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Lentivirus-induced Immune Dysregulation

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Abstract

FIV/HIV infections are associated with an early robust humoral and cellular anti-viral immune response followed by a progressive immune suppression that eventually results in AIDS. Several mechanisms responsible for this immune dysfunction have been proposed including cytokine dysregulation, immunologic anergy and apoptosis, and inappropriate activation of immune regulatory cells. Studies on FIV infection provide evidence for all three. Cytokine alterations include decreases in IL2 and IL12 production and increases in IFN γ and IL10 in FIV⁺ cats compared to normal cats. The elevated IL10:IL12 ratio is associated with the inability of FIV⁺ cats to mount a successful immune response to secondary pathogens. Additionally, chronic antigenic (FIV) stimulation results in an increase in the percent of activated T cells expressing B7 and CTLA4 co-stimulatory molecules in infected cats. The expression of these molecules is associated with T cells that are undergoing apoptosis in the lymph nodes. As ligation of CTLA4 by B7 transduces a signal for induction of anergy, one can speculate that the activated T cells are capable of T cell-T cell interactions resulting in anergy and apoptosis. The inability of CD4⁺ cells from FIV⁺ cats to produce IL2 in response to recall antigens and the gradual loss of CD4⁺ cell numbers could be due to B7-CTLA4 interactions. The chronic antigenemia may also lead to activation of CD4⁺CD25⁺ T regulatory cells. Treg cells from FIV⁺ cats are chronically activated and inhibit the mitogen-induced proliferative response of CD4⁺CD25⁻ by down-regulating IL2 production. Although Treg cell activation can be antigen specific, the suppressor function is not, and thus activated Treg cells would suppress responses to secondary pathogens as well as to FIV. Concomitant with the well known virus-induced immune suppression is a progressive immune hyper-activation. Evidence for immune hyper-activation includes polyclonal B cell responses, gradual replacement of naïve CD4⁺ and CD8⁺ T cell phenotypes with activation phenotypes (CD62L⁻, B7⁺, CTLA4⁺), and the chronic activation of CD4⁺CD25⁺ Treg cells. Thus lentivirus infections lead to severe immune dysregulation manifested as both chronic immune suppression and chronic immune activation. FIV infection of cats provides a number of advantages over other lentivirus infections as a model to study this immune dysregulation. It is a natural infection that has existed in balance with the cat's immune system for thousands of years. As such, the natural history and pathogenesis provides an excellent model to study the long term relationships between AIDS lentivirus and host immune system function/dysregulation.

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Keywords

FIV; AIDS; Immune suppression; Immune regulation

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1. Introduction

During the last two decades, Feline Immunodeficiency Virus (FIV) infection in the domestic cat has become an excellent comparative model for studying many aspects of HIV infection, and in particular the immunopathogenesis of the disease. As their names imply, these infections are associated with progressive immune suppression eventually leading to the development of AIDS. However, after 20 years of research, the interactions of the viruses with their respective host immune systems are not fully understood. Indeed, infections with these lentiviruses result in an immunologic paradox. There is an early, acute phase anti-virus immune response that is not sustained, followed by the well documented progressive immune suppression. However, along with this immune suppression is evidence for global immune hyper-activation. This paper will review the studies documenting the immunopathogenesis of FIV over the last 20 years and present proposed mechanisms for the immune dysregulation that occurs with lentivirus infections.

