Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Comparative Immunology, Microbiology and Infectious Diseases 36 (2013) 549–557

Contents lists available at ScienceDirect

Comparative Immunology, Microbiology and Infectious Diseases

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

Review

Virus–host interaction in feline immunodeficiency virus (FIV) infection

Sueli Akemi Taniwaki [a], Andreza Soriano Figueiredo [b], João Pessoa Araujo Jr. [c,*]

[a] Department of Preventive Veterinary Medicine and Animal Health, School of Veterinary Medicine and Animal Science, University of São Paulo, São Paulo 05508-270, São Paulo, Brazil
[b] Laboratory of Viral Hepatitis, Oswaldo Cruz Institute (FIOCRUZ), Rio de Janeiro 21040-360, RJ, Brazil
[c] Department of Microbiology and Immunology, Biosciences Institute, Univ. Estadual Paulista (UNESP), Botucatu 18618-970, São Paulo, Brazil

ARTICLE INFO

Article history:
Received 22 February 2013
Received in revised form 28 June 2013
Accepted 2 July 2013

Keywords:
Feline immunodeficiency virus
Immunopathogenesis
Immune system dysfunction
Natural resistence
Cats

ABSTRACT

Feline immunodeficiency virus (FIV) infection has been the focus of several studies because this virus exhibits genetic and pathogenic characteristics that are similar to those of the human immunodeficiency virus (HIV). FIV causes acquired immunodeficiency syndrome (AIDS) in cats, nevertheless, a large fraction of infected cats remain asymptomatic throughout life despite of persistent chronic infection. This slow disease progression may be due to the presence of factors that are involved in the natural resistance to infection and the immune response that is mounted by the animals, as well as due to the adaptation of the virus to the host. Therefore, the study of virus–host interaction is essential to the understanding of the different patterns of disease course and the virus persistence in the host, and to help with the development of effective vaccines and perhaps the cure of FIV and HIV infections.

Contents

1. Introduction

The feline immunodeficiency virus (FIV) was initially isolated in 1986 from domestic cats that exhibited signs of immunodeficiency but were seronegative for the feline leukaemia virus (FeLV) [1]. FIV belongs to the family *Retroviridae*, the subfamily *Orthoretrovirinae*, and the genus

* Corresponding author at: Laboratório de Virologia e Diagnóstico Molecular, Departamento de Microbiologia e Imunologia, Instituto de Biociências, Universidade Estadual Paulista (UNESP), Campus de Botucatu, Distrito de Rubião Jr. s/n, Botucatu 18618-970, São Paulo, Brazil. Tel.: +55 1438800422.
E-mail addresses: staniwaki@bol.com.br (S.A. Taniwaki), andreza.figueiredo@ioc.fiocruz.br (A.S. Figueiredo), jpessoa@ibb.unesp.br, jp.cebola@gmail.com (J.P. Araujo Jr.).

0147-9571/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.cimid.2013.07.001

Lentivirus [2]. It exhibits a complex genomic organisation, which includes the structural genes *gag*, *pol*, and *env*, as well as several other genes that encode non-structural proteins. The 5′ and 3′ ends of the proviral DNA that is integrated into the host cell chromosomes comprise long terminal repeats (LTRs), which are repeated regions that contain information on the start and termination of transcription [3,4]. Because the genomic organisation and pathogenesis of FIV are similar to those of human immunodeficiency virus (HIV), FIV has been widely used as an experimental model in studies of immunopathogenesis and virus–host interactions and in the development of vaccines and antiretroviral therapies [4–8].

FIV is present worldwide and can be classified into five well-characterised subtypes (A–E) [9–13]. The prevalence of FIV varies from 1% to 44%, depending on the health status of the investigated cats [3,14–16]. The prevalence of FIV is influenced by the animals' behaviour. Free-ranging male cats in areas of high population density constitute the risk group mainly because of their greater exposure to bites, which are the main path of disease transmission, during territorial demarcation fights [3].

Infected cats do not exhibit specific clinical signs, and some animals can remain asymptomatic throughout life. FIV infection causes progressive immunosuppression that results in the development of the acquired immunodeficiency syndrome (AIDS) in cats, which, similar to human HIV infection, increases susceptibility to secondary and opportunistic infections. Concomitantly, FIV also causes immunostimulation, which results in immune-mediated diseases [17,18].

FIV infection is one of the most important infectious diseases in cats because it causes persistent infection. The aim of the present review is to discuss the virus–host interaction in FIV infection to better understand the immunopathogenesis of this disease, particularly the immune system dysfunction. In addition, the present review seeks to establish the presence of factors that are involved in the natural resistance to FIV infection, similar to those that have been discovered in HIV-exposed seronegative humans.

2. Immunopathogenesis of FIV infection

2.1. Pathogenesis and course of disease

Following infection, viral replication occurs in dendritic cells, macrophages, and $CD4^+$ T lymphocytes. A marked viraemia is usually detected in the second week post-infection (pi), with a peak between 8 and 12 weeks, when the virus spreads across the entire organism [3,4,18,19]. During this initial stage, or the acute phase, the animals may exhibit mild to moderate clinical signs, such as fever, transient generalised lymphadenopathy, anorexia, and lethargy [4,18,20]. *Gag*-specific cytotoxic T lymphocytes ($CD8^+$) may be detected as early as the second week pi, which is prior to seroconversion [21] Two to eight weeks after infection, specific antibodies against the surface (SU) and transmembrane (TM) proteins of *env* gene, and the capsid (CA) and matrix (MA) proteins of *gag* gene might be identified [4,18].

Despite the development of a cellular and humoral immune response, the animals are unable to eliminate the virus, which leads to the establishment of persistent FIV infection [4]. Nevertheless, the immune response reduces the circulating viral load, which defines the onset of the asymptomatic stage. The infected cats remain in this stage for many years, or even throughout life, with few clinical signs; however, progressive immunodeficiency with reduction in the number of $CD4^+$ T lymphocytes and an inversion of the $CD4^+/CD8^+$ ratio [3,18,19].

Finally, a proportion of FIV-positive cats reaches the second stage, or terminal phase, which correlates with the generalised lymphadenopathy, pre-AIDS, and AIDS stages of HIV infection [4,22]. This phase is characterised by severe immunosuppression and a consequent reduction in circulating antibodies, which allows the viral load increase and the development of disease s that are caused by opportunistic or secondary chronic infections, neoplasia, and neurological disorders [4,19]. Despite the progressive immunodeficiency, the course of the disease depends on the virus–host interaction, which explains why only a fraction of the animals develops the terminal phase.

