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EXPERT OPINION

Broadening the use of antiretroviral therapy: the case for feline leukemia virus

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Abstract: Antiretroviral drugs have saved and extended the lives of millions of individuals infected with HIV. The major classes of anti-HIV drugs include reverse transcriptase inhibitors, protease inhibitors, integrase inhibitors, and entry/fusion inhibitors. While antiretroviral drug regimens are not commonly used to treat other types of retroviral infections, there are instances where there is a perceived need for re-evaluation of the benefits of antiretroviral therapy. One case in point is that of feline leukemia virus (FeLV), an infection of companion felines. While vaccines exist to prevent FeLV infection and spread, they have not eliminated FeLV infection. For FeLV-infected felines and their human companions, antiretroviral therapy would be desirable and of practical importance if good options were available. Here, we discuss FeLV biology and current treatment options, and propose that there is a need for antiretroviral treatment options for FeLV infection. The comparative use and analysis of antiretroviral therapy can provide new insights into the mechanism of antiretroviral drug action.

Keywords: felid, cancer, antiviral, gammaretrovirus, lymphocyte, veterinary

Introduction

Retroviruses are a large group of RNA viruses that are found in all vertebrates. They share many common features, such as similarities in genetic organization and mechanism of replication, and in particular for their encoding for a reverse transcriptase. These viruses are a significant source of morbidity and mortality in both humans and animals. In humans, HIV is responsible for a world-wide pandemic that continues to be a significant cause of morbidity and mortality worldwide. In animals, feline leukemia virus (FeLV) represents a significant source of mortality and is the leading cause of infectious deaths in cats. Besides its role in feline mortality, FeLV has played an important role in advancing the understanding of retroviruses in general. In fact, the characterization of FeLV as well as other animal retroviruses such as bovine leukemia virus and Rous sarcoma virus, led to the concepts and techniques that later enabled the discovery and characterization of human retroviruses including HIV.[1] Additionally, FeLV was 1) the first retrovirus in which a vaccine was developed, 2) the first retrovirus for which a practical diagnostic test was developed, and 3) the first retrovirus that elicited the development of a program whose goal was to control its spread.[1] Despite the significant achievements and understanding of FeLV biology, FeLV is still a significant source of morbidity and mortality in felines and the treatment options for infected cats are ineffective, toxic, or cost-prohibited. Here, we discuss FeLV epidemiology, pathogenicity, and current treatments as well as future drug targets that may advance the field of FeLV treatment.

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Epidemiology

FeLV is highly transmissible through saliva and nasal secretions as well as through coitus and vertical transmission from queen to kitten. Because the primary mode of transmission is through the oronasal route, its prevalence is often dictated by the extent of animal-to-animal contact. For example, the high prevalence of FeLV in the stray cat population (40%) increases the risk of infection for indoor–outdoor cats compared to indoor-only cats. Similarly, animal-to-animal contact contributes to the different rates of FeLV infection in single cat households (4%–11%) compared to multicat households whose prevalence has been reported to be as high as 70%.[2,4,5]

Containment of FeLV is difficult due to transmission routes, the time between infection and the onset of symptoms, and the ability of latently infected cats to become viremic. In fact, exposure of cats to FeLV usually leads to one of three outcomes, two of which can contribute to the spread of disease.[2–8] The first outcome is accounted for by the 10% of exposed cats that become latently infected without a detectable viremia. While these cats would not seem to be a source of infection, they can become viremic, and subsequently shed virus into the environment. The second outcome is represented by 40% of cats exposed to FeLV, and is characterized by persistent viremia and antigenemia. These cats are chronically infected, and therefore represent a significant source of viral shedding in the environment. The third outcome includes cats that become infected with FeLV, but are then able to clear the virus to the point where it is undetectable by standard testing methods. Approximately 50% of cats exposed to FeLV fall into this last group and these cats are not considered to be a reservoir for viral spread.[2,4]

