FELINE IMMUNODEFICIENCY VIRUS AND ITS RECEPTORS

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ABSTRACT

Feline immunodeficiency virus (FIV) is a lentivirus associated with an AIDS-like syndrome in the domestic cat. The hallmark of the infection is a gradual depletion of CD4+ helper T lymphocytes. The FIV enters cells by sequential interaction between its envelope glycoprotein (ENV) and the primary receptors, CD134, and subsequently with the co-receptor the chemokine receptors CXCR4. The expression of those receptors is restricted to activated cells. The FIV possesses a broad tropism for CD4+ lymphocytes, CD8+ lymphocytes, B lymphocytes and monocyte-derived macrophages. CD4+ cell has the greatest provirus burden during the acute phase of infection but during the chronic phase, asymptomatic stage, B cells bears the major FIV provirus. This change could be the result of the different way that the ENV interacts with its receptors. This review is a brief overview of the interaction between FIV and its receptors. The molecular mechanisms of this relation and the viral cell tropism with disease progression not only did are important to development of vaccine approaches and therapeutic interventions but also to the understanding of pathogenesis of lentiviruses.

INTRODUCTION

Feline immunodeficiency virus (FIV), an important viral pathogen worldwide in the domestic cat, causes a slow progressive degeneration of immune functions that eventually leads to a disease comparable to acquired immune deficiency syndrome (AIDS) in humans. FIV is unique among the nonprimate lentiviruses because in its natural host species, the domestic cat, it induces a disease similar to AIDS in humans induced by human immunodeficiency virus type 1 (HIV-1), which is characterized by a progressive depletion of CD4+ T lymphocytes (Pedersen et al. 1987). The infection causes a variable immunodeficiency syndrome characterized by recurrent gingivitis-stomatitis, cachexia, wasting, neurology, and an increased incidence of tumor development (Ackley et al. 1990, Beatty et al. 1998, Pedersen et al. 1987, Yamamoto et al. 1989). Distinctly, the ungulate lentiviruses cause diseases reminiscent of chronic inflammatory conditions while infection the bovine lentivirus seems to be inapparent (Willett and Hosie 2008). Thus FIV has been studied widely as both an important veterinary pathogen and an animal model for HIV/AIDS.
On the basis of the analysis of envelope glycoprotein (ENV), third to fifth variable regions, V3-V5, FIV has been classified into five subtypes (Kakinuma et al. 1995, Pecoraro et al. 1996, Sodora et al. 1994) a number that should be expected to increase as further studies reveal additional diversity. Recent studies identified distinct groups of FIV isolates from Unites States and New Zealand (Hayward et al. 2007, Weaver et al. 2004). Subtype-specific disagreements, in vivo, in pathogenicity have been inconsistently identified, but in vitro cell tropism and replication efficiency differ (Reggeti et al. 2008).

Progression of the disease resemble a pattern typical of that observed with primate lentiviruses, in the beginning a relatively short acute phase showed by an increment of the viral loads, low-grade fever, weight loss, lymphadenopathy, and neutropenia. The acute phase is followed by an asymptomatic period, that could be years, denoted by an antiviral immune responses, lower viral titers, a gradual decline in CD4+ cells, and few clinical symptoms. The terminal phase has an immunologic decompensation, a rise of plasma viral load, and clinical symptoms of immunodeficiency with opportunistic infections (English et al. 1994, Hosie and Beatty 2007).

Although the drop of the CD4+ cells is the mark of FIV infection, the virus has been shown to infect a variety of cell types in their respective hosts including CD4+ and CD8+ lymphocytes, B lymphocytes, cells of neuronal lineage and monocyte/macrophage lineage (Dean et al. 1996, English et al. 1993). Joshi et al. (2005) have characterized feline CD4+ CD25+ T regulatory (Treg) cells with the ability to support FIV replication. Recently, Reggeti, Ackerley and Bienzle (2008) have shown that feline dentritic cells (DCs) express specific viral receptors and are infected productively by FIV.

The specificity of the virus-receptors interaction is the earliest determinant of cell tropism and a decisive factor in the pathogenesis of viral disease (Willett et al. 2006b). Despite the similarities in the clinical disease and pathogenesis of FIV and HIV-1, these viruses use distinct receptors and have different in vivo target cell ranges. The primate lentiviruses HIV and simian immunodeficiency virus (SIV) stick initially to CD4, targeting the virus to helper T cells, which produces conformational rearrangement in envelope, gp 120. This conformational alteration exposes a highly conserved site for interaction with a molecule from the seven transmembrane domain
(7TM) superfamily, chemokine receptors CCR5 or CXCR4, and fusion of gp41 with the host-cell membrane (Doms and Moore 2000, Kwong et al. 1998).