2.2. Entry receptors and cell tropism

The cell tropism and the pathogenesis of the viral disease are determined by the specificity of the interaction between the viral surface proteins and the host cell receptors [4,23]. Similar to HIV infection, infection with FIV requires an initial interaction with a primary receptor and subsequent binding to a co-receptor [24]. In the case of HIV infection, the surface glycoprotein (gp120) interacts with the CD4 receptor expressed on the surface of $CD4^+$ T lymphocytes [25], which results in a conformational change in gp120 that exposes the co-receptor binding site, thereby allowing binding to the chemokine receptors CXCR4 or CCR5 [23,25]. The interaction between the co-receptor and gp120 induces a conformational change in the HIV transmembrane glycoprotein (gp41) that exposes its fusion peptide and thus allows the fusion of the viral envelope with the cell membrane [23,26]. This conformational change in the envelope proteins is an important mechanism for viral escape because the conserved regions of the surface protein, which are the target of neutralising antibodies, are not exposed prior to binding to the receptor and co-receptor [25].

In contrast to HIV, FIV uses CD134 instead of CD4 as its primary receptor. CD134, which is also known as OX40, is a member of the tumour necrosis factor and nerve growth factor receptor superfamily [24]. A large fraction of the FIV primary strains that have been isolated from infected animals, which are most likely the transmissible viruses, require initial binding to the CD134 receptor and subsequent binding to the CXCR4 chemokine receptor for productive infection [24,27]. However, some culture-adapted FIV strains do not use the CD134 receptor and are able to interact directly with the CXCR4 co-receptor [23]. The interaction between CD134 and the FIV surface protein gp95 leads to structural changes that expose the binding site of the CXCR4 co-receptor [28]. Binding to the CXCR4

co-receptor induces the exposure of a serpentine region of the FIV transmembrane protein (gp36) that binds to the cell membrane, thereby originating a hairpin structure that allows for viral fusion and entry [29]. These interactions also induce the exposure of the epitopes that are the target of neutralising antibodies [28]. Although the V3 region of gp95 is the principal immunodominant domain of FIV, the antibodies produced exhibit low neutralising activity. However, upon the binding of gp95 to soluble CD134, de Perseval et al. [28] observed that monoclonal antibodies against the surface protein inhibited FIV infections *in vitro*, which denotes a viral escape mechanism during infection.

In addition to a mechanism of viral protection against the host's immune response, the binding of the virus to cell surface receptors and co-receptors also accounts for the differentiated cell tropism that occurs throughout the course of the disease. In the case of HIV infection, binding *via* the CD4 receptor allows for entry into all $CD4^+$ T lymphocytes [24]. However, the main viral strains found during the early stages of infection are those that use the co-receptor CCR5, which is only expressed by activated memory T lymphocytes, whereas the strains isolated at later stages tend to use the CXCR4 co-receptor [30]. In the case of FIV infection, all of the viral strains tested to date interact with the CXCR4 co-receptor, which, in cats, is highly expressed in activated T cells, B cells, and monocytes [23,31]. Nevertheless, the need to interact with the primary receptor CD134, which is more abundantly expressed in activated $CD4^+$ T lymphocytes, constrains the initial infection and consequently results in a depletion of the $CD4^+$ T-cell subgroup that plays a vital role in the development of the antigen-specific cellular immune response [23,24].

Therefore, although these viruses use different entry receptors, the initial target of both FIV and HIV is the activated T lymphocytes [24]. However, with the progression of infection, the host's immune response exerts a positive selective pressure on the virus [32]. The high error rate of the reverse transcriptase enzyme, which is involved in retroviral replication, leads to mutations that result in the generation of a wide variety of different viral genomes within a single individual (quasispecies) and allows for a small changes of the surface proteins that alters their recognition by the immune system (antigenic drift) [33]. Kraase et al. [32] found a greater accumulation of mutations in the FIV *env* gene amongst cats diagnosed with late infection (322 weeks pi) compared with animals with acute infection (12 weeks pi). These mutations were mainly found in the glycosylated regions, which is an additional mechanism that is used by viruses to evade the immune system. In addition, a single mutation involving the loss of a glycosylation site (T271I, N269G, or N269D) might give rise to mutants that are less dependent on the receptor CD134 [32,34]. Similar to the culture-adapted FIV prototypes, the viral variants that bind directly to the co-receptor CXCR4 are likely more susceptible to neutralising antibodies [32]. Thus, the presence of these viruses in the circulation during the asymptomatic phase must be transient; however, when the animals reach the terminal phase, which is characterised by severe immunosuppression, the viruses begin to circulate again [32] and increase the number of infected cells, including $CD4^+$ and $CD8^+$ T lymphocytes, B lymphocytes, and astrocytes [3,23,35].

2.3. Immune system dysfunction

As mentioned above, a cellular and humoral antiviral immune response occurs during the acute phase of the infection, which reduces the viral load. However, the infection persists as a result of the viral evasion mechanisms (*e.g.*, glycosylation of the viral envelope proteins, camouflage of the immunodominant epitopes through structural changes of the envelope glycoproteins after binding to the host cell, and antigenic drift) and the immune dysfunction that occurs after infection. With the progression of the FIV infection, two opposing events occur that result in immune dysfunction: immunosuppression and hyperactivation of the immune system [7]. A summary of the events that promote the immune dysfunction are shown in Fig. 1.

2.3.1. Immunosuppression

The immunosuppression caused by FIV infection manifests as a loss of response to viral antigens, a loss of response to mitogens, and the inability to launch a primary immune response against secondary pathogens [7]. Torten et al. [36] observed that, together with the progression of the disease (25–44 months pi), the infected cats exhibited a reduction in their response to T-dependent immunogens but an adequate response to T-independent immunogens. In addition, these researchers observed a reduction in lymphocyte proliferation, which is induced by mitogens in the infected cats. An alteration in cytokine production, immune anergy, and apoptosis, and a hyperactivation of regulatory T cells are the mechanisms that might explain the immune system dysfunction.