2. Anti-virus immune responses

2.1 Humoral Immune Response

In experimental infections, antibody to FIV antigens can be detected by ELISA or Western blot as early as 2–4 weeks post infection (p.i.) (Egberink et al., 1992; English et al., 1994; Yamamoto et al., 1988). Most of these Abs are directed to Gag and Env and persist throughout the course of the infection (Yamamoto et al., 1988; Egberink et al., 1992; English et al., 1994). Neutralizing Abs, directed to the V3 region of the envelope have been documented in both naturally and experimentally infected cats (Lombardi et al., 1993; Tozzini et al., 1993). The role of these Abs in controlling virus infection is controversial in that most studies utilize the feline fibroblast cell line CRFK as targets for infection. Sera exhibiting high titers of neutralizing activity on CRFK cells had a much lower neutralizing titer when assayed on feline lymphocytes (Siebelink et al., 1993; Tozzini et al., 1993). Additionally, it appears that the presence of neutralizing antibodies does not correlate with virus clearance or disease progression, as virus titers are similar in symptomatic and asymptomatic cats (Yamamoto et al., 1991; Tozzini et al., 1993). However, cats without detectable neutralizing Ab have been reported to progress more rapidly to AIDS-like disease than those with titers, and, interestingly, passively transferred sera from vaccinated cats or from FIV-infected cats protected cats challenged with FIV (Hohdatsu et al., 1993).

2.2 Cell-mediated Immune Response

FIV infection results in an increase in circulating CD8⁺ T cells that occurs early after infection and is sustained throughout the asymptomatic phase of infection, only to decline as the cat develops AIDS-like disease (Ackley et al., 1990; Tompkins et al., 1991; English et al., 1994). The increase in CD8⁺ T cell numbers is associated with the development of CD8⁺ antiviral activity through both cytotoxic (Song et al., 1992; Song et al., 1995; Beatty et al., 1996; Burkhard et al., 2001; Flynn et al., 2002) and non-cytotoxic mechanisms (Bucci et al., 1998a; Hohdatsu et al., 1998; Gebhard et al., 1999; Choi et al., 2000; Flynn et al., 2002) and has been linked to a decline in plasma viremia (Bucci et al., 1998a; Hohdatsu et al., 2003).

Beatty et al. (1996) detected anti-FIV Gag-specific CD8⁺ cytotoxic activity in peripheral blood as early as 2 weeks post infection, and the activity remained high through the acute phase

infection, up to 21 weeks post infection (p.i.). The cytotoxic activity was antigen specific and MHC Class I restricted, indicating these cells were classic CD8⁺ CTLs. By 62 weeks p.i. the CTL activity in the PBL was no longer detectable, but anti-Gag and anti-Env precursor CTLs (pCTL) were present in the lymph nodes as late as 127 p.i.. Flynn et al. (2002) reported similar CTL kinetics, with activity present in the PBL during the acute but not the asymptomatic phase of infection, while pCTLs were present in the lymph nodes (LN) and spleen during the asymptomatic phase. Others have also been able to detect anti-Gag, Pol, and Env pCTLs in lymph nodes and spleens of chronically FIV-infected cats (Song et al., 1992; Song et al., 1995).

A population of antigen-nonspecific, non-cytotoxic, anti-viral CD8⁺ cells has also been described in FIV and HIV infections (Beatty et al., 1996; Levy et al., 1996; Bucci et al., 1998a; Choi et al., 2000; Flynn et al., 2002). These cells suppress virus replication in CD4⁺ T cells in a non-cytotoxic, non-MHC restricted manner by either a contact-dependent (Bucci et al., 1998a; Gebhard et al., 1999) or -independent mechanism (Levy et al., 1996; Hohdatsu et al., 1998; Choi et al., 2000). Bucci et al. (1998a) detected non-cytotoxic, contact-dependent anti-viral CD8⁺ cell activity at 6 weeks p.i. that correlated with decreased cell-associated virus by 12 weeks p.i. These cells were characterized by a decrease in expression of the CD8 β chain, and increased MHC class II molecules (Bucci et al., 1998b; Gebhard et al., 1999). High anti-viral CD8⁺ cell function correlated with low plasma viremia, suggesting these cells may play a role in reducing virus load. Flynn et al. (2002) were able to demonstrate non-cytotoxic anti-FIV CD8⁺ cell function as early as 1 week p.i. and prior to the emergence of CTL activity. In contrast to Bucci et al. (1998a), they found no correlation between the anti-FIV activity and virus load, nor did they determine whether activity was contact-dependent or -independent. There is evidence for contact-independent mechanisms of anti-FIV CD8 cell function. Hohdatsu et al. (1998) and Choi et al. (2000) have shown that culture supernatants from CD8⁺ T cells from FIV-infected cats were able to suppress FIV replication in both autologous and heterologous target cells. Later studies by Hohdatsu et al. (2003) showed this activity did not correlate with CD8⁺ T cell numbers but was significantly correlated to plasma viremia in that low anti-virus activity was found in cats with high plasma viremia.

