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Mini review

Molecular epidemiology of feline immunodeficiency virus in the domestic cat (*Felis catus*)

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ABSTRACT

Studying the evolutionary mechanisms of feline immunodeficiency virus in the domestic cat (*Felis catus*), FIV_{Fca}, provides a good comparison to other lentiviruses, such as HIV and FIV_{Pco} in the cougar (*Puma concolor*). We review the current epidemiological and evolutionary findings of FIV_{Fca}. In addition to the five accepted FIV_{Fca}, subtypes, several recent phylogenetic studies have found strains that form separate clades, indicative of novel subtypes. In New Zealand cats, these strains of unknown subtype have been found to be involved in complex patterns of intergenic recombination, and whole genome sequences are required to resolve these. Evidence of recombination events has been documented with the highest levels in the *env* gene, the region involved in host cell receptor recognition. Several cases of FIV_{Fca} multiple infections, both inter- and intra-subtype, have been reported. The findings of both unknown subtypes and relatively high levels of recombination suggest the need for further testing of the current vaccine. Limited studies on the evolutionary rate of FIV_{Fca} document a value twice to three times that of FIV in the cougar, a result suggesting the different levels of co-adaptation between the viruses and their respective hosts. We studied the tissue distribution of FIV_{Fca} in feral domestic cats, finding the first case of FIV compartmentalisation, a phenomenon well documented in HIV-1 patients.

1. Introduction

Feline immunodeficiency virus (FIV) is a lentivirus that infects members of the Felidae and Hyaenidae (Troyer et al., 2005), and each host species usually has its own FIV strain (Brown et al., 1994; Carpenter et al., 1996, 1998; Troyer et al., 2005; Franklin et al., 2007; Pecon-Slattery et al., 2008). The strain that circulates in populations of the domestic cat (*Felis catus*), FIV_{Fca}, is pathogenic and can lead to feline AIDS, with symptoms similar to that produced by human immunodeficiency virus (HIV) in humans (Pedersen et al., 1989; Bendinelli et al., 1995; VandeWoude and Apetrei, 2006). Furthermore, shared characteristics of HIV-1 and FIV_{Fca}, such as the worldwide distribution, the occurrence of recombinants, and high viral RNA loads in plasma suggest that FIV_{Fca} is a good model for HIV-1 (Carpenter et al., 1998; Yamamoto et al., 2002; Yamamoto et al., 2007).

In other host species, such as the African lion (*Panthero leo*) and the North American cougar (*Puma concolor*), FIV is apparently less pathogenic than in the domestic cat (Carpenter and O'Brien, 1995; Carpenter et al., 1996; Bull et al., 2003; Brennan et al., 2006; Roelke et al., 2006). The difference in the disease status of these hosts suggests that FIV has persisted in the lion and cougar much longer than FIV in the domestic cat, such that a period of host

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adaptation has occurred (Carpenter et al., 1996). This hypothesis is also supported by a higher prevalence and greater genetic variation of FIV in lion and cougar populations compared to the domestic cat (Brown et al., 1994; Carpenter and O'Brien, 1995; Biek et al., 2003). The similarity between FIV_{Fca} and HIV-1, and the difference between FIV_{Fca} and, for example, FIV_{Pco} in the cougar, provide two important reasons for studying FIV_{Fca}.

Here we provide a general overview of the prevalence, subtypes and recombination of FIV_{Fca}, and include some recent findings on the evolutionary rate and tissue distribution of FIV in the domestic cat. For this review, we define three categories of domestic cat populations: companion, feral, and stray. Companion cats are pets; owned by and reliant on humans. Feral cats are free-ranging, inhabit rural areas like forest and scrubland, and have minimal or no human contact. Stray cats are also free-ranging but inhabit urban areas and have some human contact.

2. Prevalence of FIV_{Fca} in *F. catus* populations

2.1. Companion cat prevalence

Generally, the prevalence of FIV_{Fca} in companion cat populations worldwide is about 4–12% (Courchamp and Pontier, 1994). Companion cats in the USA and Canada have FIV prevalence at the lower end of the range, between 1% and 7% in low-risk and high-risk cats, respectively (Shelton et al., 1989; Yamamoto et al., 1989; O'Connor et al., 1991). In contrast, companion cats in Japan have a higher prevalence value, of up to 44% in clinically ill cats, which is suggested to be the result of relatively higher cat density (Ishida et al., 1989). The worldwide distribution of FIV_{Fca} in domestic cats is thought to be a result of low virulence levels and low rates of transmission of the virus (Fromont et al., 1997).