Although several studies have quantified the cytokines in FIV-infected cats, the profile of cytokine alteration is not yet well established (Table 1). This cytokine alteration is likely related to the infection stage, especially in relation to the reduction of $CD4^+$ T lymphocytes and the inversion of the $CD4^+/CD8^+$ ratio, as well as the different methods that have been used for the quantification of the proteins or transcripts. Lawrence et al. [37] observed a significant increase in the production of interleukin-1 (IL-1), IL-6, and tumour necrosis factor alpha (TNFα) in peripheral blood mononuclear cells (PBMCs) in response to mitogens (concanavalin A (ConA) and pokeweed mitogen (PWM)) in FIV-positive cats with or without signs of immunosuppression. In addition, a significant reduction of IL-2 was observed in symptomatic animals, which also exhibited reduced lymphocyte proliferation in response to mitogens [37]. An increased bioactivity of TNFα and IL-6 was observed in alveolar macrophages before (four weeks pi) and after (10 weeks pi) the inversion of the $CD4^+/CD8^+$ ratio [38]. The same study also observed an increased expression of TNFα, IL-6, IL-10, and interferon-gamma (IFNγ). An increased expression of IFNγ and a reduced expression of IL-2 and IL-12 were observed in infected cats after the inversion of the $CD4^+/CD8^+$ ratio 24 weeks pi [39].

FIV-infected cats do not exhibit a primary immune response against a secondary infection by either

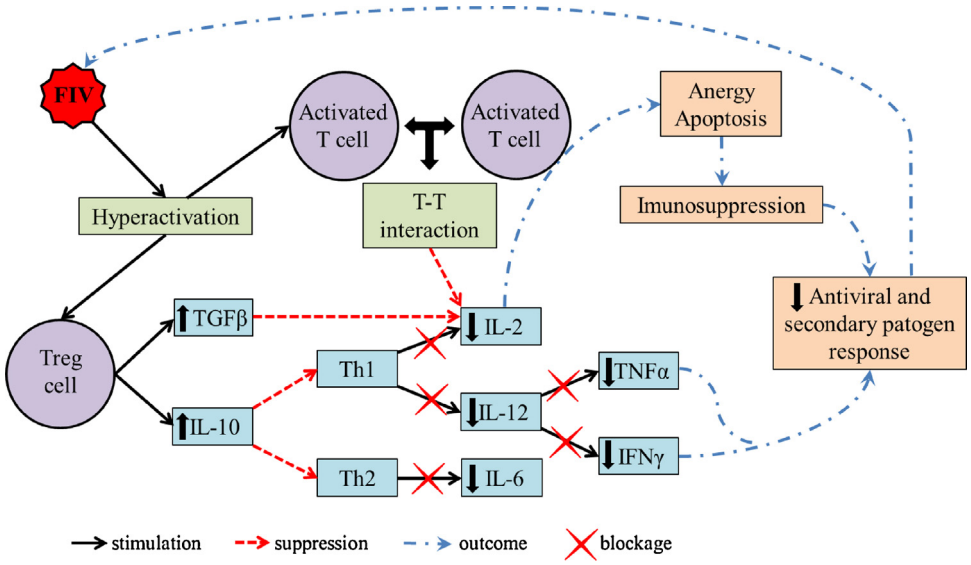

Fig. 1. Hyperactivation and immunosuppression in FIV infection. FIV infection causes hyperactivation of Treg cells, which suppress the production of IL-2, IL-12, IL-6, IFNγ and TNFα by increased production of IL-10 and TGFβ. Moreover, the T-T cell interaction induced by hyperactivation of T cells suppresses IL-2 production, which results in anergy and apoptosis. The consequent immunosuppression causes decrease in antiviral and secondary pathogen response. Finally, reduced antiviral response allows for FIV chronic antigenaemia and hyperactivation of immune system.

Toxoplasma gondii [39] or *Listeria monocytogenes* [40]. FIV- and *T. gondii*-co-infected animals exhibit increased expression of IL-10 before and after the infection by the secondary pathogen. The high production of IL-10 suppresses the production of Th1 (IL-2, IL-12, and IFNγ) and Th2 (IL-6) cytokines, which explains the inability to contain the infection by *T. gondii* [39]. Dean et al. [41] observed that FIV-positive cats, especially animals with chronic infections (after the inversion of the $CD4^+/CD8^+$ ratio), exhibited higher numbers of colony-forming units of *L. monocytogenes* in the lymph nodes. In addition, the innate immune response of these cats with chronic infection was unable to contain the secondary infection four days after inoculation, unlike animals with acute infection or FIV-negative cats [41]. This reduction in the response to infection by *L. monocytogenes* might be due to increased IL-10 expression, which inhibits the production of TNFα in macrophages [40]. In contrast to Levy et al. [39], Dean et al. [40] did not observe a reduction in the levels of IL-2 and IFNγ, most likely because the animals from the latter study did not exhibit an alteration of the $CD4^+/CD8^+$ ratio. Nevertheless, both studies observed an increase in the IL-10/IL-12 ratio, which explains the deficient response to the secondary pathogen because IL-12 stimulates IFNγ and TNFα production and IL-10 suppresses the production of IL-12 by dendritic cells [7,42]. Therefore, there is an important change in cytokine production that results in a deficient response to secondary pathogens.

Both FIV and HIV infections are associated with a progressive loss of T-cell function, which is caused by the suppression of IL-2 production, and an increased programmed cell death (apoptosis) of T cells in the lymph nodes [7]. Immune anergy is the functional inactivation of T or B lymphocytes following antigenic stimulation due to inadequate amounts of co-stimulatory molecules (*e.g.*, B7.1 and B7.2) in antigen-presenting cells or to the presence of inhibitory CTLA-4 (cytotoxic T lymphocyte-associated antigen 4) receptors [43]. The binding of B7 molecules to the CD28 receptor, which is expressed in T lymphocytes, stimulates the release of IL-2 and consequently the clonal expansion that is needed to mount an effective immune response, whereas the binding of B7 to the CTLA4 receptor suppresses the release of IL-2 and thus terminates the immune response [43]. In addition, antigen recognition induces the production of pro-apoptotic proteins, but the activity of these proteins is neutralised by anti-apoptotic proteins in the normal response to microorganisms [43].

Guiot et al. [44] observed that FIV-infected cats exhibited increased apoptosis that affected all lymphocyte types ($CD4^+$ and $CD8^+$ T lymphocytes, B lymphocytes, and

Table 1
Cytokines production and immune response of cats infected with FIV.