3. Immune Suppression

Despite an early, robust anti-FIV/HIV immune response that reduces plasma viremia, the virus is not cleared and a progressive immune dysfunction develops, evidenced first by a loss of response to virus antigens, followed by an inability to respond to recall antigens, and finally a loss of mitogen responses (Clerici et al., 1989; Balough et al., 1991; Torton et al., 1991). This dysfunction is accompanied by an inability to mount a primary immune response to secondary pathogens that require a functional cell-mediated immune (CMI) response (Davidson et al., 1993b; Dean et al., 1998). While the development of these secondary infections can be attributed to the decline in CD4⁺ cell numbers and the resulting decrease in cytokines (IL-2, IFN- γ) required for a successful CMI response, numerous studies indicate that the immune dysfunction develops before a decrease in CD4⁺ cell numbers (Clerici et al., 1989; Balrough et al., 1991; Torton et al., 1991; Davidson et al., 1993b). We developed a *Toxoplasma gondii*-FIV co-infection model that allowed us to examine FIV-induced dysfunctions in the CMI response (Davidson et al., 1993a; Davidson et al., 1993b). Normal cats challenged with *T. gondii* develop a transient chorioretinitis that resolves three to four weeks post challenge. However, in FIV-infected cats, as early as 16 weeks p.i., *T. gondii* challenge results in generalized toxoplasmosis in 100% of the cats and a 50% – 75% mortality (Davidson et al., 1993b; Yang et al., 1996). This suggests that severe T cell immune dysfunction develops early after lentivirus infection. Similar poor CMI responses were reported by Dean et al. (1998) using a *Listeria monocytogenes* challenge system. Following *L. monocytogenes* infection, the draining LNs of FIV-infected cats enlarged more slowly than those of uninfected cats, and

clinically, the FIV-infected cats showed signs of systemic bacterial infection while the uninfected cats remained clinically normal. Several mechanisms responsible for this immune dysfunction have been proposed, including cytokine dysregulation (Clerici and Shearer, 1993), immunologic anergy and increased programmed cell death (apoptosis) (Miedema, 1992), and inappropriate activation of immune regulatory cells (Ascher and Sheppard, 1990). There is evidence for all three mechanisms in the FIV model system.

3.1 Cytokine Dysregulation

A number of studies have demonstrated altered cytokine levels in FIV infections. Lawrence et al. (1995) reported poor proliferative responses accompanied by decreased IL2 and increased IL6 and TNF α production by PBMC from FIV-infected cats in response to mitogen stimulation. These altered responses were associated with the presence of clinical signs. Elevated levels of IL6 and TNF α mRNA and protein production have been reported in macrophages from acute-phase FIV-infected cats (Ritchey et al., 2001; Avery and Hoover, 2004). With the division of CD4 $^{+}$ cells into two subsets based on cytokine production (TH1: IL12, IL2, IFN γ ; TH2: IL4, IL5, IL6, IL10), Clerici and Shearer (1993) proposed that HIV induced a TH1 to TH2 shift, resulting in the inability to mount a successful CMI response. However, further analysis in both HIV (Graziosi et al., 1994; Meroni et al., 1996; Than et al., 1997) and FIV (Dean and Pedersen, 1998; Levy et al., 1998; Ritchey et al., 2001; Avery and Hoover, 2004; Levy et al., 2004) infections did not support a clear cut TH1 to TH2 shift. Although decreases in the TH1 cytokines IL2 and IL12 and increases in the TH2 cytokines IL10 and IL6 were found, elevated levels of IFN γ were also a consistent finding in both infections.