FeLV replication

FeLV was first described by Jarrett et al in 1964 who isolated viral particles from lymphomas obtained from infected cats.[9] Using electron microscopy, Jarrett et al described the infectious agent as being similar in appearance to murine leukemia virus (MuLV). Later studies confirmed FeLV to be a retrovirus. FeLV is a "simple" retrovirus, in that it encodes for 3 genes common to all retroviruses (*gag*, *pol*, and *env*), but lacks many of the additional genes found in complex retroviruses such as HIV.[6,7,10] As with other retroviruses, the *gag* gene encodes for structural proteins while the *pol* gene encodes for the enzymatic proteins necessary for reverse transcription of the FeLV genome, integration of its DNA into the host genome, and processing of viral proteins. Finally, *env* encodes for 2 envelope proteins that determine cellular tropism, including p15E, a transmembrane protein, and the associated external envelope protein, gp70.[1] Amino acid variation in the virus envelope protein has led to the division of FeLV into 4 different subtypes that defines their cell tropism: A, B, C, and T (see Table 1).[11–13] Subtype A is considered to be the founder, transmitted form of FeLV, with all other subtypes arising through mutations in FeLV-A Env or by recombination events with one of the endogenous FeLVs (enFeLV) contained within the cat genome.[1,14] The enFeLV has an incomplete genome, is not replication competent, and is theorized to have originated hundreds of thousands of years ago when a cat ate a mouse that was viremic with murine leukemia virus (MuLV). Such an event enabled the incorporation of the MuLV genome into the genome of the cat's germ line cells.[15,16]

Cell-free FeLV gains entry into target cells when the envelope protein binds to the appropriate host receptor that is dependent on the FeLV subtype (Table 1). Once inside of the target cell, the RNA genome is reverse transcribed into viral DNA by the viral protein reverse transcriptase.[17–20] The viral DNA is then transported into the nucleus where it integrates into the host genome through the enzymatic action of viral integrase. The integrated viral DNA is then transcribed to produce RNA that serves as both viral progeny as well as mRNA for the translation of viral proteins. Translated Gag and Pol proteins are then trafficked to the cell membrane where the new virions bud from the cell membrane. As the virion buds, proteolytic cleavage of viral proteins causes structural changes in the virion that are necessary for viral maturation and the formation of infectious virus particles.[17–20]

Pathobiology

FeLV usually enters the feline host through the oronasal route either through mutual grooming, biting, or a shared food source.[21–23] In the pharynx, FeLV infects the tonsillary B-lymphocytes and monocytes which can enter the draining lymph nodes.[24] The draining lymph nodes serve as a site of replication and as an entry point for the virus to enter the bloodstream. Once in the bloodstream, the virus can gain access to and infect cells in the bone marrow.[1] This represents a critical point in the infection process as it is thought that a persistent infection can be avoided if the immune system can mount an appropriate response before cells in the bone marrow are infected.[25] Once the virus becomes systemic, it infects epithelial cells in the intestines, stomach, trachea, and salivary glands and is shed into the environment. Persistently

Table 1 Description of feline leukemia virus (FeLV) subtypes, their tropism, and prevalence in infected cats

FeLV subtype[a]	Tropism	Receptor used for entry	Prevalence in infected cats	Other
A	Kidney, liver, T-cells, small intestines	THTR1 (thiamine transport protein)	100%	Considered original transmitted FeLV
B	Wide range of tissues	Pit1 and Pit2	Occurs with FeLV A in 49% of infected cats	Arose through recombination of FeLV A and endogenous sequences
C	Erythroid progenitor cells	FLVCR1 (heme exporting protein)	1%	Arose through mutations in FeLV A env
T	T cells	Pit1 in combination with co-receptor, FeLIX	Unknown	Arose from evolution of FeLV A (mutation and recombination)

Notes: [a]The four subtypes of FeLV arose through mutation and recombination. Each subtype uses different host receptors for cell entry, resulting in different tissue tropism. For more information on FeLV subtypes, see text and references therein.

