Feline immunodeficiency virus infection—a model for HIV and AIDS?

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Feline immunodeficiency virus (FIV) is a lymphotropic lentivirus first isolated in California from domestic cats suffering from various clinical syndromes suggestive of underlying immunodeficiency. Since then, infection has been shown to be common in domestic cats throughout the world. Surveys generally detect FIV antibody in 1–12% of "healthy" cats and 10–20% of "sick" cats and closely related viruses have been detected in both captive and wild non-domestic felids. Although discovered only recently, FIV is also now one of the most studied feline viruses with a correspondingly large literature. The aim of this review is, therefore, to provide only a brief introduction to the field, concentrating particularly on those features of interest to comparative medicine.

FIV is a typical lentivirus in terms of its morphology and overall genome organisation but is more closely related to the other non-primate lentiviruses than to HIV. There are significant differences between the genomes of FIV and HIV, e.g., the presence in FIV of a long leader sequence S to the major env glycoprotein gene, similar to that seen in Visna virus, and a pol gene-encoded dUTPase not found in primate lentiviruses. Spliced sequences encoding rev function have been identified in FIV but equivalents of nef and tat have not been identified. One aspect of FIV infection which might make it an attractive model for study of lentivirus evolution, both within individual hosts and between populations, is sequence variation in the env gene. The variation occurs mainly in nine clusters but two of which (V1 and V2) are in the leader sequence (which also encodes part of rev), and, therefore, do not form part of the mature envelope glycoproteins. Four clusters (V3–V6) occur in the region encoding the major surface glycoprotein (gp120) and three (V7–V9) in the transmembrane glycoprotein (gp41). Several of the variable regions have been shown to be epitopes for virus neutralising antibody. Analysis of sequence variation across V3–V5 suggests that domestic cat FIV isolates can be divided into at least three distinct subtypes which cluster geographically. The amounts of variation within and between subtypes of FIV and HIV are strikingly similar, but far less variation among serial isolates from individual cats is seen than among HIV isolates from individual patients. Interestingly, the proportion of potentially silent nucleotide changes (as in contrast to changes that result in amino acid changes) in FIV env sequences is greater than that generally seen in HIV and may reflect greater co-adaptation of FIV and the domestic cat.

The natural epidemiology of FIV in domestic cats differs enormously from that of HIV in man. FIV is shed in the saliva and the main mechanism of transmission is thought to be through bites. Thus, most infected cats are adult (> 5 years old); males are generally twice as likely to be infected as females; free-roaming cats and non-pedigree cats are more frequently infected than cats kept at home and pedigree animals. As might be expected, prevalence is especially high among farm and feral cats (24–38% antibody prevalence).

Transmission from queens to kittens via milk has been recorded, but appears to play little role in the epidemiology of field infection. In addition, cats can be infected experimentally by most mucosal routes, including oral, vaginal and rectal and (D. A. Harbour, personal communication).

For most studies of pathogenesis, cats have been inoculated with cell-associated or cell-free FIV by subcutaneous, intramuscular, intravenous or intraperitoneal injection. The susceptibility of cats to infection and the severity of primary-stage clinical signs decrease with age, and most experiments have been done with cats inoculated as kittens. In such instances, virus can be re-isolated from blood after 1–3 weeks and antibody can be detected by ELISA after 3 weeks, although inoculation of low doses can significantly lengthen the time before viraemia and antibody detection. Cells susceptible to infection include CD4, CD8 and B-lymphocytes, macrophages and astrocytes. The CD4 antigen is not necessary for infectivity and recent studies suggest that the feline CD9 antigen may be the FIV receptor. A mild
lymphadenopathy with pyrexia and leucopenia usually develops 4–6 weeks after inoculation and lasts several months.\textsuperscript{2,23} and this corresponds with a shift in virus distribution from predominantly T cells to macrophages and B cells.\textsuperscript{25,26} Acute infection is also marked by a rapid expansion in the CD8\textsuperscript{+} lymphocyte population,\textsuperscript{27} possibly similar to that more recently observed in man during acute HIV infection.\textsuperscript{28} Once recovered from the acute illness, cats remain healthy for at least several years—indeed, although in-vitro and in-vivo assays suggest progressive deterioration of immune function with time (e.g., decreased absolute T-cell numbers; decreased CD4\textsuperscript{+}:CD8\textsuperscript{+} ratios; decreased lymphoproliferation responses to mitogens and antigens; decreased MHCII expression; decreased titres of antibody, particularly IgM), it has proved difficult to reproduce the types of diseases seen in the field even in cats in which in-vitro assays suggest marked immunosuppression.