FIV infection has provided a powerful model to examine cytokine expression prior to and during FIV infection, as well as the cytokine responses following challenge of FIV $^{+}$ cats with a secondary pathogen. We analyzed constitutive cytokine production by lymph node cells from normal and FIV $^{+}$ cats before and after challenge with *T. gondii* and found that FIV infection caused an increase in constitutive IFN γ , TNF α , and IL10 mRNA expression and a decrease in IL2 and IL12 mRNA in the lymph nodes during the acute stage infection (Levy et al., 1998; Levy et al., 2004). Following *T. gondii* challenge, IL12, IL2, and IFN γ mRNA levels increased in normal cats, indicating a normal immune response. These cats developed mild chorioretinitis and recovered by two weeks post challenge. In contrast, IL2, IL6, IFN γ , and IL12 mRNAs were suppressed in the FIV-*T. gondii* co-infected cats, whereas IL10 remained at the high pre-challenge levels, and these cats developed severe, generalized toxoplasmosis. Similar findings were reported by Dean et al. (1998) using an FIV-*L. monocytogenes* model. In both studies, prior to secondary challenge, the ratio of IL10 to IL12 in the FIV $^{+}$ cats was greatly elevated compared to normal cats. These data suggest that FIV-induced immunodeficiency may be derived from a failure to generate an IL-12 dependent response, in part due to elevated levels of IL10, which is known to suppress IL12 production by dendritic cells. In a more recent study, Dean et al. (2006) reported a significant increase in bacterial numbers in FIV $^{+}$ cats compared to control cats as early as one day following *L. monocytogenes* infection, suggesting a poor innate immune response in the FIV $^{+}$ cats. In support of this, addition of IL15 increased NK activity and dramatically decreased the bacterial counts in co-infected cats (Dean et al., 2006). In summary, although a clear TH1 to TH2 shift does not occur in FIV infection, the cytokine dysregulation leads to suppressed innate and CMI responses, resulting in the inability of an FIV $^{+}$ cat to mount a primary immune response to a secondary pathogen.

3.2 Immunologic Anergy and Apoptosis

Immunologic anergy can be defined as the inability of CD4 $^{+}$ T cells to produce IL2 and proliferate in response to restimulation. This lack of IL2 then leads to apoptosis of the stimulated cells. One of the manifestations of FIV/HIV-induced immune suppression is the loss of response to recall antigens, and it has been suggested that these viruses prime T cells

for anergy and apoptosis. There is ample evidence of apoptosis in lymphoid tissues of asymptomatic FIV-infected cats and HIV-infected patients (Guiot et al., 1993; Finkel et al., 1995; Muro-Cacho et al., 1995; Sarli et al., 1998). The degree of apoptosis does not correlate with either the stage of disease or virus burden, and is found throughout the cortical and medullary areas of infected LNs rather than being restricted to germinal centers, as is seen in normal LNs (Muro-Cacho et al., 1995; Sarli et al., 1998). Additionally, histochemical analysis has shown that many apoptotic cells in LN in HIV infection are not infected with virus (Finkel et al., 1995; Muro-Cacho et al., 1995) and the apoptosis is not restricted to CD4⁺ cells, but also involves CD8⁺ cells and B cells in both HIV and FIV infection (Finkel et al., 1995; Muro-Cacho et al., 1995; Sarli et al., 1998). What contribution virus-infected lymphocytes make to the apoptosis observed in LN of HIV-infected patients and FIV-infected cats is not known, but the evidence suggests that it is minimal and that other, indirect mechanisms are responsible.

