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HIV Without AIDS: The Immunological Secrets of Natural Hosts

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1. Introduction

Human Immunodeficiency Virus (HIV) infection causes Acquired Immune Deficiency Syndrome (AIDS), while its ape and monkey progenitor Simian Immunodeficiency Virus (SIV) does not cause AIDS in its nonhuman primate natural reservoir hosts. Astonishingly, AIDS is avoided despite findings in a number of these host primate species indicating they too harbor high levels of virus replication that kills off CD4 T cells. These primate species that are so called "natural hosts" of SIV, essentially have HIV without ever getting AIDS.

The elucidation of the exact mechanisms allowing natural SIV hosts to avoid disease progression may prove decisive in the battle to understand HIV pathogenesis for the purpose of preventative or curative HIV and AIDS therapy. Comparative studies in natural and nonnatural hosts of lentiviral infections (i.e. HIV or SIV) have defined essential distinguishing features, opening up new avenues for possible therapeutic and preventative intervention.

In this chapter, we will describe recent and past breakthroughs that come from comparing lentiviral infections in AIDS-free natural hosts, to immunocompromised nonnatural hosts. In addition, we will discuss how the knowledge derived from the study of natural hosts may inform the design of novel therapies and vaccine strategies for HIV-infected humans.

1.1 A brief history of HIV

The observation in the late '70s and early '80s of a previously unrecognized adult-onset immunodeficiency associated with Kaposi's sarcoma (a skin cancer now known to be caused by Herpes Virus 8) and *Pneumocystis carinii* (a yeast-like fungus now known as *Pneumocystis jiroveci*) pneumonia signaled the beginning of one of the most devastating tragedies of modern times: the AIDS epidemic. Early epidemiological hypotheses on the etiologic agent of this disease included sexually transmitted pathogens as well as toxic "street" drugs (Centers for Disease Control (CDC), 1982; Harris et al., 1983). During these early years, basic and clinical researchers alike began furiously searching for the causes of AIDS, which culminated in 1983 with the discovery of the Human Immunodeficiency Virus (Barre-Sinoussi et al., 1983).

A series of studies in molecular virology and epidemiology conducted in subsequent years have delineated both the timing and geographical origin of the AIDS pandemic. The African city of Kinshasa (formerly known as Leopoldville), in the Democratic Republic of the Congo,

is the place where the oldest known HIV-infected samples were discovered in a lymph node biopsy from 1960 and a blood-plasma sample from 1959 (Paul M Sharp & Beatrice H Hahn, 2008). In 1998, Zhu et al. estimated that HIV-1 originated in the 1940's or early 1950's, and also proposed that the split between HIV-1 and HIV-2 must have occurred considerably earlier (T. Zhu et al., 1998). Ten years later, Worobey et al. proposed the origin of HIV-1 to be anywhere from 1884-1933, a range corresponding to the rise of urban populations in the Leopoldville/Kinshasa area (Worobey et al., 2008). Collectively, these observations and models have refuted the controversial speculation that experimental polio vaccine formulations from the 1950's were responsible for the AIDS epidemic (Worobey et al., 2004). Subsequent studies indicated that HIV infection in humans arose from cross-species transmission of viruses that naturally infect African nonhuman primates (NHP), which are referred to as natural hosts for SIV (P M Sharp & B H Hahn, 2010). The next section will describe the different African nonhuman primates infected with SIV, focusing on those that infected giving rise to HIV-1 and HIV-2.

1.2 Introduction to natural hosts

At least 40 monkey species in Africa have been found to be naturally infected with species-specific strains of SIVs, and usually with a high prevalence. In the vast majority of cases the virus is designated by a three-letter abbreviation of the infected nonhuman primates (NHP) species name to differentiate between SIV strains (VandeWoude and Apetrei, 2006). For example, SIVcpz is the virus isolated from chimpanzees (*Pan troglodytes*), SIVsmm from sooty mangabeys (*Cercocebus atys*), SIVmnd from mandrills (*Mandrillus sphinx*), SIVagm from African green monkeys (AGM), and so on. The viruses that infect the different species of AGM are named SIVagm.ver (Vervet monkey), SIVagm.gri (Grivet monkey), SIVagm.sab (Green monkey), SIVagm.tan (Tantalus monkey). Table 1 lists the different African nonhuman primates infected with SIV.

These natural hosts for SIV represent an extremely large reservoir of lentiviruses potentially infecting other species. Phylogenetic analyses revealed that there have been cross-species transmissions of divergent viral strains since the beginning of the evolution of primate lentiviruses (Courgnaud et al., 2003; Hirsch, Dapolito, Goeken, & Campbell, 1995; P M Sharp & B H Hahn, 2010). For instance, HIV-2 emerged from the west African natural host sooty mangabey (*Cercocebus atys*) in at least eight cross-species events into the human population (Wertheim & Worobey, 2009), while the origins of HIV-1 have been more controversial. Four HIV-1 lineages originating in chimpanzees have been independently transmitted across species to infect humans, though one or two may have come via gorillas (P M Sharp & B H Hahn, 2010; Takehisa & Miura, 2010). Most HIV-1 isolates resemble viruses found in a chimpanzee subspecies (*Pan troglodytes troglodytes*) native to areas in and around Cameroon, Gabon and Equatorial Guinea, including the areas around Kinshasa (Gao et al., 1999; P M Sharp & B H Hahn, 2010). HIV-1 group M, responsible for a suggested 98% of the global epidemic, as well as rare groups N and O, are endemic in the aforementioned areas. Hunting chimpanzees for food, which is thought to be the method of cross-species transmission is also common in this central African region (Gao et al., 1999). In addition, the SIVs that have been isolated from Asian macaques, the most commonly used primate model of HIV infection, appear to have been transmitted from captive sooty mangabeys (reviewed in I. Pandrea, Sodora, Silvestri, & Apetrei, 2008).

Genus	Species/subspecies	Virus
African green monkeys (*Chlorocebus*)	Vervet monkey (*C. pygerythrus*) Grivet monkey (*C. aethiops*) Green monkey (*C. sabaeus*) Tantalus monkey (*C. tantalus*)	SIVagm.ver SIVagm.gri SIVagm.sab SIVagm.tan
Black and white colobus (*Colobus*)	Manted guereza (*C. guereza*) Western red colobus (*Piliocolobus badius)* Olive colobus (*Procolobus verus)*	SIVcol SIVwrc SIVolc
Chimpanzee (*Pan*)	Western chimpanzee (*P. troglodytes troglodytes*) Eastern chimpanzee (*P. troglodytes schweinfirthii*)	SIVcpz.ptt SIVcpz.pts
Guenons (*Cercopithecus*)	Sykes' monkey (*C. mitis*) L'Hoest monkey (*C. lhoesti*) Sun-tailed monkey (*C. solatus*) De Brazza monkey (*C. neglectus*) Mona (*C. mona*) Mustached monkey (*C. cephus*)	SIVsyk SIVlhoest SIVsun SIVdeb SIVmon SIVmus
Lophocebus	Black mangabey (*Lophocebus aterrimus*)	SIVbkm
Mandrills (*Mandrillus*)	Mandrill (*M. sphinx*) Drill (*M. leucophaeus*)	SIVmnd/SIVmnd2 SIVdrl
Talapoins (*Miopithecus*)	Angolan talapoin (*M. talapoin*)	SIVtal
White-eyelid mangabeys (*Cercocebus*)	Sooty mangabey (*C. atys*) Red-capped mangabey (*C. torquatus*)	SIVsmm SIVrcm

Table 1. Natural SIV hosts (reviewed on (VandeWoude & Apetrei, 2006))

Most of the naturally occurring SIVs do not cause disease in their natural hosts (Paiardini, et al., 2009); however, they can be highly pathogenic when replicating in nonnatural hosts, such as rhesus macaques and humans. Wild chimpanzee studies of SIV prevalence and pathogenicity, made possible by testing stool samples, have recently demonstrated that SIV positive chimpanzees die at a faster rate than their uninfected counterparts –a 9.8-15.6-fold increased death hazard) (Keele et al., 2009). While searching for the age and origins of the chimpanzee SIV, a major breakthrough came when it was noticed that the 5' region of the chimpanzee SIV genome closely matches that found in red-capped mangabeys (*Cercocebus torquatus*), but the 3' end closely resembles SIVs found in greater spot-nosed (*Cercopithecus nictitans*), mustached (*Cercopithecus cephus*) and mona monkeys (*Cercopithecus mona*). Based on these findings, SIV_{cpz} is thought to be a recombination of viruses ancestral to those found in red-capped mangabeys, mona, spot-nosed and mustached monkeys (Paul M Sharp, Shaw, & Beatrice H Hahn, 2005). The data suggest that chimpanzees have not evolved along with their own SIV for very long, and may represent a necessary evolutionary stage for the virus to enable cross-species transmission into humans. In a recent study, Worobey et al. established that SIV is at least 32,000 years old, based on Bioko Island geography and SIV relatedness of the various African nonhuman primates on the island. The authors conclude

that humans may have had previous encounters with this virus over time, and that natural hosts that show low pathogenicity to SIV have arisen likely as "a consequence of long-term host-virus coevolution" (P M Sharp & B H Hahn, 2010; Worobey et al., 2010) .