2.2. Feral cat prevalence

Worldwide studies of feral and free-ranging cats have found FIV_{Fca} prevalence of about 8–19% (Baneth et al., 1999; Winkler et al., 1999; Ostrowski et al., 2003; Danner et al., 2007; Hayward, 2009) but see Carpenter et al. (1998) and Yamaguchi et al. (1996). The higher FIV_{Fca} prevalence observed in feral cats compared to companion cats may be explained by differences in behavioural patterns and the main route of FIV transmission. Feral cats tend to be free-ranging and more aggressive in their interactions with other cats, and as such, have a higher frequency of biting encounters (Courchamp et al., 1998). For this same reason, male, sexually mature cats are at the highest risk of FIV_{Fca} infection (Hosie et al., 1989; Courchamp et al., 1998; Levy et al., 2006).

3. FIV_{Fca} subtypes

Five FIV_{Fca} subtypes, A to E (Fig. 1) have been established based on phylogenetic analyses of sequences from the *env* V3–V5 region (Sodora et al., 1994; Kakinuma et al., 1995; Pecoraro et al., 1996). Recent papers have also used the *gag* gene to confirm the *env* clades (Kakinuma et al., 1995; Duarte et al., 2002; Steinrigl and Klein, 2003; Reggeti and Bienzle, 2004; Weaver et al., 2004; Hayward and Rodrigo, 2008). Subtypes A, B and C are most widespread worldwide, with subtype D only found in Japan and Vietnam (Kakinuma et al., 1995; Nakamura et al., 2003) and subtype E only found in Argentina (Pecoraro et al., 1996). The four subtypes A to D are found in cat populations from Japan (Kakinuma et al., 1995; Nishimura et al., 1998) but see Yamamoto et al. (2007) for worldwide FIV prevalence and subtype distribution details. There appears to be subtype-specific differences in disease, for example, subtype A infection has been reported to be associated with neurological disease (Nishimura et al., 1996; de Rozieres et al., 2008) while subtype B is less likely to be symptomatic (Bachmann et al., 1997).

In addition, sequences of unknown subtype have been documented. Eleven FIV_{Fca} isolates from Texas were tentatively designated subtype F (Weaver et al., 2004). More recently, these Texas sequences were assigned as a subclade within subtype B and the Portuguese sequences were proposed as subtype F (Fig. 1) (Duarte and Tavares, 2006). Furthermore, 18 *env* sequences from New Zealand (NZ) cats have been identified as distinct from any previously described subtype, designated U-NZenv (Fig. 1) (Hayward et al., 2007; Hayward and Rodrigo, 2008). Phylogenetic analyses of *gag* and *pol* sequences from NZ cats also showed evidence of one and two unknown subtypes, respectively, although the samples included in these unknown clades were not identical across the three genes (Hayward and Rodrigo, 2008). The finding that the NZ *env* unknown subtype group is not monophyletic across the three main genes leads us to question the suitability of FIV_{Fca} subtyping using the *env* V3–V5 region only. In light of recent sequencing technologies and the HIV-1 nomenclature recommendations that at least two full-length genomes from epidemiologically unrelated hosts are required to name a new subtype (Robertson et al., 1999), a precautionary approach in designating new subtypes is suggested.

The Fel-O-Vax vaccine (Fort Dodge), which is commercially available in a number of countries including USA, Australia, Japan and NZ, confers protection against subtypes A, B and D but has not yet been tested on subtype C, despite the wide distribution of this subtype (Yamamoto et al., 2002; Kusuhara et al., 2005). Furthermore, the findings of FIV strains of unknown subtypes suggest further testing of the vaccine in cat populations is warranted.

4. Recombination in FIV_{Fca}

Retroviruses have been documented to have relatively rapid rates of recombination due to the presence of a diploid genome (that is, two identical copies of ssRNA) and the occurrence of multiple infection (Hu and Temin, 1990). Naturally occurring multiple FIV_{Fca} infection, either as a result of co-infection or superinfection, has been identified in cats from Australia, USA and NZ (Kyaw-Tanner and Robinson, 1996; Bachmann et al., 1997; Kann et al., 2007;