Apoptosis regulates the cellular repertoire throughout life and is induced by engagement of specific cellular surface receptors with their ligands. The B7 co-stimulatory molecules binding to CTLA-4 is a T cell lineage specific apoptosis pathway that regulates normal immune responses. The B7 family (B7.1, B7.2) of co-stimulatory molecules are normally found on professional antigen presenting cells. They interact with CD28 and CTLA4 on T cells to either stimulate IL2 synthesis and thus an immune response (B7-CD28) or to terminate the response (B7-CTLA4) by suppressing IL2 production (Bluestone, 1997). While CD28 is constitutively expressed on T cells, CTLA4 is expressed only after T cells have been activated via their TCR. As the binding avidity of the B7 molecules for CTLA4 is 50–100 times greater than for CD28, negative signaling would dominate over activation on cells expressing both CD28 and CTLA4.

Although the B7 molecules are normally found on APC, studies have shown that they are expressed on activated T cells in situations of chronic antigenic stimulation (Folzenlogen et al., 1997; Ranheim and Kipps, 1994). As FIV infection results in a chronic antigenemia, we examined the expression of B7 and CTLA4 on CD4⁺ and CD8⁺ T cells from FIV⁺ cats. We found a significant increase in the percentage of CD4⁺ and CD8⁺ T cells that express B7.1 and B7.2 molecules in FIV⁺ cats compared to uninfected cats (Tompkins et al., 2002). The percentage of B7 positive T cells increased with disease progression such that in cats with long-term infections (> 7 yrs), up to 75% of the T cells in the LNs expressed B7.1/2. We also demonstrated an increase in surface CTLA4 expression on CD4⁺ and CD8⁺ T cells from FIV⁺ cats compared to controls and that a majority of the CTLA4 positive cells also expressed B7. Importantly, the expression of B7.1/2 and CTLA4 correlated with spontaneous T cell apoptosis in the LN and PBMC of FIV⁺ cats (Tompkins et al., 2002). As ligation of CTLA4 by B7 transduces a signal for down-regulation of IL2 and induction of anergy and apoptosis, we speculated that persistent antigenic stimulation as a result of FIV infection chronically induces B7⁺CTLA4⁺ T cells capable of T-T interactions that result in T cell anergy and apoptosis. In support of this, we have shown that anti-B7.1 or IL2 treatment of cultured purified CD4⁺ cells from FIV⁺ cats significantly inhibits spontaneous apoptosis, as would be expected if apoptosis were the result of B7⁺-CTLA4⁺ mediated T-T interactions (Bull et al., 2004; Vahlenkamp et al., 2004a). Such T-T interactions could explain the progressive loss of T cell immune function and increase in lymph node T cell apoptosis that is the hallmark of FIV and HIV infection. Additionally, as not all anergized cells progress to apoptosis, this mechanism could also explain the decreased IL2 production and immune unresponsiveness seen prior to CD4⁺ cell loss.

3.3 Activation of Immune Regulatory Cells

A number of studies have now documented the existence of a population of CD4⁺ cells with immune regulatory function (Treg cells). While early studies suggested that the thymus was the sole reservoir of Treg cells (Sakaguchi et al., 1995; Maloy and Powrie, 2001), recent

evidence indicates that Treg cells may also be induced in the periphery, particularly under conditions of chronic immune stimulation such as chronic infectious disease (Iwashiro et al., 2001; Belkaid et al., 2002; Hori et al., 2002). These observations led Bluestone and Abbas (2003) to propose the existence of two subsets of Treg cells that differ in terms of their target antigens and role in the immune response. The thymus-derived “natural” Treg cells develop during the normal process of T cell maturation, are self-antigen specific, and survive in the circulation as a long-lived population surveying the immunological landscape for potential autoimmune cells. The second subset of “adaptive” Treg cells is activated in the peripheral lymphoid tissue, purportedly in response to antigenic stimulation, and plays a major role in modulating immune responses to infectious agents and other inflammatory conditions.