infected cats can demonstrate symptoms of disease anywhere from weeks to years after infection. FeLV-mediated disease typically falls into one of two major categories – cytoproliferative or immunosuppressive.[1]

Cytoproliferative diseases associated with FeLV include leukemias, lymphomas, fibrosarcoma, and associated myeloproliferative disorders.[4,26] Most cytoproliferative diseases are attributed to insertional mutagenesis, a process by which FeLV DNA integrates at a site in the cat's genome that disrupts or deregulates expression of proteins involved in the regulation of cell cycle, cell survival, or apoptosis.[27–32] In contrast, FeLV plays an indirect role in the formation of feline fibrosarcoma. Specifically, fibrosarcoma is caused by dual infection by both FeLV and feline sarcoma virus (FSV). FSV is a replication-defective virus that encodes an oncogene that drives cellular transformation.[33–36] Therefore, FeLV serves as a helper virus, providing FSV with the proteins necessary for its replication, thereby allowing for expression of the FSV oncogene.[33–36]

Besides having cytoproliferative effects, FeLV also mediates a significant loss of immune function. This immune suppression is due to a progressive loss of T and B lymphocytes as well as neutrophils. Immune suppression leads to secondary infections such as bacterial or fungal infections that would not be a significant source of morbidity in an otherwise healthy cat.[37–40] Although the exact mechanism of FeLV-mediated immunosuppression is not clear, evidence supports 3 distinct mechanisms of action. First, immune suppression may be a result of FeLV-mediated myeloproliferative disorder.[2,14] This disorder leads to an over-proliferation of incompetent mature or immature white blood cells within the bone marrow that eventually overcrowd hematopoietic cells, thereby decreasing red blood cell production and leading to a hindrance of the immune system. Second, the virus may be cytopathic or induce cellular apoptosis, although most evidence indicates that this may be specific for FeLV subtype T. Third, it has been suggested that the transmembrane envelope protein, p15E, may have immunosuppressive properties.[41–44] For example, p15E has been reported to inhibit production of mitogenic lymphokines in T cells and has been shown to inhibit lymphocyte function without affecting receptor function.[42,43] Additionally, while p15E is not known to be cytotoxic, lymphocyte populations that are exposed to FeLV decline in size.[41–44] FeLV-mediated immunosuppression allows for secondary infections such bacterial, parasitic, and other viral infections. One example includes the blood borne parasitic infection, hemobartonellosis, which is seen with the subgroup C infections and results in anemia with a hemolytic aspect.[1]

Other diseases are associated with FeLV in which the mechanisms remain unclear. For example, neurological diseases and infertility are seen in FeLV-infected cats, though it is not clear how FeLV replication causes these disorders. Also, FeLV-C is known to cause a nonregenerative aplastic anemia. While the mechanism is not clear, it has been suggested that the anemia may be due to FeLV's use of the heme export receptor, FLVCR1, leading to a toxic accumulation of heme in erythroid progenitor cells and decreasing their numbers.[45,46] Figure 1 provides a summary of FeLV pathogenesis.

Therapeutics: vaccines and limitations

Besides containment of infected cats, commercially available vaccines for FeLV such as Pfizer's Leukocell® or Merial's Purevax® are marketed and may significantly reduce FeLV spread and viral reservoir development. These

particular vaccines are derived from chemically inactivated antigens or are of recombinant viral origin, respectively, and do not offer sterilizing immunity (ie, these vaccines essentially prime the cat's immune system enabling it to clear the virus upon exposure).[8,47,48] The American Association of Feline Practitioners reserves the vaccination regimen for high-risk populations such as indoor–outdoor cats and catteries rather than including it as part of the core vaccines.