As above mentioned, and in obvious contrast with HIV infection in humans, which almost invariably leads to AIDS if left untreated, SIV infection in natural African NHP hosts is typically non-progressive. The infected animals live an apparently normal lifespan, without experiencing any signs of illness whether in the wild or captivity (Paiardini ann rev med). The fact that HIV causes a deadly disease in humans while its simian counterparts are virtually non-pathogenic in their natural hosts remains one of the fundamental mysteries of modern medicine, and it is widely recognized that the elucidation of the exact mechanisms allowing natural SIV hosts to avoid disease progression may prove critical in terms of HIV pathogenesis, therapy, and vaccines. Over the past few years, comparative studies in natural and nonnatural hosts of lentiviral infections have shed light on a number of critical distinguishing features.

2. Immunology and virology of HIV and SIV infections

2.1 Viral loads

2.1.1 Nonnatural hosts for HIV and SIV infections

As previously noted, HIV and SIV infections in humans and Asian macaques were generated from cross-species transmissions of viruses that naturally infect nonhuman primates in Africa. These primate lentiviruses replicate very efficiently *in vivo*, with the vast majority of HIV-infected humans and SIV-infected Asian macaques showing approximately 10^8 virions per milliliter of plasma during the acute phase of infection (Picker, 2006) (figure 1). Tracking SIV-infected macaques has been and continues to be indispensible for our understanding of virus kinetics at all stages of infection and in key tissues (i.e. gut and lymph node). Information obtained early in the infection process when virus replication begins and the adaptive immune response is underway, is vital to our ability to rationally design effective treatment and preventative strategies.

As the infection advances into the chronic phase, viral load in plasma declines and stabilizes to its "set point" (figure 1). This stage is reached once the immune system develops antibodies in an attempt to fight the virus. The behavior of the virus at set point is characterized by three major factors: (i) viral load remains relatively stable for several years; (ii) individuals who have a higher set point level have faster progression to AIDS; and (iii) shortly before the development of clinical AIDS, viral load increases. Despite declining levels of viral replication from peak viremia to set point, other factors persist, such as generalized immune activation, that play important roles in damaging a progressively dysfunctional immune system.

2.1.2 Natural hosts for SIV infections

Worth noting is the point that both in the acute and chronic phases of infection, the levels of plasma viremia are similar in HIV-infected humans and SIV-infected natural hosts, such as sooty mangabeys and African green monkeys (figure 1) (Picker, 2006) . The implication of the data is clear and extremely important: the presence of a cytophatic virus that replicates at high levels is not sufficient, by itself, to induce AIDS. In other words, additional factors are required for disease progression in HIV-infected humans and SIV-infected rhesus macaques.

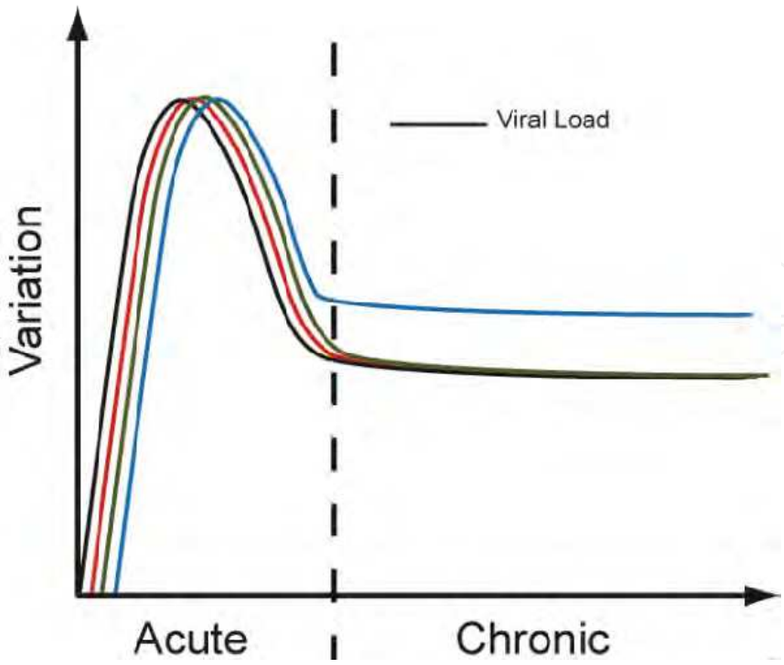

Fig. 1. Viral load in natural and nonnatural host species.
Natural host species (sooty mangabeys —, African green monkeys —) and nonnatural host species (humans —, rhesus macaques —) have similar levels of viremia in the acute and chronic phase of infection. Originally published in *Blood* Online. Brenchley JM & Paiardini M. Immunodeficiency lentiviral infections in natural and nonnatural hosts. *Blood*. Prepublished April 19, 2011; DOI:10.1182/blood-2010-12-325936.

2.2 CD4 T cell homeostasis

2.2.1 Nonnatural hosts for HIV and SIV infections

The depletion of CD4 T cells is the immunological hallmark of progressive HIV infection. The loss of circulating CD4 T cell numbers at levels below 200 cells/ml of blood coincides with onset of opportunistic infections. As such, a better understanding of the dynamics of CD4 T cell depletion is essential when studying the pathogenesis of HIV infection. Depletion of CD4 T cells from the peripheral blood is generally quite slow, with HIV-infected humans losing approximately 40 CD4 T cells per µl of blood per year during the chronic phase of infection (Moore, Keruly, Richman, Creagh-Kirk, & Chaisson, 1992).

The study of SIV-infected macaques has provided important information on the dynamics of CD4 T cell depletion, particularly in the early phase of infection and in anatomical locations difficult to study in HIV-infected humans. In particular, a series of influential studies have elucidated the early consequences of pathogenic HIV and SIV infections at the level of mucosal tissues, showing that the depletion of CD4 T cells is more rapid and severe at this site than in the peripheral blood or secondary lymphoid organs (figure 2) (Brenchley, Schacker, et al., 2004a; Douek, Mario Roederer, & Koup, 2009; Guadalupe et al., 2003; Haase, 2005; Mehandru et al., 2004; T Schneider et al., 1995; Veazey et al., 1998). Other observations underpin the reasons why the mucosal tissues undergo such stress: (i) the large majority of CD4 T cells located in the effector mucosal sites show a memory, activated, CCR5+

phenotype, (ii) the majority of newly transmitted HIV and SIV strains are CCR5-tropic, and (iii) primate lentiviruses preferentially infect activated CD4 T cells (Z. Zhang et al., 1999; Brenchley, Hill, et al., 2004b; Brenchley, Silvestri, & Douek, 2010; Veazey et al., 2000; Y . Zhang et al., 2000). As such, a large fraction of mucosal-resident CD4 T cells represent a highly susceptible target for virus replication, especially at a time when no antiviral adaptive immune response has yet been generated. Using the macaque SIV model, it was demonstrated that mucosal memory CD4+CCR5+ T cells are the earliest targets of the virus regardless of the route of infection (Veazey et al., 1998), and the majority (70-95%) of CD4 T cells in the jejunum, ileum, and colon are depleted in less than three weeks post infection (Li et al., 2005; Mattapallil et al., 2005). Due to the large surface area of the gastrointestinal (GI) tract, this severe loss of mucosal CD4 T cells during the acute phase of infection likely translates to depletion of most CD4 T cells within the body.