Increase	Decrease	Immune response	Reference
IL-1, IL-6, TNFα	IL-2	Decreased response to mitogen	Lawrence et al. [37]
IL-6, IL-10, TNFα, IFNγ			Ritchey et al. [38]
IL-10[a,b], IFNγ[a],	IL-2[a,b], IL-6[b], IL-12[a,b]	Decreased response to *T. gondi* infection	Levy et al. [39]
IL-10[b]	TNFα[b]	Decreased response to *L. monocytogenes* infection	Dean et al. [40]

[a] Before co-infection with secondary pathogen.
[b] After co-infection with secondary pathogen.

natural killer (NK) cells). This increased apoptosis was directly correlated with an increase in the animal's age and the duration of the infection and with a reduction in the numbers of $CD4^+$ T cells [44]. The increase in the apoptosis of $CD4^+$ and $CD8^+$ T cells in both the lymph nodes and the blood of FIV-positive cats might be related to an increase in the levels of $CD4^+$ and $CD8^+$ T cells with a $B7^+CTLA4^+$ phenotype [45]. An increase in $B7^+$ T cells was observed in animals with acute infection (<6 months), asymptomatic animals (1–5 years), and mainly animals with terminal infection (8–10 years) that exhibit a chronic secondary oral or respiratory infection and, in most cases, the presence of B-cell lymphoma at necropsy [45]. The chronic activation of T cells co-expressing B7 and CTLA-4 and the possibility of a T-T interaction mediated by the binding of B7.1/B7.2 to the CTLA-4 receptor induce a bidirectional suppression of IL-2 that results in anergy and apoptosis [7,45,46]. Therefore, this mechanism causes immunosuppression with a progressive loss of T cells and premature termination of the immune response against pathogens [45,46].

The regulatory T (Treg) cells are mostly $CD4^+$ cells that express high levels of CD25 (alpha chain of the IL-2 receptor), and their function is to regulate the activation of other T cells [43]. The Treg cells depend on the transcription factor Foxp3 and IL-2 to maintain their function and produce cytokines, such as IL-10 and tumour growth factor beta (TGFβ), that block the activation of lymphocytes and macrophages [43]. There are two different types of Treg cells: the thymus-generated natural Treg cells, which are related to the suppression of auto-immune T cells and the maintenance of tolerance to self-antigens, and the adaptive or induced Treg cells, which regulate the response of $CD4^+$ and $CD8^+$ T cells to pathogens (*e.g.*, bacteria, fungi, intracellular parasites, and viruses) and are activated in the peripheral lymphoid tissues [47–49]. The function of the induced Treg cells is to avoid the tissue damage that is caused by excessive inflammation in response to pathogens [49,50]. However, certain pathogens modulate the activity of these Treg cells and thus cause persistent chronic infection [48].

Mexas et al. [49] showed that Treg cells ($CD4^+CD25^+$) are the target of acute FIV infection since these cells exhibit high viral mRNA levels two weeks after infection, which correlates with the peak of viraemia. The establishment of persistent chronic infection may be related to the infection of $CD4^+CD25^+$ cells because these cells are activated during acute infection in the presence of the Foxp3 transcription factor and TGFβ and suppress the production of IL-2, thus inhibiting the antiviral response of the helper T cells [48]. In cats, the $CD4^+CD25^+$ cells are unable to proliferate in response to antigenic or mitotic stimulation due to the lack of IL-2 production, and exhibit the ability to suppress the proliferation of the $CD4^+CD25^-$ cells when activated [51]. In addition, during the disease progression, Treg cells act as a reservoir of infection, where the virus might replicate at low rates without becoming a target of the immune response because these cells exhibit anergic characteristics [49]. Although cats with chronic FIV infection exhibit the same proportion of $CD4^+CD25^+$ cells as FIV-negative animals, the $CD4^+CD25^+$ cells of FIV-positive cats exhibit a greater expression of B7.1 and B7.2 molecules in both the lymph nodes and the blood, as well as a greater CTLA-4 expression in the lymph nodes [51]. The expression of these molecules explain the immunosuppression mechanism associated with the Treg cells ($CD4^+CD25^+B7^+CTLA4^+$) that are activated by FIV during the progression of the disease.

2.3.2. Hyperactivation of the immune system

In addition to progressive immunosuppression, FIV-positive cats also exhibit marked hyperactivation of B and T cells [7]. The total protein levels are increased in FIV-infected cats due to an increase in the gamma globulins [52]. In one study, two FIV-positive cats with B-cell lymphoma exhibited an increase in B lymphocytes, increased IgG (from the beginning to the end of the follow-up period, which corresponded to 50–300 weeks pi), and a progressive increase in IgA [53]. Takano et al. [54] also observed higher globulin levels in FIV-positive cats at the terminal phase compared with animals in the asymptomatic phase or those that were FIV-negative. An increase in the levels of B cells with surface immunoglobulins (sIg^+) and negative for CD21, which represent cells that are differentiated for antibody production, was observed in the asymptomatic cats and more evident in animals in the terminal phase, which suggests that this finding might be related to the emergence of immunosuppression signs [54]. The activation of B lymphocytes corresponds to a polyclonal and non-virus-specific activation because antibodies against heterologous non-viral antigens were detected six to eight weeks after infection, remained until the end of the study (90 weeks pi), and did not exhibit cross-reactivity with FIV viral recombinant antigens [55]. Furthermore, neither the stimulation of B lymphocytes nor hypergammaglobulinemia were caused by co-infection with other pathogens because the study used specific pathogen free (SPF) animals that were experimentally infected with FIV [55]. Therefore, the hyperactivation caused by FIV is responsible for the appearance of immune-mediated diseases, such as chronic gingivitis-stomatitis and glomerulonephritis, myeloproliferative neoplasms, and lymphomas [18].