Partial explanation of the process of infection with FIV was provided by discovery that all primary isolates and laboratory strains of virus use CXCR4 as a coreceptor for infection. The data suggest that the usage of chemokine receptors for infection may be a conserved property of lentiviruses and may play a decisive role in the immunodeficiency associated with lentivirus infection (Willett et al. 1997). Expression of the CXCR4 is the limiting factor in the productive infection of cells by FIV and that the standard of CXCR4 expression and the relative affinity of surface glycoprotein, SU, for CXCR4 control the amount of virus spread and cytopathogenicity (de Parseval et al. 2004).

The FIV has a same kind of pattern of receptor usage than HIV-1; however, CD 134 rather than CD4 is the beginning binding partner, and subsequent interaction with CXCR4 permits cells entry (Shimojima et al. 2004). CD134 was primary described as MRC OX-40, an antigen expressed on activated rat CD4+ T belonging to tumor necrosis factor receptor/nerve growth factor receptor (TNFR/NGFR) superfamily (Mallett et al. 1990, Paterson et al. 1987). The SU of FIV, gp95, binds to activated cells expressing CD134, the 43-kDa receptor. Pre-treatment of virus with soluble CD134 facilitates infection of CD134−/CXCR4+ cells, showing that the binding receptor changes the conformation of SU to promote intense affinity binding to CXCR4 (de Parseval et al. 2005). Studies have indicated that FIV infection of certain cells may occur solely mediated via CXCR4 if expression of the chemokine receptor is sufficiently high (de Parseval and Elder 2001).

Ectopic expression of CD134 allows feline cells permissive for infection with all strains of FIV tested from different geographical origin and phylogentic subtype. News Studies revealed differential utilization of feline CD134 by FIV. Primary isolates of FIV could be put on at least two groups as evidence on their interactions with CD134. The expression of first cysteine-rich domain (CRD1) of feline CD134 alone is enough to confer nearly optimal receptor function for infection with strains such as PPR, subtype A, and B2542, subtype B, although pathogenic primary strains of virus, such as GL8, subtype A, GPGamma, subtype C, and NCSU1, subtype B, need extra determinants, the second cysteine-rich domain, CRD2, in the CD134 and at that rate the CD134 form a functional receptor (Willett et al. 2006a, Willett et al. 2006b).
Other determinants within the viral envelope glycoprotein could contribute to virus tropism. Sequence variations and conformational changes within the ENV are responsible for determining receptor usage to FIV (Lerner and Elder 2000). Chemokine receptor tropism has been linked to sequence variations of envelope surface protein in the primate lentiviruses (Cho et al. 1998). That same region in FIV is a major neutralization domain and also an important determinant for cell tropism (Siebelink et al. 1995, Vahlenkamp et al. 1997, Verschoor et al. 1995). The mutation in the V3 is sufficient to convert a non-CRFK tropic virus into a CRFK-tropic virus (Verschoor et al. 1995). Other domains of SU distinct from V3 are also important determinants and/or codeterminants of cytotropism to HIV 1 (Palmer et al. 1996). Recent paper has showed that a single glycosylation site ablated in the envelope of the FIV, first and second variable domains (V1V2), can modulate the ENV-CD134 interaction. The removal of a single site for N-linked glycosylation is sufficient to swap strains from complex to a minimal interaction (Willett et al. 2008).

Some strains of primate lentiviruses can get interaction directly with the co-receptors (Kolchinsky et al. 2001). These CD4-independent strains may be more sensitive to neutralising, the chemokine receptor binding site could be more exposed to antibodies, but they would have a broader cell tropism in vivo where CD4 expression could be low, like central nervous system (CNS) (Hoffman et al. 1999, Kolchinsky et al. 2001, Martin et al. 2001).

In the FIV infection the provirus levels are higher in CD4+ T cells during acute phase of infection, while B cells contain the majority of provirus during the chronic phase (Dean et al. 1996, English et al. 1993). Possibly with disease progression, FIV may either lose its dependence of bind to CD 134 or interact more efficiently with CXCR4. The link between the nature of the ENV-CD134 interaction and the broadening of viral cell tropism with disease progression will be an important avenue of future research (Willett et al. 2006b). The virus tropism may be influenced by several factors, including the affinity of the viral envelope for the receptors, the level of expression of the receptors, the conformational heterogeneity of the viral envelope as well as the receptors, and/or presence of attachment cofactors such as heparin sulphate proteoglycans, HSPGs, and a specific C-type lectin expressed on dendritic cells, DC-SIGN (de Parseval et al. 2004).

Recently, a paper has revealed that CXCR4 and CD134 genes expression in all lymphocytes, monocyte-derived cells and dentritic cells. The CXCR4 gene expression
has downregulation after mitogen stimulation. Differences in CD134 gene expression showed more pronounced between different cell types, consistent with predominant expression on CD4+ T cells (Reggeti et al. 2008).