While there is a general consensus on the dramatic loss of mucosal CD4 T cells, the exact mechanisms accounting for this depletion are not completely clear, with evidence pointing in different directions. Direct virus-mediated killing of infected CD4 T cells is responsible for the earliest (within days of infection) loss of CD4 T cells (Mattapallil et al., 2005) and CD95-mediated activation induced cell death of uninfected bystander CD4 T cells (Li et al., 2005) accounts for the subsequent depletion (within weeks). Of note, recent studies comparing multiple GI sites have shown anatomic-specific differences in the extent of CD4 T cell loss in chronically SIV-infected rhesus macaques, with CD4 T cell depletion being more severe in the small intestine compared to the large intestine (L. D. Harris, Klatt, et al., 2010a). Due to the complexity of performing longitudinal mucosal collections and sampling multiple anatomic sites, similar comparative analysis has not, systematically, been performed in humans. Therefore it is debatable whether this phenomenon extends to HIV-infected individuals.

Based on these findings, a new model of AIDS pathogenesis has been proposed. That is to say, the early and complex dysfunction of the mucosal immune system induces a significant impairment of mucosal barrier integrity resulting in a series of pathogenic sequelae that become mostly apparent during chronic infection. The best characterized consequences of damage to the mucosal barrier are the translocation of microbial products from the intestinal lumen into systemic circulation, and the establishment of high levels of chronic immune activation. From this relatively new point of view, the depletion of CD4 T cells from mucosal tissues during acute HIV or SIV infection is a key determinant of disease progression [1, 49-52].

2.2.2 Natural hosts for SIV infection

One of the most peculiar features of natural hosts of SIV infection is their ability to preserve healthy levels of peripheral CD4 T cells, despite levels of plasma viremia similar or even higher than those described in HIV-infected individuals (Chakrabarti et al., 2000; Rey-Cuillé et al., 1998; Silvestri et al., 2003). For instance, approximately 90% of SIV-infected sooty mangabeys maintain CD4 T cell counts comparable to those observed in uninfected animals (Sumpter et al., 2007). This is a clear difference compared to the progressive depletion of circulating CD4 T cells that characterize pathogenic HIV and SIV infections in humans and rhesus macaques (figure 2).

Intriguingly, two recent studies aimed at investigating the kinetics of mucosal CD4 T cells during SIV infection of sooty mangabeys and African green monkeys (Gordon et al., 2007; I. V. Pandrea et al., 2007b) demonstrated that just like HIV-infected humans and SIV-infected

rhesus macaques, SIV-infected sooty mangabeys manifest a rapid and severe depletion of mucosal CD4 T cells (figure 2). In the first study, Gordon et al. showed that memory CD4 T cells are rapidly and severely depleted from the mucosal sites (but not from peripheral blood or lymph nodes) of SIV infected sooty mangabeys, with kinetics remarkably similar to those observed during pathogenic SIVmac infection of macaques (Gordon et al., 2007). In the second study, Pandrea et al. observed a similar level of mucosal CD4 T cell depletion in African green monkeys compared to rhesus macaques during the acute phase of SIV infection (I. V. Pandrea et al., 2007b). Notably, the early loss of mucosal CD4 T cells does not progress further after reaching a stable plateau in sooty mangabeys and is followed by a partial recovery of these cells in African green monkeys—trends that contrast with that described in pathogenic HIV and SIV infections in humans and rhesus macaques where mucosal CD4 T cell depletion becomes increasingly more severe as disease progresses to AIDS.

Intriguingly, despite levels of CD4 T cells in the gut comparable to those described in HIV-infected humans who progress to AIDS, sooty mangabeys and African green monkeys maintain normal mucosal immune function, as indicated by the maintenance of an intact mucosal barrier, the complete absence of any increased susceptibility to infections, and the lack of microbial translocation (Brenchley, Price, Schacker, Asher, et al., 2006a; Estes et al., 2010; Gordon et al., 2007; I. V. Pandrea et al., 2007b). These findings raise an important question of how SIV-infected natural hosts maintain mucosal immunity and avoid progression to AIDS despite the loss of mucosal CD4 T cells. One might hypothesize that in sooty mangabeys, preservation of CD4 T cell homeostasis in the peripheral blood compensates for the loss of mucosal CD4 T cells, and is sufficient to maintain a functional immune system. This hypothesis, however, is not consistent with the observation that a fraction of naturally and experimentally infected sooty mangabeys experience a variable but significant (with animals showing <100 cells/ul blood) loss of CD4 T cell in blood and tissues, while still remaining healthy and AIDS-free (Milush et al., 2007; Mir, Gasper, Sundaravaradan, & Sodora, 2011; Sumpter et al., 2007; Taaffe et al., 2010). The evidence indicates that even a generalized depletion of CD4 T cells, per se, is not sufficient to induce progression to AIDS in natural hosts for SIV. This leaves unanswered the question of how SIV-infected sooty mangabeys can afford to lose CD4 T cells but maintain mucosal immunity and avoid progression to AIDS.

To answer this question, several, non-mutually exclusive mechanisms have been suggested in the past few years. One possibility is that the lack of other pathogenic factors, in particular chronic immune activation, protects the CD4 T cell depleted mucosa of sooty mangabeys (Mirko Paiardini et al., 2009b). An alternative possibility is that the immune system of natural hosts evolved to be less dependent on CD4 T cells, with other cell types carrying on the CD4 T cell helper functions. In particular, two recently published studies of sooty mangabeys and African green monkeys showed the presence of a significant fraction of that despite lacking CD4 expression, indeed act as CD4 T cells; this allows the immune system to maintain "classical" helper functions that otherwise would be lost (Milush et al., 2011, Beaumier et al., 2009). A third possibility is that despite being quantitatively similar, the depletion of CD4 T cells is qualitatively different in pathogenic and nonpathogenic lentiviral infections. This last possibility implies that natural hosts for SIV are able to preserve certain critical CD4 T cell subsets, in the context of generalized CD4 T cell depletion, sufficient for maintaining a functional immune system.

Two of these mechanisms, i.e. the lack of immune activation and the preservation of the homeostasis of selective CD4 T cell subsets, are described in more details in the next sections.

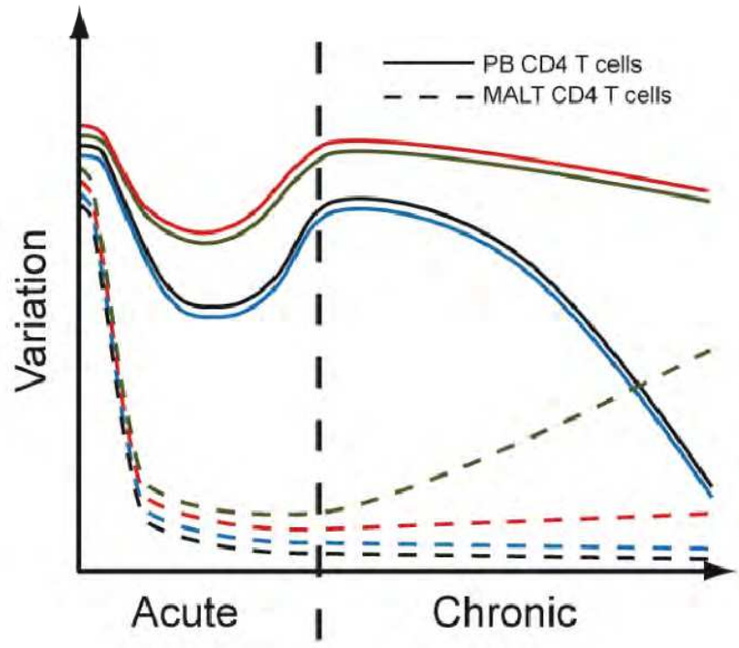

Fig. 2. CD4 T cell homeostasis in natural and nonnatural hosts.
In both pathogenic (humans ——, rhesus macaques ——) and nonpathogenic (sooty mangabeys —— and African green monkeys ——) HIV/SIV infection, CD4 T cells are rapidly lost in the mucosal associated lymphoid tissue (MALT, dotted lines). In contrast to pathogenic infection, CD4 T cells are generally preserved in the peripheral blood (PB, solid lines) of natural host species. Originally published in *Blood* Online. Brenchley JM & Paiardini M. Immunodeficiency lentiviral infections in natural and nonnatural hosts. *Blood*. Prepublished April 19, 2011; DOI:10.1182/blood-2010-12-325936.