Although derived from different compartments, natural and adaptive Treg cells are indistinguishable both phenotypically and functionally. Phenotypically, Treg cells constitutively express CD25, which is the alpha chain of the IL2 receptor, and CTLA4 (Sakaguchi et al., 1995; Read et al., 2000). When activated, they also express B7 molecules, CD62L, and TGF β (Nakamura et al., 2001; Piccirillo and Thornton, 2004). What distinguishes CD4⁺CD25⁺ Treg cells from CD4⁺CD25⁺ T-helper cells is the expression of the *forkhead* family transcription factor Foxp3, which is required for Treg cell homeostasis and function (Chen et al., 2003; Walker et al., 2003; Fantini et al., 2004). Functionally, Treg cells are anergic in that they do not produce IL2 and do not proliferate in response to mitogens (Maloy and Powrie, 2001). When stimulated via their TCR, Treg cells inhibit proliferation and induce apoptosis of other activated CD4⁺ or CD8⁺ T cells. This suppression is mediated through a cell contact-dependent mechanism that transduces a signal for transcriptional down-regulation of IL-2, resulting in anergy and apoptosis (Thornton and Shevach, 1998; Shevach et al., 2001). Although activation of CD4⁺CD25⁺ cells is, with some exceptions (e.g. LPS and IL2), antigen-specific, once activated, they suppress CD4⁺ and CD8⁺ T cell responses in an antigen non-specific manner (Thornton and Shevach, 1998).

The phenotype of activated Treg cells (CD4⁺, CD25⁺, CTLA4⁺, B7⁺) is reminiscent of the activated CD4⁺B7⁺CTLA4⁺ cells described above that we have shown to be associated with anergy and apoptosis. We therefore analyzed the phenotype and function of CD4⁺CD25⁺ T cells in normal and FIV⁺ cats. Similar to human and mouse Treg cells, feline CD4⁺CD25⁺ cells constitute about 5–10 percent of the peripheral T cell population, fail to produce IL2 and proliferate in response to Con A stimulation, and are relatively resistant to activation-induced programmed cell death (Joshi et al., 2004; Vahlenkamp et al., 2004b). Importantly, freshly isolated CD4⁺CD25⁺ T cells from asymptomatic FIV⁺ cats, but not normal cats, suppress the proliferative response of ConA-stimulated autologous CD4⁺CD25⁺ T cells in a dose-dependent manner. This suppression is contact dependent and correlates with the down-regulation of IL2 production, suggesting that the Treg cells are activated *in vivo* in response to FIV infection. Flow cytometric analysis confirmed the activation phenotype of the Treg cells in the FIV⁺ cats, revealing significant up-regulation of the co-stimulatory molecules B7.1, B7.2, and CTLA4 on their surface (Vahlenkamp et al., 2004b). Subsequent to our studies, there were several reports of expansion and activation of CD4⁺CD25⁺ cells with Treg cell characteristics in HIV infection (Aandahl et al., 2004; Kinter et al., 2004; Weiss et al., 2004; Andersson et al., 2005) and SIV infection (Kornfeld et al., 2005; Estes et al., 2006).

Why Treg cells would be activated in lentivirus infection is not clear, nor is it known if the activated cells are virus antigen specific. Estes et al. (2006) reported activation of Treg cells during the very early acute phase of SIV infection, and we have also documented an early activation of Treg cells in acute FIV infection. One can speculate that activation of Treg cells during the early acute stage of FIV/HIV infection could result in suppression of T cell immune responses before epitope specific CD4⁺ Th and CD8⁺ T effector cells could clonally expand and develop an effective immune response, thus contributing to the establishment of a persistent

infection and chronic antigenemia. Although there is no direct evidence for this in FIV/HIV infection, in support of this speculation, studies on Hepatitis B and Hepatitis C virus infections suggest that the CD4⁺CD25⁺ Treg response to these viruses may determine if the host develops a strong T cell immune response and resolves the infection or has a diminished immune response and establishes a persistent viremia (Rushbrook et al., 2005; Xu et al., 2006).