In the interaction of the virus-receptors is important to do regard of the host condition, receptors expression, strains involved and its genetic standard and environment condition. The cells infections by lentiviruses involve specific interactions between the viral envelope and yours receptors resulting in a conformational change that enables fusion of the viral and cellular membranes. Further dissection this interaction should be crucial to understanding of FIV infection, pathogenesis and clinical signs seen in the cats.

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REFERENCES

Ackley CD, Yamamoto JK, Levy N, Pedersen NC, Cooper MD 1990. Immunologic abnormalities in pathogen-free cats experimentally infected with feline immunodeficiency virus. *J. Virol.* 64: 5652-5655.

Beatty JA, Lawrence CE, Callanan JJ, Grant CK, Gault EA, Neil JC, Jarrett O 1998. Feline immunodeficiency virus (FIV)-associated lymphoma: a potential role for immune dysfunction in tumourigenesis. *Vet. Immunol. Immunopathol.* 65: 309-322.

Cho MW, Lee MK, Carney MC, Berson JF, Doms RW, Martin MA 1998. Identification of determinants on a dualtropic human immunodeficiency virus type 1 envelope glycoprotein that confer usage of CXCR4. *J. Virol.* 72: 2509-2515.

de Parseval A, Chatterji U, Morris G, Sun P, Olson AJ, Elder JH 2005. Structural mapping of CD134 residues critical for interaction with feline immunodeficiency virus. *Nat. Struct. Mol. Biol.* 12: 60-66.
de Parseval A, Elder JH 2001. Binding of recombinant feline immunodeficiency virus surface glycoprotein to feline cells: role of CXCR4, cell-surface heparans, and an unidentified non-CXCR4 receptor. *J. Virol.* 75: 4528-4539.

de Parseval A, Ngo S, Sun P, Elder JH 2004. Factors that increase the effective concentration of CXCR4 dictate feline immunodeficiency virus tropism and kinetics of replication. *J. Virol.* 78: 9132-9143.

Dean GA, Reubel GH, Moore PF, Pedersen NC 1996. Proviral burden and infection kinetics of feline immunodeficiency virus in lymphocyte subsets of blood and lymph node. *J. Virol.* 70: 5165-5169.

Doms RW, Moore JP 2000. HIV-1 membrane fusion: targets of opportunity. *J. Cell Biol.* 151: F9-14.

English RV, Johnson CM, Gebhard DH, Tompkins MB 1993. In vivo lymphocyte tropism of feline immunodeficiency virus. *J. Virol.* 67: 5175-5186.

English RV, Nelson P, Johnson CM, Nasisse M, Tompkins WA, Tompkins MB 1994. Development of clinical disease in cats experimentally infected with feline immunodeficiency virus. *J. Infect. Dis.* 170: 543-552.

Hayward JJ, Taylor J, Rodrigo AG 2007. Phylogenetic analysis of feline immunodeficiency virus in feral and companion domestic cats of New Zealand. *J. Virol.* 81: 2999-3004.

Hoffman TL, LaBranche CC, Zhang W, Canziani G, Robinson J, Chaiken I, Hoxie JA, Doms RW 1999. Stable exposure of the coreceptor-binding site in a CD4-independent HIV-1 envelope protein. *Proc. Natl. Acad. Sci. USA* 96: 6359-6364.

Hosie MJ, Beatty JA 2007. Vaccine protection against feline immunodeficiency virus. *Aust. Vet. J.* 85: 302-303.
Kakinuma S, Motokawa K, Hohdatsu T, Yamamoto JK, Koyama H, Hashimoto H 1995. Nucleotide sequence of feline immunodeficiency virus: classification of Japanese isolates into two subtypes which are distinct from non-Japanese subtypes. J. Virol. 69: 3639-3646.

Kolchinsky P, Kiprilov E, Sodroski J 2001. Increased neutralization sensitivity of CD4-independent human immunodeficiency virus variants. J. Virol. 75: 2041-2050.

Kwong PD, Wyatt R, Robinson J, Sweet RW, Sodroski J, Hendrickson WA 1998. Structure of an HIV gp120 envelope glycoprotein in complex with the CD4 receptor and a neutralizing human antibody. Nature 393: 648-659.

Lerner DL, Elder JH 2000. Expanded host cell tropism and cytopathic properties of feline immunodeficiency virus strain PPR subsequent to passage through interleukin-2-independent T cells. J. Virol. 74: 1854-1863.

Mallett S, Fossum S, Barclay AN 1990. Characterization of the MRC OX40 antigen of activated CD4 positive T lymphocytes--a molecule related to nerve growth factor receptor. Embo J. 9: 1063-1068.