3. Immune activation

3.1 Immune activation markers and their role as predictors of disease progression

The establishment of a state of chronic, generalized immune activation is a characteristic feature of pathogenic HIV infection in humans and SIV infection in macaques (Douek D Ann REv Med 2009; Sodora DL AIDS 2009). A large number of scientific evidence clearly shows that HIV infection is associated with high frequencies of numerous immune cell types, including CD4 and CD8 T cells, B cells, NK cells, and monocytes, that express markers of activation, proliferation, and apoptosis (reviewed in Sodora et al., 2008).

The strong association between immune activation and AIDS pathogenesis is well documented. A large 2006 study that took place over 20 years probing 2,801 treatment naïve HIV-1 infected patients concluded that only a small percent of CD4 loss variability could be attributed to HIV-1 RNA plasma viral loads, suggesting other factors, mainly immune activation, were likely responsible for CD4 T cell decline (Rodríguez et al., 2006). CD4 T cell recovery during antiretroviral treatment is mitigated when there are higher frequencies of CD4 and CD8 CD38+HLA-DR+ T cells (Hunt et al., 2003). Naïve CD8 T cells defined by

CD45RA and CD62L expression are lost in parallel with CD4 T cells, regardless of the stage of disease progression and despite rises in total numbers of CD8 T cells (M Roederer et al., 1995). Low levels of CD69, an early marker of activation, and increased T regulatory cells have been associated with HIV-resistant individuals (Card et al., 2009), along with low levels of HLA-DR+CD38+ CD4 T cells and Ki-67+ CD4 and CD8 T cells (Koning et al., 2005). Upon stimulation, activation markers CD80, CD86 and CD70 are increased in HIV infected patients (Wolthers et al., 1996). Other soluble activation markers have also been found in serum and plasma to be increased in HIV infected patients including beta$_2$-microglobulin (Grieco et al., 1984), IL-2 receptor (Sethi & Näher, 1986; Pizzolo et al., 1987), tumor necrosis factor (Reddy, Sorrell, Lange, & Grieco, 1988) tumor necrosis factor receptor II (Fahey et al., 1998) and others.

A recurrent trend in research focusing on immune activation is the consistent importance of CD38 as a marker of disease prognosis. CD38, otherwise known as cyclic ADP ribose hydrolase, is an ectoenzyme transmembrane glycoprotein that correlates with other cell activation markers and is associated with enhanced cell to cell adhesion, cytokine production and T-cell activation (Deeks et al., 2004). According to a Giorgi et al. study referenced over 330 times (ISI Web of Knowledge^{SM}), CD4 and CD8 T cell expression of CD38 is increased in clinically defined AIDS patients who survived less than 6 months versus those who survived greater than 18 months (J V Giorgi et al., 1999; Sandler et al., 2011). While the level of HIV RNA is a good predictor of disease progression early in infection, and CD4 T cell count is as good if not better later in infection, CD38 levels on CD8 T cells is a good early and late predictor (Janis V Giorgi et al., 2002). Activated CD8+CD38+CD45RO+ T cells predict CD4 T cell decline (Bofill et al., 1996), though CD8+HLA-DR+ cannot (J V Giorgi et al., 1993). An activation set-point measured by CD38 expression on CD4 and especially CD8 T cells arises early in infection and is relatively stable and able to predict subsequent CD4 T cell decline even without considering viral load (Deeks et al., 2004). Also, increased HLADR+CD38+ T cells in elite controllers with low plasma virus loads is associated with decreased CD4 counts (Hunt et al., 2008), in tune with the idea that T cell activation promotes HIV disease progression (Fahey et al., 1998).

Soluble markers of immune activation, that are more easily measurable than cellular activation, have also been shown to have prognostic value and predict HIV disease progression with comparable efficiency to CD4 counts and viral load measurements (Liu et al., 1997). In particular, neopterin, produced by macrophages upon IFNg stimulation (Melmed, Taylor, Detels, Bozorgmehri, & Fahey, 1989), beta$_2$-microglobulin for general lymphoid activation (Chitra, Bakthavatsalam, & Palvannan, 2011; Fahey et al., 1990), and soluble IL-2 receptor (Sethi & Näher, 1986) have all been shown to be elevated and predictive of disease progression to varying degrees (Fahey et al., 1998). Increased soluble CD14 levels, a marker of monocyte activation that also correlated with IL-6, C-reactive protein, serum amyloid A and D-dimer, independently predicts mortality in HIV patients (Sandler et al., 2011).

In summary, the HIV-associated immune activation (i) is characterized by high frequencies of numerous immune cell types expressing markers of activation, proliferation, and apoptosis; (ii) predicts the tempo of progression to AIDS independently from, and more accurately than viral load; (iii) strongly correlates with the efficacy of antiretroviral therapy (ART) in reconstituting the immune system of HIV-infected individuals. Although the benefits of being able to predict or modify the course of disease during acute HIV infection

would likely be substantial, the value of immune activation biomarkers has largely been detected during chronic HIV infection due to the obvious constraints of human studies.

3.2 Causes and consequence of HIV-associated chronic immune activation

The causes of the chronic immune activation and subsequent immunopathogenesis in HIV infected patients is unsettled. Whether or not immunopathogenesis is mainly caused by the virus or the immune response to the virus has been the object of a long scientific debate. While some have focused on the virus and its direct cytophathicity by claiming "it's the virus stupid" (Cohen, 1993), others counterclaimed, "it's the immune system, stupid" (STEP perspective, 1999; Smith, 2006). Further studies in humans, natural hosts of SIV, rhesus macaque models of progressive infection and even mice models of immune activation have helped to clarify that the cause of HIV pathogenesis is multifactorial, with both viral and host factors contributing to progression to AIDS. Moreover, many arms of the immune system aside from infected CD4 T cells are dysregulated.

A particularly salient example of how immune activation alone damages the immune system comes from a transgenic mouse model of chronic immune activation triggered by CD27-CD70 costimulation. The mice showed uncanny familiarity with HIV disease without a virus present, with constant costimulation and TCR antigen stimulation leading to thymic involution, T cell turnover, loss of naïve T cell populations, and progressive inability of T cells to respond ex vivo upon stimulation (Tesselaar et al., 2003).

Possible explanations for HIV-associated chronic immune activation is a long list: gut damage and microbial translocation (Brenchley, Price, & Douek, 2006b), loss of T helper 17 (Th17) cells (Brenchley et al., 2008), loss of regulatory T cells (Hunt et al., 2011, Card et al., 2009), expansion and exhaustion of HIV-specific T cells (Khaitan & Unutmaz, 2011) decreased lymphopoiesis and increased depletion of central memory CD4 T cells (T_{CM}), both resulting in increases in homeostatic proliferation (Brenchley et al., 2010; Okoye et al., 2007; M Paiardini et al., 2009a; Picker et al., 2004; Sauce et al., 2011) and latent or newly acquired infections due to general immunodeficiency (Ford, Puronen, & Sereti, 2009).

In particular, special emphasis has been recently placed on the role played by the complex dysfunction of the mucosal immune system typical of pathogenic HIV and SIV infections in humans and rhesus macaques. The HIV-associated mucosal immune dysfunction is characterized by the loss of integrity of the mucosal barrier and the translocation of microbial products from the intestinal lumen into systemic circulation. Alexander and collaborators defined microbial translocation as "passage of both viable and nonviable microbes and microbial products, such as endotoxin across the intestinal barrier." They show that microbial translocation of microbes and microbial products occurred because of alterations in mucosal balance (Alexander et al., 1990).