In addition to their potential role in suppressing anti-viral immune responses, it is easy to imagine how activated Treg cells would contribute to the more global immune suppression characteristic of FIV/HIV infection. Although activation of Treg cells can be antigen specific, once activated, these cells can suppress in a non-antigen specific manner by down-regulating IL2 production. Chronic FIV antigen presentation would maintain activated Treg cells, which in turn would dampen the response to newly presented antigens from a secondary infection as well as explain the decrease immune responsiveness and IL2 production prior to CD4⁺ T cell loss. This negative immunoregulatory property of activated CD4⁺ Treg cells is well-documented in a number of infectious diseases (Iwashiro et al., 2001; Singh et al., 2001; Belkaid et al., 2002; Hori et al., 2002).

4. Immune Hyper-activation

Although lentiviruses are generally thought of as inducing immune suppression, paradoxically there is a generalized state of progressive immune hyper-activation of both B and T cells throughout the course of the infection. B cell hyper-activation is manifested as a polyclonal hypergammaglobulinemia. Naturally and experimentally infected cats develop a polyclonal IgG response to both viral and non-viral antigens that can be detected as early as six weeks post infection (Ackley et al., 1990; Flynn et al., 1994). This gammopathy correlates histologically with a high degree of plasmacytosis in and around germinal centers, which increases during the course of infection (Bendinelli et al., 1993).

T cell immune hyper-activation is seen in both the CD4⁺ and CD8⁺ cell populations. FIV infection is associated with a CD8⁺ T cell lymphocytosis that develops during the acute phase infection and is maintained until late stage disease develops (Tompkins et al., 1991; Willett et al., 1993; English et al., 1994). Phenotypic analysis of circulating CD8⁺ cells from FIV⁺ cats demonstrated a decrease in the expression of the CD8 β chain, increased MHC class II molecules, and a progressive down-regulation of CD62L, a surface marker that is lost on activated T cells, resulting in more than 70% CD62L negative cells of the total CD8 β ⁺ population in the peripheral blood of long-term (>7 years) infected cats (Bucci et al., 1998b; Willett et al., 1993; Gebhard et al., 1999;). Further analysis revealed a progressive loss of the naïve CD8 α ⁺ β ^{hi}CD62L⁺CD44^{lo}CD49d^{lo}CD18^{lo} phenotype and a concurrent expansion of a CD8 α ⁺ β ^{lo}CD62L⁻CD44^{hi}CD49d^{hi}CD18^{hi} activation phenotype in the circulation throughout the course of infection (Gebhard et al., 1999). Loss of CD62L and increase in the adhesion molecule (CD44) and integrin (CD49d, CD18) expression on the surface of CD8⁺ cells is indicative of an activation phenotype and therefore suggests that naïve CD8⁺ cells are largely replaced by activated CD8⁺ cells during FIV infection. Analysis of CD62L expression on CD4⁺ cells from FIV⁺ cats reveals a pattern similar to that seen on CD8⁺ cells in that there is an increase in CD4⁺CD62L⁻ T cells with time after infection. Up to 80% of the total CD4⁺ cells in long-term (>7 years) infected cats lack CD62L, consistent with an activation phenotype (Vahlenkamp et al., 2006). Further evidence of chronic and progressive T cell activation comes from the analysis of B7.1/2 and CTLA4 co-stimulatory molecules as discussed previously. As FIV infection progresses from acute to long-term, the percent of B7⁺ CD4⁺ and CD8⁺ T cells increases such that approximately 80% of the total CD4⁺ and CD8⁺ cells express B7.1 and/or B7.2. In the case of CD8⁺ cells, B7 expression is largely confined to the CD8 α ⁺ β ^{lo} cell population (Tompkins et al., 2002).

