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Editorial

Feline models of viral pathogenesis: Opportunity knocks

Historically, veterinary research has frequently adapted methods and treatments from human medicine. However, the opportunity exists for veterinary research to lead the way, as illustrated by the study of neuropathology caused by feline immunodeficiency virus (FIV) and its application to human immunodeficiency virus (HIV) infection, reviewed by Dr. Nicola Fletcher and her colleagues in this issue of *The Veterinary Journal* (Fletcher et al., 2011). The authors have identified an important gap in our understanding of HIV neurological disease pathogenesis and propose a rational study design for the use of a cat model to address this deficit, reminding us of the importance of such animal models in enhancing our understanding natural disease processes.

FIV is an excellent naturally-occurring model of HIV/AIDS (Phillips et al., 1994; Henriksen et al., 1995; Brennan et al., 2006; VandeWoude and Apetrei, 2006; Stump and VandeWoude, 2007; Elder et al., 2010). Unlike naturally-infected primates, domestic cats are frequently subject to intense veterinary observation, which provides us with evidence of the natural variation in disease progression and the range and severity of associated clinical signs. Furthermore, extensive knowledge of the evolutionary relationships between domestic cats and related Felidae (Johnson et al., 2006), many of which harbor similar viruses (Troyer et al., 2005; Pecon-Slattey et al., 2008), provides an evolutionary perspective on the host–viral relationship (Troyer et al., 2008). The diversity in habitat, behaviour, and natural history of feline species known to be infected with species-specific strains of FIV (Troyer et al., 2005), provides an opportunity to assess the effects of host genetic background, variations in immune response to infectious agents, and disease transmission dynamics in a range of natural settings.

Unlike the study of lentivirus infection in humans and most other naturally-infected primates, with cats there is the benefit of access to outbred colonies and specific pathogen-free animals. As with HIV infection in humans, FIV strains of varying virulence and neurotrophism infect cats (Barlough et al., 1993; Lerner and Elder, 2000; de Rozieres et al., 2004a,b, 2008; Huitron-Resendiz et al., 2004; Elder et al., 2010). The feline-FIV model is the only experimental system where parental and chimeric viruses can be used to infect a natural host in a relatively inexpensive and uncontroversial setting. Such studies are used to elucidate viral correlates of pathogenicity, mechanisms of cell entry, and variations in the host immune response (Lerner and Elder, 2000; de Rozieres et al., 2008; Lin et al., 2010; Poss et al., 1990).

Perhaps central to the utility of this model is the fact that our understanding of the molecular genetics of the cat has come of age; genomic studies will enhance our understanding of host genetic influences on lentivirus infection and progression. Several genetic similarities between cats and humans make these

studies particularly relevant including similar degrees of gene organisation, chromosome structure, genetic variation, and patterns of linkage disequilibrium (Pontius et al., 2007; Menotti-Raymond et al., 2008; O'Brien et al., 2008). By the end of 2010, the 8× coverage sequencing and annotation of the cat genome will be complete – a 2× sequence is already available (Pontius et al., 2007). The development of a 75,000 single nucleotide polymorphism (SNP) chip is being funded by the Morris Animal Foundation through Hills Pet Food and an expression array is in the pipeline. Transgenic cats have been created to express the HIV-1 viral restriction factor TRIM5 α (E. Poeschla, personal communication), underscoring the importance of the feline model in the study of viral pathogenesis. The development of in vitro systems such as the blood–brain barrier reviewed by Fletcher et al. (2011) add to the arsenal of tools available for FIV research.

While the cat-FIV model of HIV/AIDS is perhaps most directly relevant to human medicine, Felidae harbor several viruses that are related to and may shed light on human infectious agents. Feline coronavirus (FeCoV), a distant relative of the human severe acute respiratory syndrome (SARS) virus, is commonly found in domestic and feral cat populations worldwide, with a seroprevalence ranging from 20% to 100%. However <10% of seropositive cats develop the associated fatal disease, feline infectious peritonitis (Pedersen, 2009). Study of FeCoV infection in the cat thus provides an opportunity to evaluate both viral and host genetic correlates of pathogenicity (Regan and Whittaker, 2008; Brown et al., 2009). The study of feline leukemia virus (FeLV), related to human T-cell leukemia virus, has contributed significantly to our knowledge of viral carcinogenesis and oncogene function (Jarrett et al., 1964; Hardy et al., 1973; Mullins et al., 1990; Gardner, 2008). Infection with different strains of FeLV result in a variety of host responses ranging from viral clearance by the host to persistent sub-clinical infection, to the development of B- or T-cell lymphomas (Mullins et al., 1990). Through the construction of recombinant virus chimeras and in vivo challenge studies, it has been shown that changes in the envelope gene of the virus can alter the spectrum of disease caused by FeLV (Overbaugh and Bangham, 2001; Chandhasin et al., 2005a,b).