Numerous evidences demonstrated the translocation of bacteria and bacterial products into the bloodstream in pathogenic HIV and SIV infections. Lipopolysacharides (LPS), which is excreted from gram-negative bacteria and act as an endotoxin, is one of the bacterial products that is translocated into the bloodstream and can therefore be used as an indicator of microbial translocation. Circulating LPS levels were increased in chronically HIV-infected individuals and SIV-infected rhesus macaques during the chronic phase of the disease, and LPS levels were associated with increased levels of soluble CD14, a marker of monocyte response to LPS (Brenchley, Price, Schacker, Asher, et al., 2006a). Of note, a recent case-control study demonstrated that soluble CD14 is an independent predictor of mortality in

HIV infection, with individuals falling in the highest quartile of sCD14 levels having a 6-fold higher risk of death than those in the lowest quartile, even after adjusting for inflammatory markers, CD4 T cell count, and HIV RNA level (Sandler et al., 2011). Moreover, another study demonstrated that microbial translocation was detected by the presence of 16S ribosomal DNA in 95% of untreated HIV-infected patients observed (Jiang et al., 2009). Interestingly, plasma LPS levels were found to be higher with drug abuse, or co-infection with hepatitis-c virus (HCV) (Ancuta et al., 2008).

Due to the immediacy of these events, and the fact that translocating products are bioactive in vivo, the gut breakdown and associated microbial translocation cascade has been thought to stoke the fire of, or at least contribute to, the establishment of high levels of innate and adaptive immune activation (Brenchley, Price, & Douek, 2006b; Douek et al., 2009). Evidence supporting this model comes from the fact that plasma levels of LPS are significantly increased, and correlate with the level of systemic immune activation in chronically HIV infected individuals and SIV infected rhesus macaques. Even uninfected CD4 T cells in the gut dive to extremely low numbers after just weeks of infection, as bacterial products rise in the blood of HIV infected patients. In a more recent study, Nowroozalizadeh and collaborators found elevated levels of plasma LPS in both individuals infected with HIV type 1 and HIV type 2. Furthermore, they showed that the severity of microbial translocation correlates with CD4 T cell count and viral load independently of HIV type, as well as with defective innate and mitogen responsiveness (Nowroozalizadeh et al., 2010).

Due to its broad impacts on several cell types of the innate and adaptive immune response, HIV-associated immune activation may damage the immune system in many different ways. Depletion of CD4 T cells in the gut and peripheral blood in the acute phase and beyond leads to vacancies in the T cell receptor repertoire that threatens immune resources normally in reserve to fight new, latent or mutating infections (Simons et al., 2008). Certain CD4 T cell specificities are preferentially lost. For instance, CD4 T cells specific for *Mycobacterium tuberculosis* (MTB) are lost quickly compared to those for CMV, likely due to lower expression of CCR5 ligand MIP-1b on MTB specific CD4 T cells (Geldmacher et al., 2010). Cytokines and other soluble factors (as described in the section about activation markers) are at dangerously abnormal levels. Th17, an IL-17 producing CD4 T cell subset critical for mucosal immunity are preferentially depleted (Brenchley et al., 2008). B cell dysfunction is also pronounced as HIV impacts activation states, hypergammaglobulinemia, exhaustion, and impaired antibody production against vaccination and infections (reviewed in Shen & Tomaras, 2011).

In spite of the large number of immune abnormalities that have been described, there are still unanswered questions about the exact mechanisms by which this virus causes progressive disease, possibly because so many constituents are impacted.

4. Depletion of Th17 cells and loss of mucosal barrier integrity

An important mechanism that appears to link loss of mucosal barrier integrity, microbial translocation and the establishment of immune activation is the preferential depletion of Th17 cells, a recently identified CD4 T cell subset that produce IL-17 and IL-22 and play a critical role in antimicrobial mucosal immunity. In particular, IL-17 and IL-22 (i) induce epithelial cells to express cytokines (i.e., IL-6 and GM-CSF), chemokines (i.e., IL-8, CXCL1, CXCL10, and CCL20) and metalloproteinases critical for the recruitment, activation and

migration of neutrophils to areas of bacterial infection; (ii) promote the production of antimicrobial molecules, such as defensins; and (iii) regulate the integrity of the epithelial barrier by stimulating the proliferation and survival of GI enterocyte and the transcription of tight junction proteins (Aujla et al., 2008; Dandekar, George, & Bäumler, 2010; Guglani & Khader, 2010; Liang et al., 2006; Milner, Sandler, & Douek, 2010; Ouyang & Valdez, 2008; Romagnani, 2008; Zheng et al., 2008). Consistent with their important role in antimicrobial immunity, Th17 cells confer protection against several extracellular pathogens, such as *Candida albicans*, *Klebsiella pneumoniae*, *Citrobacter rodentium*, *Mycobacteria tuberculosis*, *Staphylococcus aureus*, *Bacteroides fragilis*, *Escherichia coli* (Huang, Na, Fidel, & Schwarzenberger, 2004; Khader et al., 2007; Ouyang & Valdez, 2008). Given the role of Th17 cells in mucosal immunity, and the observed mucosal immune dysfunction associated with HIV infection, we and others investigated the homeostasis of Th17 during pathogenic lentiviral infection, showing that Th17 cells are preferentially depleted in the gastrointestinal tracts of HIV-infected humans and SIV-infected macaques (Brenchley et al., 2008; Cecchinato et al., 2008; d'Ettorre, Mirko Paiardini, Ceccarelli, Silvestri, & Vullo, 2011; Favre et al., 2009; Gordon et al., 2010; Raffatellu et al., 2008). Moreover, Raffatellu and colleagues showed that in healthy SIV-negative rhesus macaques, the gene expression profile induced by S. typhimurium in ileal loops is dominated by Th17 responses, including the expression of IL-17 and IL-22; and severe depletion of mucosal Th17 cells in SIV-infected rhesus macaques resulted in an impaired mucosal barrier function and increased S. *typhimurium* dissemination (Raffatellu et al., 2008). Furthermore, loss of mucosal Th17 cells has been associated with increased systemic immune activation and disease progression in both HIV-infected humans and SIV-infected rhesus macaques (Cecchinato et al., 2008; Gordon et al., 2010; Hartigan-O'connor, Hirao, McCune, & Dandekar, 2011). Consistent with the model linking depletion of Th17 cells with compromised antimicrobial immunity, it has been shown that patients with dominant negative stat3 gene mutations, common in hyperimmunoglobulin E syndrome or the more biblical Job's syndrome, in which CD4 T cells are unable to differentiate into Th17 cells, are exquisitely susceptible to bacterial infections (Milner et al., 2008).

Collectively, these studies demonstrate that pathogenic HIV and SIV infections are associated with a preferential and sustained depletion of mucosal Th17 cells, the severity of which correlates with the structural and immunological maintenance of the mucosal barrier, the levels of immune activation, and progression to AIDS. These observations further elucidate the immunodeficiency of HIV disease and provide a mechanistic basis for the mucosal barrier breakdown that characterizes HIV infection.

5. Immunology of natural hosts for SIV

5.1 Absence of chronic immune activation

A very large body of evidence clearly demonstrated that, in sharp contrast with all the known models of pathogenic HIV infection, nonpathogenic SIV infection of natural hosts is characterized by the absence of high levels of chronic immune activation, assessed as the fraction of cells expressing markers of activation and proliferation, in the context of continuous virus replication (figure 3) (Mirko Paiardini et al., 2009b; Silvestri et al., 2003; Silvestri, Mirko Paiardini, I. Pandrea, Lederman, & Sodora, 2007). Consistent with their lower levels of immune activation, infected sooty mangabeys show no increase in lymphocyte apoptosis, lymph node structural damage, thymic involution, or loss of naïve T cell populations—all of

which are normally attributed to chronic immune activation (Silvestri et al., 2003). Furthermore, naturally SIV-infected sooty mangabeys preserve the ability to properly regulate cell cycle progression when compared to SIV-infected macaques (Paiardini M JV 2006).