The stimulation of $CD4^+$ and $CD8^+$ T cells starts during the acute phase of FIV infection and continues throughout the disease progression [7]. The increase in the number of activated $CD8^+$ T cells ($CD8\beta^{low}CD62L^-$) suggests that the naïve $CD8^+$ T cells are replaced by the activated $CD8^+$ T cells during FIV infection. The same phenomenon occurs with the $CD4^+$ T cells, which reduce the expression of CD62L during the course of infection (reviewed in [7]). In addition, and as mentioned above, the increased expression of B7 molecules and CTLA-4 by activated $CD4^+$ and $CD8^+$ T cells might alter the host's immune response [45]. Tompkins and Tompkins [7] suggested that FIV infection activates $CD4^+$, $CD8^+$ and Treg ($CD4^+CD25^+$) T cells. The activation of Treg cells inhibits the production of IL-2 and IFNγ through the production of TGFβ and thus reduces the immune response against FIV through the induction of anergy and apoptosis, which allows for continuous viral replication and chronic antigenaemia. In turn, chronic antigenaemia causes hyperactivation of the $CD4^+$/$CD8^+$ T cells and Treg cells, which results in anergy and apoptosis due to the activity of the Treg cells and an inappropriate T-T

cell interaction due to the binding of B7/CTLA-4, which are expressed in larger amounts in activated T cells [7]. This uncontrolled hyperactivation of immune system causes progressive immunosuppression and a reduction in the immune response to secondary infections.

3. Factors of natural resistance to lentivirus infection

Major efforts have been devoted in recent years to the discovery of novel alternatives to the treatment, and perhaps even cure, of HIV infection. For that purpose, many studies seek to understand the factors that are involved in the natural resistance to HIV-1 infection that occurs in some individuals who, despite a history of frequent (sexual, parenteral, or vertical) exposure to the virus, do not exhibit any serologic evidence of infection or any sign of immunodeficiency [56]. These high-risk exposed but seronegative (ESN) individuals seem to have genetic and immunological factors that reduce their susceptibility to infection, although a single factor individually may not account for this characteristic [57].

Amongst the genetic factors involved in the slow progression of AIDS and resistance to HIV infection, the following have been identified: alleles of human leucocyte antigen (HLA), the presence of activators or the absence of inhibitors of the genes encoding KIR (killer immunoglobulin-like receptor) molecules, a genetic polymorphism of the chemokines RANTES (regulated on activation normal T-cell expressed and secreted), macrophage inflammatory protein (MIP)-1α, and MIP-1β and their receptors [56,57]. Amongst these alterations, the deletion of 32 base pairs of the gene encoding the CCR5 receptor (CCR5Δ32) is strongly correlated with resistance to HIV infection [58]. Dean et al. [59] observed that approximately 10% of the studied population ($n > 600$), which included healthy controls, ESN individuals, and HIV-positive individuals with and without signs of AIDS, had the CCR5Δ32 allele. This mutation causes a change in the reading frame of amino acid 185 that generates a non-functional protein with a premature termination codon [58,59]. Individuals who are homozygous for the CCR5Δ32 allele are strongly protected against HIV infection because these individuals lack a functional CCR5 co-receptor on their cell surface [59,60]. All of the CCR5Δ32/Δ32 homozygous individuals were ESN individuals, whereas none amongst the 1343 HIV-positive individuals exhibited this genotype [59]. In addition, $CCR5^{+}/\Delta32$ heterozygous individuals exhibited some degree of resistance to infection; and when infected, their viral load is lower, and their progression of AIDS is slower compared with that observed in $CCR5^{+}/^{+}$ homozygous individuals [59]. There is still no evidence of any mutations in the FIV receptors that confer a natural resistance to infection in cats. Currently, the following are known: the *in vitro* infectivity of FIV decreases in a large fraction of strains with the use of a feline/human hybrid CD134 receptor, the human CD134 receptor is not functional for FIV entry [61], and mutations in the human CXCR4 co-receptor (D187A) prevent the *in vitro* entry of FIV [62].

Nevertheless, although a deletion in the CCR5 co-receptor gene grants a high natural resistance to HIV infection, this mutation is not found in all ESN individuals. Therefore, other factors might also be involved. The host's innate immunity contributes to the protection against HIV infection mainly through the activity of NK cells and a large production of IFNγ. In addition, an increased production of β-chemokines (*e.g.*, CC chemokine ligand (CCL)2, CCL3 (MIP-1α), CCL4 (MIP-1β), CCL5 (RANTES), and CCL11), α-chemokines (stromal cell-derived factor-1 (SDF-1)), peroxiredoxin II, $CD8^{+}$ cell antiviral factor (CAF), NK cell stimulatory factor B, IL-22 (cytokine involved in the production of acute-phase proteins), defensins, and ribonucleases have been associated with protective effects [revised in 56,57]. The innate immune response mediated by cellular restriction factors, such as APOBEC3 (apolipoprotein B mRNA-editing catalytic polypeptide 3), Trim5α (tripartite motif protein), and tetherin, inhibits the viral replication of retroviruses and thus blocks the establishment of infection after the virus has entered the host cell [57,58].

APOBEC3 deaminates cytidine residues in RNA and single-stranded DNA, thereby converting cytosine (C) into uracil (U) or thymine (T), which alters the encoding of the viral proteins [8,63]. According to recent observations in humans, exposure to HIV increases the expression of APOBEC3G, and ESN individuals exhibit a higher expression of this protein compared with non-exposed individuals. In addition, APOBEC3G reduces the susceptibility to HIV infection *in vitro* [56–58]. In cats, the action of APOBEC3G was investigated with three exogenous feline retroviruses: FIV, FeLV, and feline syncytium-forming virus (FeSFV), which is different from the first two viruses because it is considered non-pathogenic in nature [8]. FeLV exhibited reduced infectivity *in vitro* when APOBEC3 proteins were present, which might explain the occurrence of abortive and regressive infection in some of the cats that had contact with the virus [8,64]. FeLV belongs to the genus *Gammaretrovirus* and does not have the accessory genes *vif* and *bet*, which are found in species that belong to the genera *Lentivirus* and *Spumavirus*, respectively [33], and are associated with the inactivation of APOBEC3 [65]. An exception is the equine infectious anaemia virus (EIAV), which is the only lentivirus that lacks the *vif* gene, but it exhibits resistance to feline APOBEC3 [8]. Several studies have shown that retroviruses are inhibited by the action of APOBEC3 in non-susceptible species, which explains the host specificity and enables its therapeutic use [63]. Although APOBEC3 exhibits an antiviral effect, viruses have mechanisms that prevent the action of this protein in the natural host, and cause a persistent infection. The same is true with tetherins, which exert an antiviral action by preventing the release of viral particles. Dietrich et al. [66] showed that the release of FIV and HIV-1 particles was inhibited by the transient expression of the feline tetherin. However, FIV replication did not decrease when the expression of tetherin was stable, which probably occurs in natural infection. Furthermore, the cell-to-cell spread of the virus is facilitated by the increase in syncytium formation [66,67]. According to some studies, the feline Trim5α is truncated and does not exhibit any antiretroviral effect [66,67]. Therefore, further investigation of restriction factors, especially their importance in the prevention

and treatment of infection, is warranted because orthologous restriction factors were shown to inhibit infection by retroviruses.