There are several reasons why these FeLV vaccines are likely reserved strictly for the high-risk populations. The link between FeLV vaccine and feline sarcoma is likely to play an important role in why these vaccines are not part of the core vaccines. Vaccine-associated sarcoma (VAS) is an aggressive malignant tumor which requires aggressive surgery and often chemotherapy to treat.[2,14,49] The association of VAS is a significant reason why many owners and breeders choose not to vaccinate their cats against FeLV. A second reason why the FeLV vaccine is not part of the core vaccines is that a closed population of indoor-only cats is not susceptible to FeLV, making the risk of VAS greater than the risk of infection. A third factor that might limit the use of the FeLV vaccine is that its efficacy is still not known and is difficult to determine. Further complicating the issue is that the biological response to FeLV exposure differs significantly among cats. For example, 50% of cats clear the virus, 40% become persistently infected, and another 10% become latently infected. Finally, efficacy may need to be determined by using age-matched groups, given that younger cats are more susceptible to a pathogenic infection than older individuals.[2,14,50] Analyzing the result from studies that have examined efficacy is difficult because of the differences in the study design, viral strain used, and age at which cats were challenged with virus.

Many owners choose not to vaccinate their cats for fear of VAS and because the efficacy of the vaccine is not clear. The unvaccinated cat population as well as the stray cat population remains at risk for FeLV and is a significant source for FeLV transmission. The prevalence of FeLV in the cat population is evident in veterinary care where there is a significant demand for the treatment of FeLV.

Therapeutics: antiviral drug targets and opportunities

The lack of effective treatment options leads most owners to choose palliative care for FeLV-infected cats. Palliative care may include medications to treat infections, pain management, nutritional support, or any other care with the goal of keeping the cats comfortable and improving their quality of life.

Although some antivirals and immune modulators have been reported to improve the quality or quantity of life for FeLV infected cats, no studies have convincingly shown that any antivirals or immune modulators actually improve the quality or quantity of life for FeLV-infected felines in a clinically useful form. Among antivirals used to treat FeLV, azidothymidine (AZT) was the first antiretroviral used to treat HIV. AZT is a nucleoside analog that becomes incorporated into the viral DNA during reverse transcription of the RNA genome to double-stranded DNA. AZT lacks the 3′ hydroxyl group necessary for DNA polymerization, which results in termination of viral DNA synthesis. Although AZT is the primary antiviral used clinically to treat FeLV, there is little, if any, literature to support its ability to improve the course of the disease once infection is established. Some studies have suggested that treatment of cats 24 hours prior to infection up until 24 hours after infection might delay or minimize infection,[51,52] but there have been no well-designed studies to address the efficacy of AZT to prolong the lives of cats with established infection. The studies that indicate that AZT might be efficacious demonstrated that even minor improvements in disease indicators were associated with drug-related toxicities. For example, animals treated with daily doses of 30 and 60 mg/kg had elevated antibody titers, suggesting that their immune system was better able to respond to infection, although all animals receiving these doses demonstrated drug-related toxicities.[53] Thus, the main limitation for the use of AZT is its lack of apparent efficacy at tolerable doses.

Similar to antivirals, studies reporting the efficacy of immune modulators, lack appropriate controls and/or have not been independently verified. One of the immune modulators with little to no support for efficacy is lymphocyte T-cell immune modulator (LTCI). LTCI is a protein produced by a thymic stromal epithelial cell line whose manufacturers claim induces cytokines that activate CD8 cytotoxic T cells to attack virally infected cells. It is also claimed that LTCI leads to clinical improvement in FeLV-infected cats. These claims are not documented in the peer-reviewed literature, and the data supplied by the manufacturers do not argue strongly for improvements that would translate into an improvement in the quality of life or length of life for FeLV-infected animals.[54]

Another immune modulator, inactivated parapox ovis virus, strain D1701 (Baypamun®, Bayer, Leverkusen,