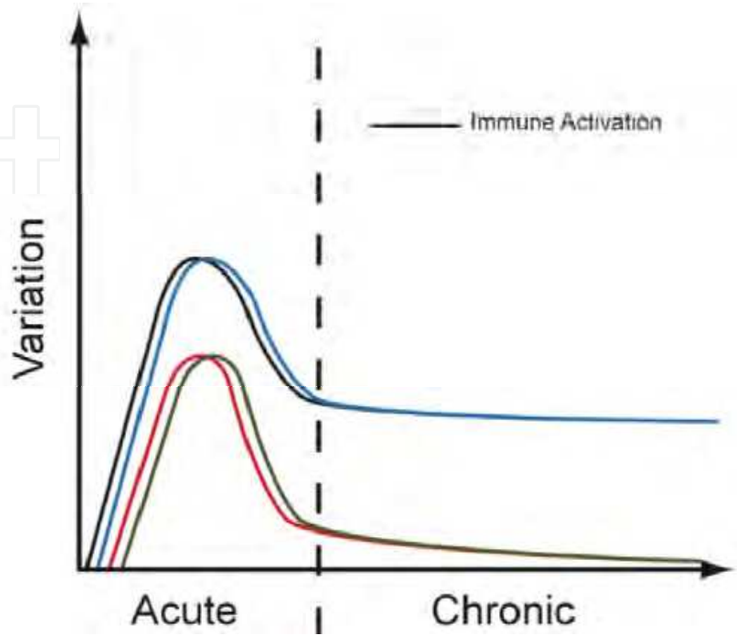

Fig. 3. Immune activation in natural and nonnatural hosts.
In contrast to pathogenic HIV/SIV infection (humans —— , rhesus macaques ——), nonpathogenic SIV infection in natural hosts (sooty mangabeys —— and African green monkeys ——) is associated with the resolution of immune activation during chronic infection. Originally published in *Blood* Online. Brenchley JM & Paiardini M. Immunodeficiency lentiviral infections in natural and nonnatural hosts. *Blood*. Prepublished April 19, 2011; DOI:10.1182/blood-2010-12-325936.

Interestingly, the consistently low levels of chronic immune activation in natural hosts does not result from intrinsically attenuated innate immune responses, but rather from active immuno-regulatory mechanisms that allow these animals to tune-down the immune response during the transition from the acute to the chronic phase of infection (figure 3). The initial studies of natural SIV infections were performed during chronic infection and were not able to inform early events. Indeed, more recent studies designed to characterize the acute phase of SIV infection consistently show that, as described for progressive infection, nonprogressive SIV infection is also associated with an early increase in T cell proliferation and activation (Gordon et al., 2007; Kornfeld et al., 2005; I. V. Pandrea et al., 2007b; Silvestri et al., 2005). This phenotype is very common among several natural hosts, even those less characterized than sooty mangabeys and African green monkeys. For instance, transient levels of immune activation have been described in Mandrills, in which CD4 and CD8 HLA-DR+ cells at first increase but then return to normal levels by day 60 post-infection (Onanga et al., 2006), as well as in Caribbean African green monkeys, which show a rapid increase in CD8 HLA-DR+ T cells and then a rapid return to baseline 2-3 weeks post-infection, while having no changes in CD4 HLA-DR+ T cell frequencies (Kornfeld et al., 2005; I. Pandrea et al., 2006). Furthermore, the rapid resolution of acute immune activation has also been shown at a genetic level in sooty

mangabeys and African green monkeys from microarray data of early infection revealing that interferon stimulated genes are upregulated early in both natural and nonnatural hosts. Only natural hosts reduce their expression in blood and lymph nodes to near pre-infection levels in the acute to chronic phase transition (4-6 weeks), while macaques fail to resolve their early interferon stimulated gene response (Bosinger et al., 2009; Jacquelin et al., 2009; Lederer et al., 2009). Finally, immunohistochemical and immunofluorescent analyses recently demonstrated a robust IFN-α response in the lymph nodes of sooty mangabeys, African green monkeys, and rhesus macaques in the acute phase of SIV infection, which is later resolved only in mangabeys and African green monkeys (L. D. Harris, Tabb, et al., 2010b).

The finding that naturally SIV-infected sooty mangabeys do not experience elevated levels of chronic immune activation in the context of high levels of viral replication further confirms the association between chronic immune activation and disease progression, and highlights the clinical importance of defining the mechanisms accounting for the establishment of high levels of chronic activation, or lack thereof, in pathogenic and nonpathogenic lentiviral infections.

5.2 Preservation of Th17 cells and mucosal integrity

Homeostasis of mucosal Th17 cells is a feature that distinguishes pathogenic HIV/SIV infections of humans and rhesus macaques, where these cells are preferentially depleted, from nonprogressive SIV infection of sooty mangabeys and African green monkeys, wherein Th17 cells are preserved at healthy frequencies (Brenchley et al., 2008; Cecchinato et al., 2008; Favre et al., 2009; Hartigan-O'connor et al., 2011; Mirko Paiardini, 2010; Raffatellu et al., 2008).

As previously described, studies in natural hosts demonstrated that a significant depletion of mucosal CD4 T cells alone is not sufficient to cause AIDS (Gordon et al., 2007; I. V. Pandrea et al., 2007b), suggesting that preservation of a specific CD4 T cell subset may allow the maintenance of mucosal integrity in the context of generalized CD4 T cell depletion. An increasing number of experimental evidence suggests that Th17 cells represent this specific subset. Indeed, Th17 cells are depleted in all the known models of pathogenic HIV/SIV infection, and preserved in all the known models of nonprogressive HIV/SIV infection including natural hosts for SIV, human long-term non-progressors and rhesus macaque elite controllers (Brenchley et al., 2008; Cecchinato et al., 2008; Favre et al., 2009; Mirko Paiardini, 2010). Specifically, we showed that whereas human Th17 cells are preferentially diminished compared to IFNg secreting Th1 cells in the gastrointestinal tracts of HIV-infected people, sooty mangabey Th17 cells are maintained in blood and the gastrointestinal tract (Brenchley et al., 2008). Likewise, while pigtailed macaques lose most IL-17 producing CD4 T cells by day 10 post-infection, African green monkeys show no decline (Favre et al., 2009). Intriguingly, in nonprogressive infections of sooty mangabeys and African green monkeys preservation of healthy frequencies of Th17 cells is associated with maintenance of mucosal immunity, absence of microbial translocation and low levels of chronic immune activation (figure 4) (Brenchley, Price, Schacker, Asher, et al., 2006a). Finally, Th17 cells were measured in human long-term non-progressors (n=14) and were found to be at levels equivalent to uninfected controls and those successfully (i.e., viral loads <50 copies/mL) treated with antiretroviral therapy in the colon and peripheral blood (Ciccone et al., 2011).

To understand how natural hosts preserve Th17 cells and mucosal immunity might be central to the development of therapeutic interventions aimed at improving mucosal immunity in HIV-infected individuals. While the exact cause accounting for this phenotype

is still unclear, several non-mutually exclusive mechanisms have been proposed, including the increased susceptibility to HIV/SIV infection of Th17 cells and its CD4+CCR6+ and CD4+CD161+ T cell precursors (Gosselin et al., 2010; Kader et al., 2009; Monteiro et al., 2011; Prendergast et al., 2010) and the defective generation of Th17 cells in nonnatural versus natural hosts. Very recent and unpublished observations suggest that loss of CD4+IL-21+ T cells and CD103+ dendritic cells, with reduced availability of IL-21 or retinoic acid, respectively, may significantly contribute to Th17 cell depletion in SIV-infected rhesus macaques (Cervasi B et al, CROI 2011; Klatt N et al, Keystone 2011). Consistent with their important role in Th17 cell homeostasis, CD4+IL-21+ T cells and CD103+ dendritic cells are preserved in SIV-infected SM (Cervasi B et al, CROI 2011; Klatt N et al, Keystone 2011).
Collectively, these data indicate that by preserving the balance of IL-17 and IL-22 producing Th17 cells, natural hosts for SIV maintain mucosal barrier integrity and avoid the establishment of aberrant immune activation (figure 4). As such, the data suggest that differential regulation of Th17 cell homeostasis may be central in determining the pathogenic or nonpathogenic outcome of HIV and SIV infections in primates.

