Veterinary Immunology and Immunopathology 143 (2011) 282–291

Contents lists available at ScienceDirect

Veterinary Immunology and Immunopathology

journal homepage: www.elsevier.com/locate/vetimm

Research paper

Strain-specific viral distribution and neuropathology of feline immunodeficiency virus

Craig Miller[a,*], Helle Bielefeldt-Ohmann[b], Martha MacMillan[a], Salvador Huitron-Resendiz[c], Steven Henriksen[d], John Elder[e], Susan VandeWoude[a]

[a] *Department of Microbiology, Immunology, and Pathology, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO, USA*
[b] *School of Veterinary Science, University of Queensland, Gatton Campus, Gatton, Qld, Australia*
[c] *Department of Neuropharmacology, The Scripps Research Institute, La Jolla, CA, USA*
[d] *Graduate College of Biomedical Sciences, Western University of Health Sciences, Pomona, CA, USA*
[e] *Department of Molecular Biology, The Scripps Research Institute, La Jolla, CA, USA*

ARTICLE INFO

Keywords:
Lentiviral neuropathology
NeuroAIDS
Feline immunodeficiency virus

ABSTRACT

Feline immunodeficiency virus (FIV) is a naturally occurring lentivirus of domestic cats, and is the causative agent of feline AIDS. Similar to human immunodeficiency virus (HIV), the pathogenesis of FIV involves infection of lymphocytes and macrophages, and results in chronic progressive immune system collapse and death. Neuropathologic correlates of FIV infection have not yet been elucidated, and may be relevant to understanding HIV-associated neurologic disease (neuroAIDS). As in HIV, FIV strains have been shown to express differential tendencies towards development of clinical neuroAIDS. To interrogate viral genetic determinants that might contribute to neuropathogenicity, cats were exposed to two well-characterized FIV strains with divergent clinical phenotypes and a chimeric strain as follows: FIV_{PPR} (PPR, relatively apathogenic but associated with neurologic manifestations), FIV_{C36} (C36, immunopathogenic but without associated neurologic disease), and Pcenv (a chimeric virus consisting of a PPR backbone with substituted C36 env region). A sham inoculum control group was also included. Peripheral nerve conduction velocity, CNS imaging studies, viral loads and hematologic analysis were performed over a 12 month period. At termination of the study (350 days post-inoculation), brain sections were obtained from four anatomic locations known to be involved in human and primate lentiviral neuroAIDS. Histological and immunohistochemical evaluation with seven markers of inflammation revealed that Pcenv infection resulted in mild inflammation of the CNS, microglial activation, neuronal degeneration and apoptosis, while C36 and PPR strains induced minimal neuropathologic changes. Conduction velocity aberrations were noted peripherally in all three groups at 63 weeks post-infection. Pcenv viral load in this study was intermediate to the parental strains (C36 demonstrating the highest viral load and PPR the lowest). These results collectively suggest that (i) 3′ C36 genomic elements contribute to viral replication characteristics, and (ii) 5′ PPR genomic elements contribute to CNS manifestations. This study illustrates the potential for FIV to provide valuable information about neuroAIDS pathogenesis related to genotype and viral kinetics, as well as to identify strains useful to evaluation of therapeutic intervention.

© 2011 Elsevier B.V. All rights reserved.

* Corresponding author at: 1619 Campus Delivery, Colorado State University, Fort Collins, CO 80523-1619, USA. Tel.: +1 970 491 7696.
E-mail address: craig.miller@colostate.edu (C. Miller).

0165-2427/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.vetimm.2011.06.006

1. Introduction

Feline immunodeficiency virus (FIV) is a naturally occurring lentivirus of domestic cats, and is widely considered to be a valuable model to study human immunodeficiency virus (HIV)-associated neurologic disease (neuroAIDS) development (Fletcher et al., 2008; Podell et al., 2000; Power et al., 1998). Similarities between FIV and HIV infections in the central nervous system (CNS) have been demonstrated through brain-entry mechanisms via the blood–brain and blood–choroid plexus barriers (Dallasta et al., 1999; Gonzalez-Scarano and Martin-Garcia, 2005; Kramer-Hammerle et al., 2005; Luabeya et al., 2000; Ryan et al., 2005), presence of astrogliosis and microgliosis in FIV and HIV-infected individuals (Everall et al., 1995; Lendhardt et al., 1988; Meeker et al., 1997; Gray et al., 1996), perivascular lympho-plasmacytic and mononuclear cell infiltration of the meninges and choroid plexus (Gray et al., 1996; Ryan et al., 2005), and overall immunodeficiency and neurological impairment (Podell et al., 1993). In addition, the structural and functional diversity that may result in the varying pathogenicity of different HIV isolates are paralleled in FIV (de Rozieres et al., 2008; Sodora et al., 1994). The viral genomic determinants responsible for these varying degrees of pathogenicity are not fully understood and further phenotypical characterization of these elements may lead to the development of more effective treatment modalities (de Rozieres et al., 2008).