What role this immune hyper-activation plays in the development of AIDS is unclear. However, it is clear that immune suppression and immune hyper-activation increase in parallel through the course of FIV infection. One can speculate that FIV antigen presentation leads to activation of T and B cells, which in turn results in activation of Treg cells to dampen the immune response. This dampened immune response then allows for continued virus replication and chronic antigenemia, which in turn, continues to activate T cells. These activated T cells, characterized by expression of B7 and CTLA4 are capable of inappropriate T-T cell interactions resulting in induction of anergy and apoptosis. This chronic activation of T cells also would maintain Treg cell activation, resulting in a global immune suppression and the inability to respond to secondary infections. This model of immune hyper-activation leading to immune suppression is illustrated in Figure 1.

5. Conclusion

The parallels in lymphocyte phenotype and function, as well as disease progression, between FIV and HIV make FIV an excellent animal model for HIV pathogenesis. The importance of FIV infection of cats as a model for human AIDS is underscored by a number of findings that were subsequently discovered to be characteristics critical to the pathogenesis and natural history of HIV infection. For example, using the FIV/*T. gondii* co-infection model, Davidson et al. (1993b) demonstrated that FIV induced a profound immune dysfunction to primary infection with other pathogens early in the acute stage of lentivirus infection. Although such studies cannot be confirmed in vivo in HIV infection, in vitro T cell stimulation studies subsequently demonstrated a similar acute stage immune deficiency. In another case, chronic T cell activation and its link to T cell apoptosis was first described in the FIV model by Gebhard et al. (1999), who demonstrated that CD8 cells were chronically activated, and Tompkins et al. (2002), who demonstrated up-regulation of co-stimulatory molecules on T cells in FIV-infected cats and proposed a model for T cell-T cell interaction leading to anergy and apoptosis. These observations were subsequently shown to be true in HIV infection (Leng et al., 2002; Sousa et al., 2002; Hazenberg et al., 2003; Trabattoni et al., 2003). Perhaps the major contribution of the FIV/AIDS model is the observation that FIV preferentially infects CD4⁺CD25⁺ Treg cells (Joshi et al., 2004), and that these cells are chronically activated in vivo and capable of suppressing CD4⁺ and CD8⁺ T cells (Vahlenkamp et al., 2004b). Similar findings were subsequently reported in HIV infection (Aandahl et al., 2004; Kinter et al., 2004; Weiss et al., 2004; Andersson et al., 2005), and activation of Treg cells and their role in AIDS is now a major area of research. Thus, it is clear that studies of FIV infection have made major contributions to our understanding of lentivirus induced AIDS and that further studies in the FIV system on the molecular mechanisms of Treg cell activation and suppressor function should provide a better understanding of HIV/AIDS pathogenesis.

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Figure 1.

Model of lentivirus-induced immune hyperactivation leading to immune suppression. FIV infects lymphocytes (1), resulting in activation of virus specific CD4⁺ Th, characterized by secretion of IL2 and IFN-γ, and virus specific CD8⁺ T cells (2). Activated CD4⁺ and CD8⁺ T cells lead to activation of CD4⁺CD25⁺ Treg cells (3), which in turn suppress IL2 and IFN-γ gene transcription, resulting in anergy and loss of anti-FIV immune responses (4). Loss of the antiviral immune response allows for continued virus replication and chronic antigenemia (5), which leads to continued activation of T cells, which express B7 and CTLA4 (6). These cells are capable of inappropriate T-T cell interactions, resulting in induction of anergy, apoptosis and immune suppression (7). This chronic antigenemia and activation of T cells would also result in chronic Treg cell activation (8). These activated Treg cells are then capable of suppressing not only anti-viral immune responses, but immune responses to other antigens, thus contributing to the global immune suppression associated with FIV infection (9).