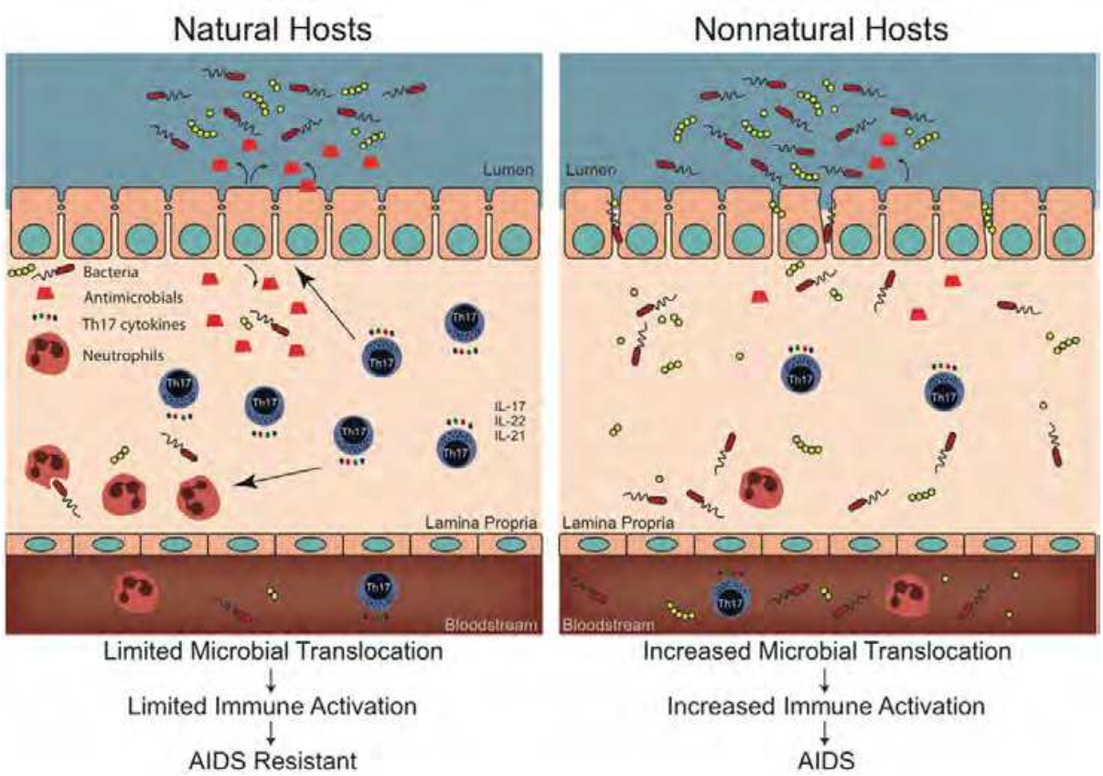

Fig. 4. Th17 cell homeostasis and mucosal immunity in natural and nonnatural hosts. Mucosal Th17 cells are preferentially depleted in nonnatural hosts (humans and RM) but preserved at healthy frequencies in natural hosts (sooty mangabeys and African green monkeys) for lentiviral infections. Th17 cells regulate antimicrobial immunity, i.e. recruiting neutrophils, maintaining tight junction integrity and stimulating antimicrobial molecule production. As such, the preservation of Th17 cells is one of the key factors limiting microbial translocation and chronic immune activation, thus contributing to the ability of natural hosts to remain AIDS-free. Adapted from (Mirko Paiardini, 2010).

5.3 Preservation of bone marrow based T cell renewal

As stated earlier, the mechanisms leading to CD4 T cell loss in HIV infection are multifactorial and still not completely defined. In addition to direct viral infection and bystander cell death, evidence has exhibited that insufficient T cell reconstitution may play a key role. Within the bone marrow, a major site of hematopoiesis and T cell proliferation, a suppression of function common in HIV-infected humans is associated with AIDS related neutropenia, thrombocytopenia and lymphopenia (Bain, 1997; Isgrò et al., 2005; Moses, Nelson, & Bagby, 1998; Silvestri et al., 2003).

Our group recently aimed to address the hypothesis that the preservation of bone marrow based proliferation and regeneration of T cells could be an important factor in regulating CD4 T cell homeostasis in progressive and nonprogressive lentiviral infections. To test this hypothesis, we utilized carboxyfluorescein diacetate succinimidyl ester (CFSE) labeling during in vitro stimulations, along with flow-cytometric intracellular measurements of the cell cycle marker Ki-67, to measure proliferation in sooty mangabeys and rhesus macaques; these assessments were performed also in the experimental setting of in vivo antibody-mediated CD4 or CD8 lymphocyte depletion (M Paiardini et al., 2009a). We discovered that SIV positive rhesus macaques have diminished proliferative capacity in bone marrow CD4 and CD8 T cells, while SIV positive SM had no decline compared to uninfected monkeys. Intriguingly, the rare subset of SIV-infected SM with low CD4 T cell count showed significantly lower levels of bone marrow proliferation when compared to SM that preserve the homeostasis of the CD4 T cell compartment (M Paiardini et al., 2009a). In addition, we found a correlation between Ki-67+ CD4 T cells and CD4 T cell count in the bone marrow but not in the peripheral blood (figure 5)(M Paiardini et al., 2009a).

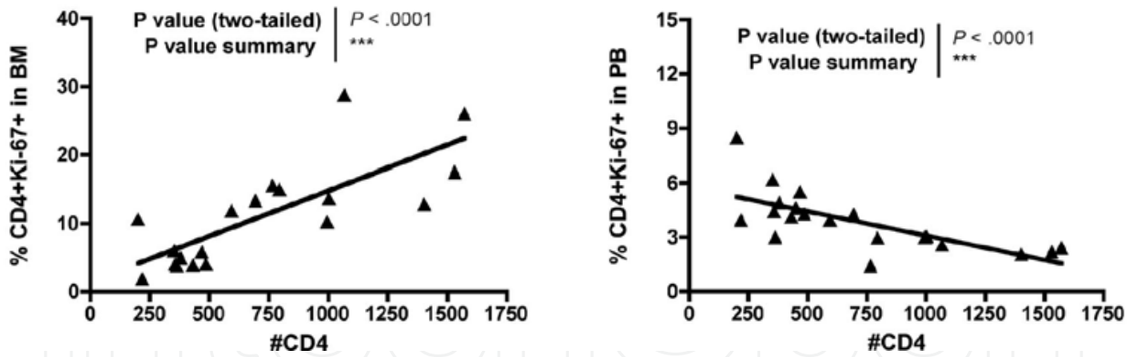

Fig. 5. Bone Marrow based CD4 T cell proliferation in sooty mangabeys.
In SIV-infected SM, blood CD4 T cell count correlates directly with the percentage of proliferating CD4 T cells in the bone marrow (BM, left panel) and inversely with the percentage of proliferating CD4 T cells in the peripheral blood (PB, right panel). This research was originally published in *Blood*. Paiardini M, *Blood*. 2009; *113*(3), 612-621.
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These findings suggest that the bone marrow is a major site of T cell proliferation in nonhuman primates, and the ability of SIV-infected sooty mangabeys to preserve the bone marrow based CD4 T cell proliferation is important for maintaining the homeostasis of the CD4 T cell compartment and avoiding progression to AIDS.