Although acquired immunity, both cellular and humoral, plays a crucial role in the resistance to HIV infection, there is not yet a consensus as to which mechanisms are truly protective. With regard to the cellular immune response in ESN individuals, some reports indicate a strong anti-HIV response by non-cytotoxic $CD8^+$ T cells, the recognition of a different epitope compared with seropositive individuals, and a greater Th1 response that is characterised by an increased production of IL-2 and IFNγ and a reduced IL-10 production [56,57]. Nevertheless, a low lymphocyte activation was also shown to reduce the susceptibility to HIV infection because lymphocyte activation is needed for viral replication and is associated with the pathogenesis of the disease [7,56]. The resistance to infection might be related to the humoral immune response mainly through the production of anti-HIV immunoglobulin A (IgA), which is present in cervicovaginal secretions, saliva, colostrum, and serum, and by the presence of autoantibodies against the CD4 receptor in ESN individuals [56,57]. In cats, anti-CD134 antibodies were observed in 63% (143/226) of FIV-positive animals, whereas these antibodies were not present in any of the SPF animals ($n = 107$) and only in 0.44% (1/225) of the diseased cats, some of which were infected by feline herpesvirus (FHV), feline coronavirus (FCoV), or FeLV but were FIV-negative [68]. In addition, the cats with anti-CD134 antibodies exhibited a lower viral load and a better state of health, which indicates the importance of these antibodies in the progression of disease [68].

4. Conclusions

The ability of animals to develop an immune response that is sufficiently robust to reduce FIV viral load, although unable to extinguish the FIV infection, may reflect an important factor for reducing the speed of disease progression. However, this factor might also increase the selective pressure and induce the accumulation of a greater number of mutations throughout the course of the infection because the virus has a greater need to adapt to survive in the host. In addition, the early reduction in the number of $CD4^+$ T lymphocytes and the consequent decrease in the $CD4^+/CD8^+$ ratio, which correlates with the emergence of immunosuppression signs, might be related to the presence of virus with mutations that favour its escape or occurs in cats unable to develop a response that restricts viral replication.

Few studies have examined the presence of factors that are involved in the natural resistance to FIV infection in cats. The identification of these factors may contribute to a better understanding of the various patterns of disease progression and help with the development of a FIV/HIV cure. The complexity of the virus–host interaction, particularly the mechanisms of viral persistence, justifies the difficulty in the development of effective vaccines and treatments. Therefore, much of this interaction must still be investigated before a full understanding of FIV infection in cats and HIV infection in humans.

Acknowledgment

This work was supported by the São Paulo Research Foundation (FAPESP) grant 2009/52979-5.

References

[1] Pedersen NC, Ho EW, Brown ML, Yamamoto JK. Isolation of a T-lymphotropic virus from domestic cats with an immunodeficiency-like syndrome. Science 1987;235:790–3.
[2] ICTVdB Management. 00.061.1.06. Lentivirus. In: ICTVdB – The Universal Virus Database, version 4; 2006. http://www.ncbi.nlm.nih.gov/ICTVdb/ICTVdB/
[3] Hartmann K. Feline immunodeficiency virus infection: an overview. Veterinary Journal 1998;155(2):123–37.
[4] Lecollinet S, Richardson J. Vaccination against the feline immunodeficiency virus: the road not taken. Comparative Immunology, Microbiology & Infectious Diseases 2008;31:167–90.
[5] Talbott RL, Sparger EE, Lovelace KM, Fitch WM, Pedersen NC, Luciw PA, et al. Nucleotide sequence and genomic organization of feline immunodeficiency virus. Proceedings of the National Academy of Sciences of the United States of America 1989;86:5743–7.
[6] Burkhard MJ, Dean GA. Transmission and immunopathogenesis of FIV in cats as a model for HIV. Current HIV Research 2003;1(1):15–29.
[7] Tompkins MB, Tompkins WA. Lentivirus-induced immune dysregulation. Veterinary Immunology and Immunopathology 2008;123:45–55.
[8] Münk C, Hechler T, Chareza S, Löchelt M. Restriction of feline retroviruses: lessons from cat APOBEC3 cytidine deaminases and TRIM5alpha proteins. Veterinary Immunology and Immunopathology 2010;34:14–24.
[9] Kakinuma S, Motokawa K, Hohdatsu T, Yamamoto JK, Koyama H, Hashimoto H. Nucleotide sequence of feline immunodeficiency virus: classification of Japanese isolates into two subtypes which are distinct from non-Japanese subtypes. Journal of Virology 1995;69(6):3639–46.
[10] Hohdatsu T, Hirabayashi H, Motokawa K, Koyama H. Comparative study of the cell tropism of feline immunodeficiency virus isolates of subtype A, B and D classified on the basis of the *env* gene V3–V5 sequence. Journal of General Virology 1996;77:93–100.
[11] Pecoraro MR, Tomonaga K, Miyazawa T, Kawaguchi Y, Sugita S, Tohya Y, et al. Genetic diversity of Argentine isolates of feline immunodeficiency virus. Journal of General Virology 1996;77:2031–5.
[12] Duarte A, Marques MI, Tavares L, Fevereiro M. Phylogenetic analysis of five Portuguese strains of FIV. Archives of Virology 2002;147(5):1061–70.
[13] Nakamura K, Suzuki Y, Ikeo K, Ikeda Y, Sato E, Nguyen NT, et al. Phylogenetic analysis of Vietnamese isolates of feline immunodeficiency virus: genetic diversity of subtype C. Archives of Virology 2003;148(4):789–91.
[14] Lara VM, Taniwaki SA, Araújo Jr JP. Occurrence of feline immunodeficiency virus infection in cats. Ciência Rural 2008;38(8):2245–9.
[15] Levy JK, Scott HM, Lachtara JL, Crawford PC. Seroprevalence of feline leukemia virus and feline immunodeficiency virus infection among cats in North America and risk factors for seropositivity. Journal of the American Veterinary Medical Association 2006;228(3):371–6.
[16] Hartmann K, Griessmayr P, Schulz B, Green CE, Vidyashankar AN, Jarrett O, et al. Quality of different in-clinic test systems for feline immunodeficiency virus and feline leukemia virus infection. Journal of Feline Medicine and Surgery 2007;9(6):439–45.
[17] Dunham SP, Graham E. Retroviral infections of small animals. Veterinary Clinics of North America Small Animal Practice 2008;38:879–901.
[18] Hosie MJ, Addie D, Belák S, Boucraut-Baralon C, Egberink H, Frymus T, et al. Feline immunodeficiency, ABCD guidelines on prevention and management. Journal of Feline Medicine and Surgery 2009;11(7):575–84.
[19] Dunham SP. Lessons from the cat: development of vaccines against lentiviruses. Veterinary Immunology and Immunopathology 2006;112:67–77.
[20] Callanan JJ, Thompson H, Toth SR, O'neil B, Lawrence CE, Willett B, et al. Clinical and pathological findings in feline