Martin J, LaBranche CC, Gonzalez-Scarano F 2001. Differential CD4/CCR5 utilization, gp120 conformation, and neutralization sensitivity between envelopes from a microglia-adapted human immunodeficiency virus type 1 and its parental isolate. J. Virol. 75: 3568-3580.

Palmer C, Balfe P, Fox D, May JC, Frederiksson R, Fenyo EM, McKeating JA 1996. Functional characterization of the V1V2 region of human immunodeficiency virus type 1. Virology 220: 436-449.

Paterson DJ, Jefferies WA, Green JR, Brandon MR, Corthesy P, Puklavec M, Williams AF 1987. Antigens of activated rat T lymphocytes including a molecule of 50,000 Mr detected only on CD4 positive T blasts. Mol. Immunol. 24: 1281-1290.
Pecoraro MR, Tomonaga K, Miyazawa T, Kawaguchi Y, Sugita S, Tohya Y, Kai C, Etcheverrigaray ME, Mikami T 1996. Genetic diversity of Argentine isolates of feline immunodeficiency virus. *J. Gen. Virol.* 77 (Pt 9): 2031-2035.

Pedersen NC, Ho EW, Brown ML, Yamamoto JK 1987. Isolation of a T-lymphotropic virus from domestic cats with an immunodeficiency-like syndrome. *Science* 235: 790-793.

Reggeti F, Ackerley C, Bienzle D 2008. CD134 and CXCR4 expression corresponds to feline immunodeficiency virus infection of lymphocytes, macrophages and dendritic cells. *J. Gen. Virol.* 89: 277-287.

Shimojima M, Miyazawa T, Ikeda Y, McMonagle EL, Haining H, Akashi H, Takeuchi Y, Hosie MJ, Willett BJ 2004. Use of CD134 as a primary receptor by the feline immunodeficiency virus. *Science* 303: 1192-1195.

Siebelink KH, Karlas JA, Rimmelzwaan GF, Osterhaus AD, Bosch ML 1995. A determinant of feline immunodeficiency virus involved in Crandell feline kidney cell tropism. *Vet. Immunol. Immunopathol.* 46: 61-69.

Sodora DL, Shpaer EG, Kitchell BE, Dow SW, Hoover EA, Mullins JI 1994. Identification of three feline immunodeficiency virus (FIV) env gene subtypes and comparison of the FIV and human immunodeficiency virus type 1 evolutionary patterns. *J. Virol.* 68: 2230-2238.

Vahlenkamp TW, Verschoor EJ, Schuurman NN, van Vliet AL, Horzinek MC, Egberink HF, de Ronde A 1997. A single amino acid substitution in the transmembrane envelope glycoprotein of feline immunodeficiency virus alters cellular tropism. *J. Virol.* 71: 7132-7135.

Verschoor EJ, Boven LA, Blaak H, van Vliet AL, Horzinek MC, de Ronde A 1995. A single mutation within the V3 envelope neutralization domain of feline immunodeficiency virus determines its tropism for CRFK cells. *J. Virol.* 69: 4752-4757.
Weaver EA, Collisson EW, Slater M, Zhu G 2004. Phylogenetic analyses of Texas isolates indicate an evolving subtype of the clade B feline immunodeficiency viruses. *J. Virol.* 78: 2158-2163.

Willett BJ, Hosie MJ 2008. Chemokine receptors and co-stimulatory molecules: unravelling feline immunodeficiency virus infection. *Vet. Immunol. Immunopathol.* 123: 56-64.

Willett BJ, McMonagle EL, Bonci F, Pistello M, Hosie MJ 2006a. Mapping the domains of CD134 as a functional receptor for feline immunodeficiency virus. *J. Virol.* 80: 7744-7747.

Willett BJ, McMonagle EL, Logan N, Samman A, Hosie MJ 2008. A single site for N-linked glycosylation in the envelope glycoprotein of feline immunodeficiency virus modulates the virus-receptor interaction. *Retrovirology* 5: 77.

Willett BJ, McMonagle EL, Ridha S, Hosie MJ 2006b. Differential utilization of CD134 as a functional receptor by diverse strains of feline immunodeficiency virus. *J. Virol.* 80: 3386-3394.

Willett BJ, Picard L, Hosie MJ, Turner JD, Adema K, Clapham PR 1997. Shared usage of the chemokine receptor CXCR4 by the feline and human immunodeficiency viruses. *J. Virol.* 71: 6407-6415.

Yamamoto JK, Hansen H, Ho EW, Morishita TY, Okuda T, Sawa TR, Nakamura RM, Pedersen NC 1989. Epidemiologic and clinical aspects of feline immunodeficiency virus infection in cats from the continental United States and Canada and possible mode of transmission. *J. Am. Vet. Med. Assoc.* 194: 213-220.