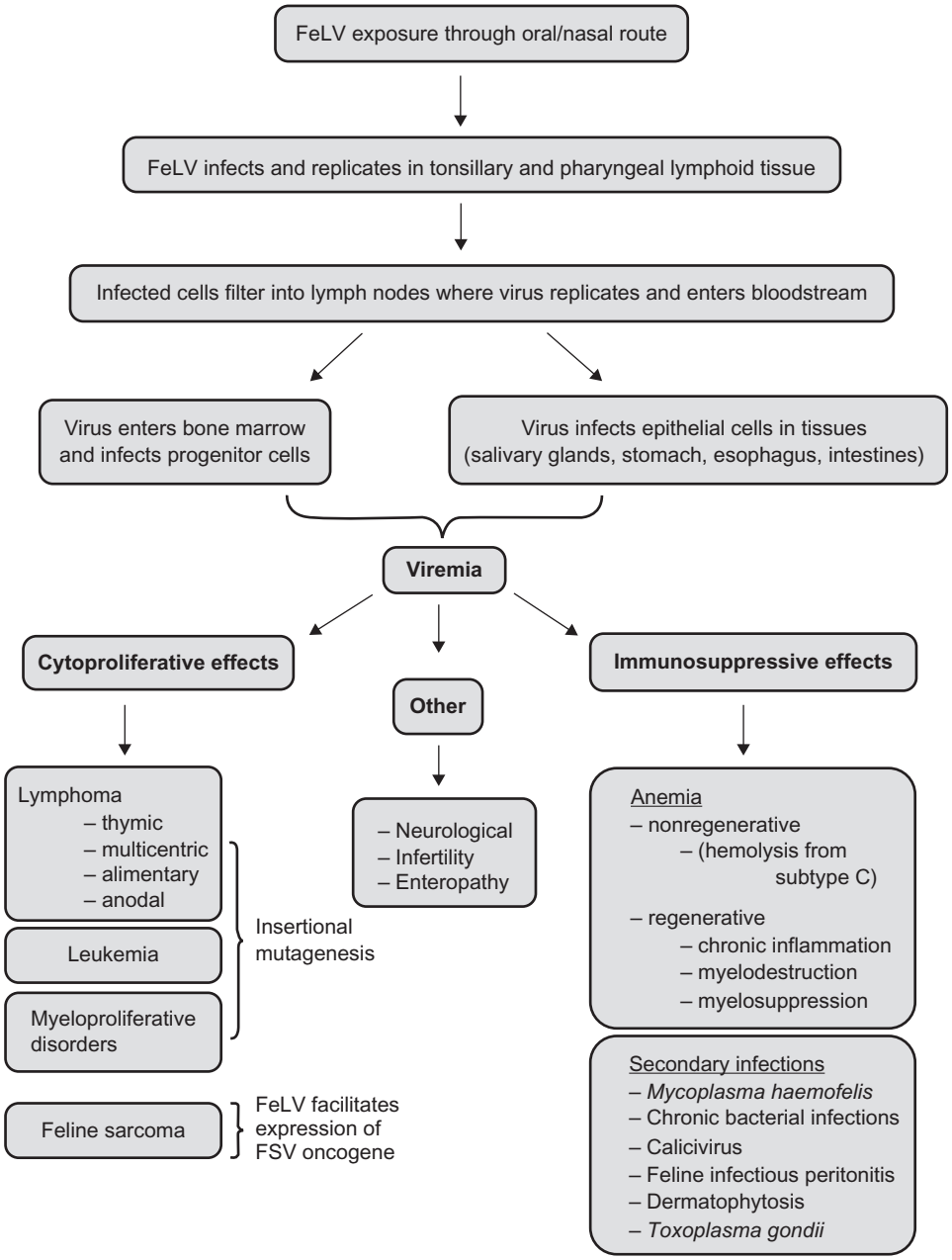

Figure 1 Pathogenesis of feline leukemia virus (FeLV) showing common entry route of virus, sites of viral replication, and pathological consequences of infection.