Five clades (A–E) have been established for FIV and most FIV subtypes are classified within clades A and B. FIV isolates in general have been shown to exhibit varying degrees of pathogenicity with one previously characterized clade C isolate (FIV_{CPG}) causing severe disease and high mortality (de Rozieres et al., 2004a,b; Diehl et al., 1995; Obert and Hoover, 2000; Sodora et al., 1994). This clade C isolate, while markedly immunopathogenic in young cats, has not been previously associated with neurologic disease, despite high peripheral viral loads (de Rozieres et al., 2004a,b). In contrast, other FIV isolates, such as those belonging to clade A, have been demonstrated to exhibit a predilection for neurologic disease development (Phillips et al., 1996; Phipps et al., 2000; Prospéro-García et al., 1994). The reason for the varied neurotropism in individual FIV isolates remains unclear and investigation of the molecular basis of various FIV strains may help to better understand neuroAIDS progression *in vivo*.

To interrogate viral genetic determinants that might contribute to neuropathogenicity, cats were exposed to two well-characterized FIV strains with divergent clinical phenotypes and a chimeric strain as follows: FIV_{PPR} (PPR, relatively apathogenic but associated with neurologic manifestations), FIV_{C36} (C36, immunopathogenic but without associated neurologic disease), and Pcenv (a chimeric virus consisting of a PPR backbone with substituted C36 env region) (de Rozieres et al., 2004a,b, 2008; Phillips et al., 1990, 1996). Examination of neuropathogenicity associated with *in vivo* infection from these strains was performed by a variety of methods. Brain sections from four anatomic locations known to be involved in human and primate lentiviral neuroAIDS were examined for pathogenic change by histological and immunohistochemical methods (Zink et al., 2006; Fletcher et al., 2008). In addition, cerebral spinal fluid (CSF) obtained from infected cats, as well as the aforementioned brain sections, were used to determine CNS viral load by RNA extraction and RT-PCR. Brainstem auditory evoked potential changes (BAEPs) were also assessed in all cats in this study at specified intervals. The findings of this study are presented in this report and reflect that the Pcenv chimera appears to be more neuropathogenic than both parental strains and that CNS viral load is not predictive of neuropathogenicity during FIV infection.

2. Methods

In vivo infections, cloning and analysis of Pcenv sequences, and FIV proviral DNA and plasma RNA quantitation were all performed as previously described (de Rozieres et al., 2008). The Pcenv chimeric virus was constructed with PPR genetic elements *ltr*, *rev2*, *gag* or *pol* and with C36genetic elements *vif*, *orfA*, *env*, and the first exon of *rev* (reviewed in Fig. 1 as presented in de Rozieres et al., 2008). Twenty, 14–16 week-old, SPF cats (Cedar River Laboratories, Ames, IA, and an SPF colony at Colorado State University [CSU], Fort Collins, CO) (de Rozieres et al., 2008) were maintained in barrier rooms within AAALAC-international accredited animal facilities in accordance with CSU IACUC-approved protocols. Three groups of cats (each $n = 5$) were inoculated intravenously with 1 ml normalized plasma obtained from cats previously infected with either PPR, Pcenv, or C36 strains as previously described (de Rozieres et al., 2008). An additional group ($n = 5$) was administered naïve plasma and used as

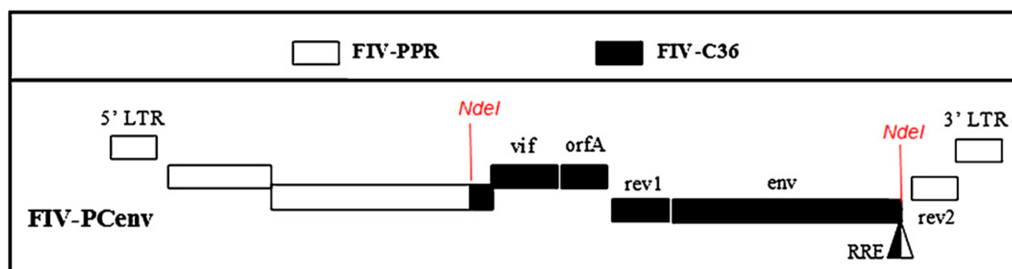

Fig. 1. Pcenv is a chimeric virus containing the 3′ regulatory elements *vif*, *orfA*, *rev*1, and *env* from a highly virulent clade C strain (C36) and the 5′ backbone of a moderately virulent clade A strain (PPR).
(from de Rozieres et al., 2008)

Download English Version:

https://daneshyari.com/en/article/2462095

Download Persian Version:

https://daneshyari.com/article/2462095

Daneshyari.com