but often overlooked resource for advancing therapies and management of HIV/AIDS.

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Conflicts of Interest:

The authors declare no conflict of interest.

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