Several studies of naturally infected cats suggest that the period between infection and onset of terminal AIDS-like disease is usually at least 3–5 years. Clinical signs seen in cats with end-stage disease are largely associated with immunosuppression and secondary infection—chronic stomatitis, chronic respiratory disease, chronic weight loss and pyrexia are reported most frequently.\textsuperscript{4} Some specific infections which have been associated with FIV infection are listed in Table I. Most of the organisms listed are normally mild pathogens or non-pathogenic in otherwise healthy cats, but are associated with more severe or chronic disease in FIV-infected cats. FIV infection has also been incriminated as the primary pathogen in lymphoma development,\textsuperscript{29} primary neurological disease,\textsuperscript{30} renal disease\textsuperscript{30} and various ophthalmic conditions\textsuperscript{31} in cats.

Two areas in which FIV infection has been especially studied as a model for HIV and AIDS are antiviral therapy and immunisation. FIV inhibition in cell culture has been described for most nucleoside-analogue reverse transcriptase (RT) inhibitors tested, including 3'-azido-3'deoxythymidine (AZT), 2',3'dideoxythymidine (ddC), 2',3'didehydro-2'-3'dideoxythymidine (d4T), 2',3'dideoxythymidine (ddT), 2',3'dideoxynosine (ddA), 2',3'dideoxycytidine (ddC), 2',3'dideoxyinosine (ddI), 2',3'dideoxythymidine (ddT), 2',3'dideoxynosine (ddI), 2',3'dideoxyinosine (ddI), and 4-amino-3,6-disulphonato-1,8-naphthalimide derivatives\textsuperscript{34} inhibit FIV replication, but TIBO does not.\textsuperscript{34} FIV infection of cell cultures can also be inhibited by aurintricarboxylic acid and dextran sulphates, pradimicin A and heparin.\textsuperscript{39,42} There is some field evidence that the clinical signs associated with natural FIV infection may be improved by treatment with PMEA or AZT.\textsuperscript{33,37,38} However, in cats challenged experimentally, PMEA and AZT have been shown to delay but not to prevent FIV infection.\textsuperscript{33,39-41}

Vaccination of cats with subunit vaccines has so far been unsuccessful,\textsuperscript{42-44} but some inactivated virus and cell-virus vaccines have provided protection against both homologous and moderately heterologous (9% amino acid variation in env sequence) challenge viruses.\textsuperscript{41-44} The amount of envelope glycoprotein contained in the vaccine and the adjuvants used may be significant in determining the outcome of vaccination.\textsuperscript{45} Vaccination against other moderately or more heterologous viruses (11% and 21% amino acid variation in env, respectively) was not successful.\textsuperscript{44} In a homologous system, at least, passive transfer of vaccine-induced serum and maternal antibody from vaccinated cats provided some protection even in the absence of anti-cellular antibodies,\textsuperscript{44,45} although maternal antibody does not generally afford protection to kittens.\textsuperscript{45} Little is as yet known about the doubtless important roles in protection played by anti-cellular antibody and T-cell responses, particularly after more heterologous challenge.

Although some aspects of FIV infection in cats obviously differ greatly from those of HIV infection in man, FIV infection may provide a useful model for many other aspects of HIV infection (table II).
the particular advantages of the FIV-cat model over many other models are its safety to laboratory personnel (FIV is not infectious to man), the opportunity to study lentivirus infection in a small, easily handled, outbred, natural host and the ready availability of natural cases for the study of, for example, virus evolution. From the veterinary perspective, study of FIV as a model for HIV also creates a wealth of information about a clinically important feline pathogen, so these studies, especially of immunisation and chemotherapy, may provide as much benefit to the model species as to man.

References


