

Review Article

Novel gammaherpesvirus infection in felids: a brief review

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Introduction

Alpha herpesvirus infection in domestic cats has been recognised for many years as feline herpesvirus-1 (FHV-1) is a ubiquitous virus causing upper respiratory tract and ocular pathology [1-6]. In 2014 the first gamma herpesvirus to affect felids, *Felis catus* gammaherpesvirus 1 (FcaGHV1) was detected both in domestic cats and their wild cousins the bobcats and pumas in the USA [7] and shortly afterwards internationally [8,9]. While FcaGHV1 has been detected in asymptomatic domestic cats [10] the study in domestic cats from Australia and Singapore [8] noted that infected cats were more likely to be described by attending veterinarians as sick rather than well. FcaGHV1 DNA positive cats on PCR were 2.82 (95% CI 1.24% to 6.58%) times more likely to be classed as sick when compared to PCR negative cats [8], although no further details of diseases associated with virus positivity were given. Having said that seropositive cats were noted in one study often to be PCR negative [11] as might be expected in a state of classic herpesvirus latency. On the other hand the high co-prevalence of haemoplasma infection in FcaGHV1 infected cats [12] suggests that co-transmission may occur. Associations of FcaGHV1 and feline immunodeficiency virus may lead to neoplastic change [13], although such a conjecture currently rests on comparative examples in other species, as will be discussed further below.

Some herpesvirus basics

The effects of herpesvirus infection was known at the time of the ancient Greeks with Hippocrates recognising the creeping appearance of herpetic skin lesions, giving rise to the term herpetic, or creeping in Greek. Shakespeare has the fairy Queen Mab in *Romeo and Juliet* saying "O'er ladies lips, who straight on kisses dream, which oft the angry Mab with blisters plagues, because their breaths with sweetmeats tainted are." These blisters presumably those of herpetic 'cold sores.' This is herpes simplex, a classic alpha herpesvirus with epithelial and neurotropism, exhibiting dermatological and mucosal lesions before turning to latency in a sensory nerve ganglion. Other alpha herpesviruses include the cytomegaloviruses and varicella viruses such as human varicella zoster and porcine Aujeszky's disease or pseudorabies. The beta herpes viruses are cytomegaloviruses seen in mice and humans and become latent in leucocytes. The gamma herpes viruses include human Epstein-Barr virus (EBV) [14] and human herpesvirus 8 [15].

Herpesviruses and neoplasia

Note that gamma herpes viruses, as opposed to alpha and beta herpes viruses become latent in lymphocytes and can give rise to neoplasms. The one exception here is Marek's disease caused by an alpha herpes virus and giving rise to causes paralysis, chronic wasting, blindness, and fatal lymphoma [15] The gamma herpes virus-associated neoplasms include Kaposi's sarcoma associated with HHV-8 when immune surveillance is compromised by human immunodeficiency

virus infection [16]. Burkitt's lymphoma occurs when EBV infection particularly occurs in people affected by the Philadelphia chromosome 8:14 translocation which joins the IgG heavy chain locus and the oncogene c-myc or two other rarer translocations [17]. Equine herpesvirus 5 has been associated with equine multinodular pulmonary fibrosis [18] but as yet no neoplastic change while pigtail macaque rhadinovirus causing retroperitoneal fibromatosis in macaque species [19, 20] and gamma herpesviruses have been detected in carcinomas of California sea lions (*Zalophus californianus*) [21]. Indeed gamma herpesviruses are widespread among pacific pinnipeds [22, 23]. Phocid herpesvirus 1 is an alpha herpesvirus with antigenic similarity to canine and feline herpesviruses [24] while phocine herpesvirus 2 is a gamma herpesvirus, although to date similarity to the novel FcaGHV has not been elucidated.

Gamma herpesviruses and the immune system

As noted above Kaposi's sarcoma and Burkitt's lymphoma need additional factors to allow viral oncogenesis to occur. Gamma herpesviruses persist in B lymphocytes but to reach these B cells and to reach and enter new lymphocytes they must infect other cell types. This is controlled in immunocompetent hosts by both CD4 and CD8 expressing lymphocytes. Experimental work on murine herpesvirus infection (with both MuHV-4 and MuHV-68 a naturally occurring pathogen in the rodent species *Apodemus flavicollis* (the yellow-necked-mouse) and *Clethrionomys glareolus* (the bank vole) as well as being endemic in wild British wood mice (*Apodemus sylvaticus*) has shown that these herpesviruses down regulate MHC-1 and producing immunomodulators which alter host chemokine networks as well as blocking autophagic and apoptotic pathways [25]. We are at present unclear whether the FcaGHV1 virus has the same effects on feline hosts, but it would be unusual if this were not to be the case. Such immune evasion potentially renders production of a vaccine against gamma herpesviruses a challenging task [26].

Conclusion

At present then we have a widespread novel gammaherpesvirus seen in felidae worldwide and a wide diversity of diseases caused in other species by gamma herpesviruses through different molecular mechanisms in the areas of both immunity and oncogenesis. The role of FcaGHV1 in many feline diseases where current infectious agents do not appear to answer all questions regarding pathogenesis remains and exciting new field of investigation.

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