Germany), is reported to nonspecifically activate the immune system and improve or cure FeLV-infected cats. Baypamun is reported to increase neutrophil counts and increase the production of interferon, interleukins, and tumor necrosis factor. While initial reports by Hörber and Mayr and Hörber et al reported that Baypamun cured 80% to 100% of FeLV-infected cats,[55,56] numerous independent studies have failed to find a difference in clinical response between cats treated with Baypamun and those treated with placebo.[57]

Staphylococcus protein A (SPA) is perhaps the only immune modulator with evidence to support its ability to improve FeLV-infected cats. SPA is a bacterial polypeptide purified from the cell walls of *Staphylococcus aureus* Cowan I. Although its mechanism of action is not clear, it has been shown to bind preferentially to IgG in the form of an immune complex rather than its monomeric form. It has been speculated that SPA may bind to IgG that is bound to a "blocking factor" associated with antigen–antibody complexes and that this blocking factor may facilitate tumor or virus escape from immunological control. Therefore, SPA removes antigen–antibody-blocking factor complexes, allowing the immune system to react to viral invasion. Others have suggested that

SPA may stimulate the immune system by inducing antibody synthesis, expression of interferon, and by potentiating the natural killer activity of lymphocytes. Although some studies have shown that SPA can improve the life expectancy of FeLV-infected cats, the treatment regimens described in these studies are too cost-prohibitive and demanding to be clinically useful.[58] For example, the treatment regimens required whole-body irradiation followed by treatments given twice weekly. Additionally, it took 14 to 45 treatments to clear the virus and even this many treatments did not elicit a response from all of the cats.[59] Given the conflicting results on treatment efficacy in addition to the cost and time associated with the treatments, SPA is not a clinically feasible treatment option.

Treatment options, drug targets, and the need for FeLV-based antiretrovirals

The significant morbidity and mortality associated with FeLV combined with the significant knowledge of FeLV biology and availability of antiretrovirals developed for HIV should facilitate the identification and development of new treatment options for FeLV. Perhaps one of the main problems with treating FeLV is that early treatment is almost a prerequisite for success. Since insertional mutagenesis is responsible for FeLV-mediated lymphomas and leukemias, a quick decrease in viral loads would ensure fewer integration events, thereby decreasing the likelihood of oncogenesis. Given the success in anti-HIV drugs at quickly decreasing viral loads, it is reasonable to assume that some of these drugs could be repositioned for the treatment of FeLV. The most likely classes of anti-HIV drugs that could be repositioned include the nucleoside reverse transcriptase inhibitors (NRTIs). Many of the other classes of anti-HIV drugs are structure-based small-molecule inhibitors and would therefore be unlikely to possess anti-FeLV activities. Although there are a number of NRTIs that could be repositioned to treat FeLV, in vitro and in vivo studies indicate that NRTIs may not be readily repositioned to treat FeLV infections. Biochemical studies have shown that reverse transcriptase from oncoretroviruses such as FeLV have a higher fidelity and a significantly lower susceptibility to certain nucleoside analogs compared with lentiviruses.[58] The differences in susceptibility to nucleoside analogs between lentiviral reverse transcriptases and oncoretroviral reverse transcriptases suggest that nucleoside analogs used to treat HIV will have different susceptibilities for FeLV.

Conclusion

In human medicine, improvement in treatment options is driven by the demand of those affected by the disease. A prominent example of this demand and supply is seen with conditions such as cancer and HIV, where the impact on society fueled the funding and motivation necessary to rapidly expand treatment options in a short time. Although diseases of companion animals do not have the same affect on society as those that affect humans, there is an increasing awareness of the benefits of companion animals in improving the health and well-being of humans and a trend for demanding better treatment options at whatever cost. Antiretroviral drugs and molecular tools are readily available to determine if drugs used to treat HIV could be repositioned to treat FeLV. An important factor in assessing and instituting these potential treatments is adequate funding of well-designed studies that have sufficient numbers and controls to clearly define the treatment's efficacy and potential toxicity.

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Disclosure

The authors report no conflicts of interest.

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