immunodeficiency virus experimental infection. Veterinary Immunology and Immunopathology 1992;35:3–13.
[21] Beatty JA, Willett BJ, Gault EA, Jarrett O. A longitudinal study of feline immunodeficiency virus-specific cytotoxic T lymphocytes in experimentally infected cats, using antigen-specific induction. Journal of Virology 1996;70(9):6199–206.
[22] Hosie MJ, Beatty JA. Vaccine protection against feline immunodeficiency virus: setting the challenge. Australian Veterinary Journal 2007;85:5–12.
[23] Willett BJ, Hosie MJ. Chemokine receptors and co-stimulatory molecules: unravelling feline immunodeficiency virus infection. Veterinary Immunology and Immunopathology 2008;123:56–64.
[24] Shimojima M, Miyazawa T, Ikeda Y, Mcmonagle EL, Haining H, Akashi H, et al. Use of CD134 as a primary receptor by the feline immunodeficiency virus. Science 2004;303:1192–5.
[25] Kwong PD, Wyatt R, Robinson J, Sweet RW, Sodroski J, Hendrickson WA. Structure of an HIV gp120 envelope glycoprotein in complex with the CD4 receptor and a neutralizing human antibody. Nature 1998;393:648–59.
[26] Doms RW, Moore JP. HIV-1 membrane fusion: targets of opportunity. Journal of Cell Biology 2000;151(2):F9–14.
[27] De Parseval A, Chatterji U, Sun P, Elder JH. Feline immunodeficiency virus targets activated CD4+ T cells by using CD134 as a binding receptor. Proceedings of the National Academy of Sciences of the United States of America 2004;101:13044–9.
[28] de Parseval A, Grant CK, Sastry KJ, Elder JH. Sequential CD134-CXCR4 interactions in feline immunodeficiency virus (FIV): soluble CD134 activates FIV Env for CXCR4-dependent entry and reveals a cryptic neutralization epitope. Journal of Virology 2006;80(6):3088–91.
[29] Garg H, Fuller FJ, Tompkins WA. Mechanism of feline immunodeficiency virus envelope glycoprotein-mediated fusion. Virology 2004;321(2):274–86.
[30] Bleul CC, Wu L, Hoxie JA, Springer TA, Mackay CR. The HIV coreceptors CXCR4 and CCR5 are differentially expressed and regulated on human T lymphocytes. Proceedings of the National Academy of Sciences of the United States of America 1997;94:1925–30.
[31] Willett BJ, Cannon CA, Hosie MJ. Expression of CXCR4 on feline peripheral blood mononuclear cells: effect of feline immunodeficiency virus infection. Journal of Virology 2003;77(1):709–12.
[32] Kraase M, Sloan R, Klein D, Logan N, Mcmonagle L, Biek R, et al. Feline immunodeficiency virus env gene evolution in experimentally infected cats. Veterinary Immunology and Immunopathology 2010;134:96–106.
[33] Flores EF. Virologia veterinária. 1st ed. Santa Maria: Editora da UFSM; 2007.
[34] Willett BJ, Mcmonagle EL, Logan N, Samman A, Hosie MJ. A single site for N-linked glycosylation in the envelope glycoprotein of feline immunodeficiency virus modulates the virus-receptor interaction. Retrovirology 2008;5(77), http://dx.doi.org/10.1186/1742-4690-5-77.
[35] Ishikawa M, Baba K, Shimojima M, Okada M, Shojima T, Miura T, et al. Adaptation of feline immunodeficiency virus subtype B strain TM2 to a feline astrocyte cell line (G355-5 cells). Veterinary Microbiology 2011;149:307–15.
[36] Torten M, Franchini M, Barlough JE, George JW, Mozes E, Lutz H, et al. Progressive immune dysfunction in cats experimentally infected with feline immunodeficiency virus. Journal of Virology 1991;65:2225–30.
[37] Lawrence CE, Callanan JJ, Willett BJ, Jarrett O. Cytokine production by cats infected with feline immunodeficiency virus: a longitudinal study. Immunology 1995;85:568–74.
[38] Ritchey JW, Levy JK, Bliss SK, Tompkins WA, Tompkins MB. Constitutive expression of types 1 and 2 cytokines by alveolar macrophages from feline immunodeficiency virus-infected cats. Veterinary Immunology and Immunopathology 2001;79:83–100.
[39] Levy JK, Liang Y, Ritchey JW, Davidson MG, Tompkins WA, Tompkins MB. Failure of FIV-infected cats to control *Toxoplasma gondii* correlates with reduced IL2, IL6, and IL12 and elevated IL10 expression by lymph node T cells. Veterinary Immunology and Immunopathology 2004;98:101–11.
[40] Dean GA, Bernales JA, Pedersen NC. Effect of feline immunodeficiency virus on cytokine response to *Listeria monocytogenes* in vivo. Veterinary Immunology and Immunopathology 1998;65:125–38.
[41] Dean GA, Lavoy A, Yearley J, Stanton C. Cytokine modulation of the innate immune response in feline immunodeficiency virus-infected cats. Journal of Infectious Diseases 2006;193:1520–7.
[42] Roy S, Lavine J, Chiaromonte F, Terwee J, Vandewoude S, Bjornstad O, et al. Multivariate statistical analyses demonstrate unique host immune responses to single and dual lentiviral infection. PLoS ONE 2009;4(10):e7359, http://dx.doi.org/10.1371/journal.pone.0007359.
[43] Abbas AK, Lichtman AH. Imunologia básica: funções e distúrbios do sistema imunológico. 3rd ed. Elsevier: Rio de Janeiro; 2009.
[44] Guiot AL, Rigal D, Chappuis G. Spontaneous programmed cell death (PCD) process of lymphocytes of FIV-infected cats: cellular targets and modulation. Veterinary Immunology and Immunopathology 1997;58(2):96–106.