Although each of these examples illustrates the utility of feline models for studies of viral pathogenesis, the true potential of this system has yet to be fully realized. Viral infections of *Felis catus* provide a truly unparalleled opportunity: in one small package lies the ability to go from observational studies of a naturally-occurring infection in multiple, closely-related species to experimental infections where both the viral and host genome can be manipulated, to in vitro-, in vivo-, and clinical trial-based assessment of therapeutics. As illustrated by the review by Fletcher et al.

(2011), it is hard to imagine a more ideal system for disease investigation: this is a model whose time has come.

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Jennifer L. Troyer
Laboratory of Genomic Diversity, SAIC-Frederick Inc.,
NCI-Frederick, Frederick, MD 21702, USA
E-mail address: troyerj@mail.nih.gov

Meredith A. Brown
Veterinary Science Centre, University College Dublin,
Belfield Dublin 4, Ireland

References

- Barlough, J.E., North, T.W., Oxford, C.L., Remington, K.M., Dandekar, S., Ellis, M.N., Pedersen, N.C., 1993. Feline immunodeficiency virus infection of cats as a model to test the effect of certain in vitro selection pressures on the infectivity and virulence of resultant lentivirus variants. *Antiviral Research* 22, 259–272.
- Brennan, G., Podell, M.D., Wack, R., Kraft, S., Troyer, J.L., Bielefeldt-Ohmann, H., VandeWoude, S., 2006. Neurologic disease in captive lions (*Panthera leo*) with low-titer lion lentivirus infection. *Journal of Clinical Microbiology* 44, 4345–4352.
- Brown, M.A., Troyer, J.L., Pecon-Slattery, J., Roelke, M.E., O'Brien, S.J., 2009. Genetics and pathogenesis of feline infectious peritonitis virus. *Emerging Infectious Diseases* 15, 1445–1452.
- Chandhasin, C., Coan, P.N., Levy, L.S., 2005a. Subtle mutational changes in the SU protein of a natural feline leukemia virus subgroup A isolate alter disease spectrum. *Journal of Virology* 79, 1351–1360.
- Chandhasin, C., Coan, P.N., Pandrea, I., Grant, C.K., Lobelle-Rich, P.A., Puetter, A., Levy, L.S., 2005b. Unique long terminal repeat and surface glycoprotein gene sequences of feline leukemia virus as determinants of disease outcome. *Journal of Virology* 79, 5278–5287.
- de Rozieres, S., Mathiason, C.K., Rolston, M.R., Chatterji, U., Hoover, E.A., Elder, J.H., 2004a. Characterization of a highly pathogenic molecular clone of feline immunodeficiency virus clade C. *Journal of Virology* 78, 8971–8982.
- de Rozieres, S., Swan, C.H., Sheeter, D.A., Clingerman, K.J., Lin, Y.C., Huitron-Resendiz, S., Henriksen, S., Torbett, B.E., Elder, J.H., 2004b. Assessment of FIV-C infection of cats as a function of treatment with the protease inhibitor, TL-3. *Retrovirology* 1, 38.
- de Rozieres, S., Thompson, J., Sundstrom, M., Gruber, J., Stump, D.S., de Parseval, A.P., VandeWoude, S., Elder, J.H., 2008. Replication properties of clade A/C chimeric feline immunodeficiency viruses and evaluation of infection kinetics in the domestic cat. *Journal of Virology* 82, 7953–7963.
- Elder, J.H., Lin, Y.C., Fink, E., Grant, C.K., 2010. Feline immunodeficiency virus (FIV) as a model for study of lentivirus infections: parallels with HIV. *Current HIV Research* 8, 73–80.
- Fletcher, N., Meeker, R.B., Hudson, L.C., Callanan, J.J., 2011. The neuropathogenesis of feline immunodeficiency virus infection: barriers to overcome. *The Veterinary Journal* 188, 260–269.
- Gardner, M., 2008. Search for oncogenic retroviruses in wild mice and man: historical reflections. *Cancer Therapy* 6, 285–302.
- Hardy Jr., W.D., Old, L.J., Hess, P.W., Essex, M., Cotter, S., 1973. Horizontal transmission of feline leukaemia virus. *Nature* 244, 266–269.
- Henriksen, S.J., Prospero-Garcia, O., Phillips, T.R., Fox, H.S., Bloom, F.E., Elder, J.H., 1995. Feline immunodeficiency virus as a model for study of lentivirus infection of the central nervous system. *Current Topics in Microbiology and Immunology* 202, 167–186.