[45] Tompkins MB, Bull ME, Dow JL, Ball JM, Collisson EW, Winslow BJ, et al. Feline immunodeficiency virus infection is characterized by B7+CTLA4+T cell apoptosis. Journal of Infectious Diseases 2002;185(8):1077–93.
[46] Vahlenkamp TW, Bull ME, Dow JL, Collisson EW, Winslow BJ, Phadke AP, et al. B7+C.T.L.A4+T cells engage in T-T cell interactions that mediate apoptosis: a model for lentivirus-induced T cell depletion. Veterinary Immunology and Immunopathology 2004;98:203–14.
[47] Bluestone JA, Abbas AK. Natural versus adaptive regulatory T cells. Nature Reviews Immunology 2003;3:253–7.
[48] Vahlenkamp TW, Tompkins MB, Tompkins WAF. The role of CD4+CD25+ regulatory T cells in viral infections. Veterinary Immunology and Immunopathology 2005;108:219–25.
[49] Mexas AM, Fogle JE, Tompkins WA, Tompkins MB. CD4+CD25+ regulatory T cells are infected and activated during acute FIV infection. Veterinary Immunology and Immunopathology 2008;126:263–72.
[50] Rouse BT, Suvas S. Regulatory cells and infectious agents: détentes cordiale and contraire. Journal of Immunology 2012;173(4):2211–5.
[51] Vahlenkamp TW, Tompkins MB, Tompkins WAF. Feline immunodeficiency virus infection phenotypically and functionally activates immunosuppressive CD4+CD25+T regulatory cells. Journal of Immunology 2004;172:4752–61.
[52] Gleich S, Hartmann K. Hematology and serum biochemistry of feline immunodeficiency virus-infected and feline leukemia virus-infected cats. Journal of Veterinary Internal Medicine 2009;23(3):552–8.
[53] Beatty JA, Lawrence CE, Callanan JJ, Grant CK, Gault EA, Neil JC, et al. Feline immunodeficiency virus (FIV)-associated lymphoma: a potential role for immune dysfunction in tumourigenesis. Veterinary Immunology and Immunopathology 1998;65:309–22.
[54] Takano T, Hosoya S, Shibao A, Nagasaki B, Yoshioka H, Satoh R, et al. Comparative study of the plasma globulin level, CD21(−) B-cell counts and FOXP3 mRNA expression level in CD4(+) T-cells for different clinical stages of feline immunodeficiency virus infected cats. Research in Veterinary Science 2012;92:157–61.
[55] Flynn JN, Cannon CA, Lawrence CE, Polyclonal Jarrett O. B-cell activation in cats infected with feline immunodeficiency virus. Immunology 1994;81:626–30.
[56] Taborda-Vanegas N, Zapata W, Rugele, Genetic MT. Immunological factors involved in natural resistance to HIV-1 infection. Open Virology Journal 2011;5:35–43.
[57] Restrepo C, Rallón NI, Carrillo J, Soriano V, Blanco J, Benito JM. Host factors involved in low susceptibility to HIV infection. AIDS Reviews 2011;13(1):30–40.
[58] Lederman MM, Alter G, Daskalakis DC, Rodriguez B, Sieg SF, Hardy G, et al. Determinants of protection among righ risk HIV seronegative persons: an overview. Journal of Infectious Diseases 2010;202(3):S333–8.
[59] Dean M, Carrington M, Winkler C, Huttley GA, Smith MW, Allikmets R, et al. Genetic restriction of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene, Hemophilia Growth and Development Study, Multicenter AIDS Cohort Study, Multicenter Hemophilia Cohort Study, San Francisco City Cohort, ALIVE Study. Science 1996;273(5283):1856–62.
[60] Galvani AP, Novembre J. The evolutionary history of the CCR5-Delta32 HIV-resistance mutation. Microbes and Infection 2005;7(2):302–9.
[61] Willett BJ, Mcmonagle EL, Bonci F, Pistello M, Hosie MJ. Mapping the domains of CD134 as a functional receptor for feline immunodeficiency virus. Journal of Virology 2006;80(15):7744–7.
[62] Brelot A, Heveker N, Adema K, Hosie MJ, Willett B, Alizon M. Effect of mutations in the second extracellular loop of CXCR4 on its utilization by human and feline immunodeficiency viruses. Journal of Virology 1999;73(4):576–2586.
[63] Vandewoude S, Troyer J, Poss M. Restrictions to cross-species transmission of lentiviral infection gleaned from studies of FIV. Veterinary Immunology and Immunopathology 2010;134:25–32.
[64] Münk C, Beck T, Zielonka J, Hotz-Wagenblatt A, Chareza S, Battenberg M, et al. Functions, structure, and read-through alternative

splicing of feline APOBEC3 genes. Genome Biology 2008;9(3). R48.1–R48.20.
[65] Chareza S, Slavkovic Lukic D, Liu Y, Räthe AM, Münk C, Zabogli E, et al. Molecular and functional interactions of cat APOBEC3 and feline foamy and immunodeficiency virus proteins: different ways to counteract host-encoded restriction. Virology 2012;424:138–46.
[66] Dietrich I, McMonagle EL, Petit SJ, Vijayakrishnan S, Logan N, Chan CN, et al. Feline tetherin efficiently restricts release of feline immunodeficiency virus but not spreading of infection. Journal of Virology 2011;85(12):5840–52.
[67] Zielonka J, Münk C. Cellular restriction factors of feline immunodeficiency virus. Viruses 2011;3(10):1986–2005.
[68] Grant CK, Fink EA, Sundstrom M, Torbett BE, Elder JH. Improved health and survival of FIV-infected cats is associated with the presence of autoantibodies to the primary receptor, CD134. Proceedings of the National Academy of Sciences of the United States of America 2009;106:19980–5.