- Huitron-Resendiz, S., De Rozieres, S., Sanchez-Alavez, M., Buhler, B., Lin, Y.C., Lerner, D.L., Henriksen, N.W., Burudi, M., Fox, H.S., Torbett, B.E., Henriksen, S., Elder, J.H., 2004. Resolution and prevention of feline immunodeficiency virus-induced neurological deficits by treatment with the protease inhibitor TL-3. *Journal of Virology* 78, 4525–4532.
- Jarrett, W.F., Crawford, E.M., Martin, W.B., Davie, F., 1964. A virus-like particle associated with leukemia (lymphosarcoma). *Nature* 202, 567–569.
- Johnson, W.E., Eizirik, E., Pecon-Slattery, J., Murphy, W.J., Antunes, A., Teeling, E., O'Brien, S.J., 2006. The late Miocene radiation of modern Felidae: a genetic assessment. *Science* 311, 73–77.
- Lerner, D.L., Elder, J.H., 2000. Expanded host cell tropism and cytopathic properties of feline immunodeficiency virus strain PPR subsequent to passage through interleukin-2-independent T cells. *Journal of Virology* 74, 1854–1863.
- Lin, Y.C., Torbett, B.E., Elder, J.H., 2010. Generation of infectious feline immunodeficiency virus (FIV) encoding FIV/human immunodeficiency virus chimeric protease. *Journal of Virology* 84, 6799–6809.
- Menotti-Raymond, M., David, V.A., Pflueger, S.M., Lindblad-Toh, K., Wade, C.M., O'Brien, S.J., Johnson, W.E., 2008. Patterns of molecular genetic variation among cat breeds. *Genomics* 91, 1–11.
- Mullins, J.L., Hoover, E.A., Donahue, P.R., Dewhurst, S., Quackenbush, S.L., Murphey-Corb, M., Martin, L.N., Fultz, P.N., Gallo, M.V., Reinhart, T.A., 1990. The FeLV and SIV AIDS pathogenesis models: search for and analysis of molecularly defined pathogens. *Developments in Biological Standards* 72, 167–171.
- O'Brien, S.J., Johnson, W., Driscoll, C., Pontius, J., Pecon-Slattery, J., Menotti-Raymond, M., 2008. State of cat genomics. *Trends in Genetics* 24, 268–279.
- Overbaugh, J., Bangham, C.R., 2001. Selection forces and constraints on retroviral sequence variation. *Science* 292, 1106–1109.
- Pecon-Slattery, J., Troyer, J.L., Johnson, W.E., O'Brien, S.J., 2008. Evolution of feline immunodeficiency virus in Felidae: implications for human health and wildlife ecology. *Veterinary Immunology and Immunopathology* 123, 32–44.
- Pedersen, N.C., 2009. A review of feline infectious peritonitis virus infection: 1963–2008. *Journal of Feline Medicine and Surgery* 11, 225–258.
- Phillips, T.R., Prospero-Garcia, O., Puaoli, D.L., Lerner, D.L., Fox, H.S., Olmsted, R.A., Bloom, F.E., Henriksen, S.J., Elder, J.H., 1994. Neurological abnormalities associated with feline immunodeficiency virus infection. *Journal of General Virology* 75, 979–987.
- Pontius, J.U., Mullikin, J.C., Smith, D.R., Lindblad-Toh, K., Gnerre, S., Clamp, M., Chang, J., Stephens, R., Neelam, B., Volfovsky, N., Schaffer, A.A., Agarwala, R., Narfstrom, K., Murphy, W.J., Giger, U., Roca, A.L., Antunes, A., Menotti-Raymond, M., Yuhki, N., Pecon-Slattery, J., Johnson, W.E., Bourque, G., Tesler, G., O'Brien, S.J., 2007. Initial sequence and comparative analysis of the cat genome. *Genome Research* 17, 1675–1689.
- Poss, M.L., Quackenbush, S.L., Mullins, J.L., Hoover, E.A., 1990. Characterization and significance of delayed processing of the feline leukemia virus FeLV-FAIDS envelope glycoprotein. *Journal of Virology* 64, 4338–4345.
- Regan, A.D., Whittaker, G.R., 2008. Utilization of DC-SIGN for entry of feline coronaviruses into host cells. *Journal of Virology* 82, 11992–11996.
- Stump, D.S., VandeWoude, S., 2007. Animal models for HIV AIDS: a comparative review. *Comparative Medicine* 57, 33–43.
- Troyer, J.L., Pecon-Slattery, J., Roelke, M.E., Johnson, W., VandeWoude, S., Vazquez-Salat, N., Brown, M., Frank, L., Woodroffe, R., Winterbach, C., Winterbach, H., Hemson, G., Bush, M., Alexander, K.A., Revilla, E., O'Brien, S.J., 2005. Seroprevalence and genomic divergence of circulating strains of feline immunodeficiency virus among Felidae and Hyaenidae species. *Journal of Virology* 79, 8282–8294.
- Troyer, J.L., Vandewoude, S., Pecon-Slattery, J., McIntosh, C., Franklin, S., Antunes, A., Johnson, W., O'Brien, S.J., 2008. FIV cross-species transmission: an evolutionary perspective. *Veterinary Immunology and Immunopathology* 123, 159–166.
- VandeWoude, S., Apetrei, C., 2006. Going wild: lessons from naturally occurring T-lymphotropic lentiviruses. *Clinical Microbiology Reviews* 19, 728–762.