5.4 Lower expression of CCR5 on CD4 T cells

Another feature distinguishing natural and nonnatural hosts for lentiviral infections is the expression of CCR5, the main co-receptor used by HIV and SIV in vivo, to enter CD4 T cells. A comparative, cross sectional analysis of CCR5 expression in blood, lymph nodes and rectal biopsies obtained from several natural (sooty mangabeys, African green monkeys, and others) and nonnatural (human, rhesus macaques, and others) primate host species demonstrated that natural hosts for SIV infection consistently show a paucity of CD4 T cells expressing CCR5 (I. Pandrea et al., 2007a). This lower fraction of CD4 T cells expressing CCR5 was confirmed in both infected and uninfected animals, and in all sampled tissues, including those representing the major sites of viral replication (mucosa and lymph node) and CD4 T cell depletion (mucosa) during pathogenic HIV/SIV infection. Moreover, a five year longitudinal study of SIV-infected and uninfected sooty mangabeys showed stable median fractions (between 2-4%) of CD4 T cells expressing CCR5, independent of SIV (Taaffe et al., 2010). While this observation is very consistent and clear, its interpretation has been difficult, since naturally SIV-infected sooty mangabeys show levels of virus replication comparable to those of pathogenic infections. In an ongoing effort to better understand the pathophysiologic role of this decreased fraction of CCR5+ CD4 T cells in sooty mangabeys, we recently compared the levels and kinetics of CCR5 expression in sooty mangabey and rhesus macaque CD4 T cells, as well as the phenotype in their naïve, central memory, and effector memory subsets, following in vitro and in vivo activation. By doing this, we found CD4 T cells from sooty mangabeys failed to up-regulate CCR5 as do rhesus macaques in spite of activation and proliferation found to be equal in both species upon stimulation in vitro. Intriguingly, this phenomenon was more evident in CD4 T cells with a central-memory phenotype (T_{CM}), and associated with a markedly reduced susceptibility of these cells to SIV infection. Since recent findings indicated the depletion of CD4 T_{CM} cells as a critical step in the loss of CD4 T cell homeostasis and disease progression in SIV-infected rhesus macaques (Okoye et al., 2007; Picker et al., 2004), our recent data suggests that partial protection of CD4 T_{CM} cells from SIV infection is one mechanism contributing to maintenance of a healthy immune system and avoidance of progression to AIDS in SIV-infected sooty mangabeys (Paiardini et al., 2011).

6. How natural hosts may inform the design of novel vaccine and therapeutic approaches for HIV-infected humans

The pathogenesis of HIV infection results from a complex interaction between virus and host. Studies aimed at characterizing the virus-host interactions in natural hosts have led to important findings for understanding HIV pathogenesis in humans and, even more important, have many implications for new therapies and vaccines, giving us the opportunity to stop disease progression by understanding what nature has already discovered over millennia (Sodora et al., 2009). Table 2, along with the section above, summarizes several therapeutic approaches that could attempt to mimic the critical features of nonpathogenic infection in sooty mangabeys, which could be beneficial if included in the clinical management of HIV-infected humans.

1. *Targeting chronic immune activation to slow disease progression*. Considering that chronic immune activation is a key player in HIV pathogenesis, being associated with CD4 T cell depletion and the overall functionality of the immune system, and it

is absent in nonprogressive SIV infection of natural hosts, there is a strong rationale for introducing immune suppressive molecules in the treatment of HIV-infected individuals. In this context, it is important to note that in HIV-infected humans chronic immune activation is not fully resolved even in the setting of successful antiretroviral therapy (ART), and that this residual immune activation is considered the major cause for the increased "non-AIDS" morbidity and mortality observed in individuals undergoing long-term ART (Grund, Neuhaus, Phillips, INSIGHT SMART Study Group, 2009). Since the exact mechanisms and signaling pathways responsible for chronic immune activation in HIV-infected humans are still unclear, approaches have mostly focused on using drugs with a generic immune suppressive ability, such as Cyclosporin, Rapamycin, and Hydroxychloroquine, already in use for individuals with autoimmune disorders or recipients of transplants. Hydroxychloroquine, an antimalarial drug also used to reduce inflammation in rheumatoid arthritis and lupus, has already been shown to reduce the expression of the immune activation markers CD38, Ki-67 and HLA-DR on CD8 T-cells and to decrease viral loads in HIV infected patients (Murray et al., 2010, Sperber et al., 1995).

2. *Preserving Th17 cell homeostasis by increasing their differentiation and survival*. IL-21, a multifunctional cytokine that initiates the induction of Th17 cells (Korn et al., 2007; Nurieva et al., 2007; Yang et al., 2008) could be used to test the hypothesis that increased levels of Th17 cells will sure up gut permeability, thus preventing continuous microbial translocation and immune activation. The rationale for using this cytokine comes from several findings, including the following: (i) plasma levels of IL-21 are significantly decreased in HIV infected patients (Iannello et al., 2008); (ii) CD8 T cells producing IL-21 are increased in elite controllers, (Williams et al. 2011); (iii) circulating CD4 T cells expressing IL-21 are severely lost in pathogenic SIV infection of rhesus macaques, with the extent of this depletion being associated with that of Th17 cells (Cervasi B, CROI 2011),; (iv) CD4 T cells producing IL-21 are preserved at healthy frequencies in SIV-infected sooty mangabeys (Cervasi B, CROI 2011) ; (v) finally, IL-21 is already in clinical trials for the use against renal cell carcinoma and melanoma (Hashmi & Van Veldhuizen, 2010).
3. *Targeting of CCR5 expression*. Specifically targeting expression of CCR5 and other co-receptors for HIV may be critical in preventing AIDS. A unique bone marrow transplantation demonstrated the attainability of an HIV cure, despite the unusual and unrepeatable events that led to that cure: harsh chemotherapy, total body irradiation and an unlikely hematopoietic stem cell transplantation match of a homozygous CCR5Δ32 donor (Hütter, Nowak, Mossner, Ganepola, et al., 2009a). This case report of one patient has justifiably led to excitement about future therapies using CCR5Δ32 donors as well as other entry blocking strategies in HIV infection (Hütter, Thomas Schneider, & Thiel, 2009b). Other less strenuous methods to target CCR5 have been made possible by zinc finger nuclease-mediated gene disruption, maraviroc, small interfering RNA molecules, and a number of new molecular nanotechnologies (reviewed in Cannon & June, 2011). Data obtained in sooty mangabeys suggest that these treatments may be significantly enhanced upon targeting of CCR5 expression on CD4 T_{CM} cells specifically.

Feature of HIV or SIV infections	Natural hosts	Nonnatural hosts	Possible therapeutic intervention
Chronic immune activation	No	Yes	Immune modulators of activation
Progressive loss of peripheral CD4 T cells	No	Yes	CD4 T cell renewal strategies; IL-7 and other homeostatic cytokines
Mucosal Th17 cells	Preserved	Lost	Increase Th17 cell differentiation; IL-21 and other Th17-driving factors
Frequency of CD4+CCR5+ T cells	Very low	Normal	CCR5 blockade
Mucosal integrity	Preserved	Lost	Sure up mucosal boundaries

Table 2. Critical features distinguishing pathogenic from non nonpathogenic SIV infection in nonnatural and natural hosts, respectively. The last column includes general targets for intervention derived from studying natural hosts. These approaches mimic critical features of nonprogressive lentiviral infection and could improve the clinical management of HIV-infected humans.

7. Final remarks

We firmly believe that a comprehensive elucidation of how natural hosts for SIV have co-evolved to avoid disease progression is critical for understanding the mechanisms of AIDS pathogenesis in HIV-infected humans. The elucidation of these mechanisms may translate into major advances in prevention and therapy of HIV infection and AIDS.

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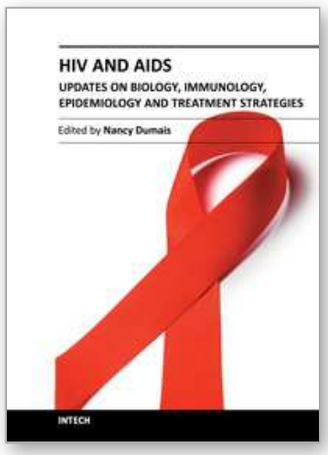

HIV and AIDS - Updates on Biology, Immunology, Epidemiology and Treatment Strategies
Edited by Dr. Nancy Dumais

ISBN 978-953-307-665-2
Hard cover, 694 pages
Publisher InTech
Published online 26, October, 2011
Published in print edition October, 2011

The continuing AIDS pandemic reminds us that despite the unrelenting quest for knowledge since the early 1980s, we have much to learn about HIV and AIDS. This terrible syndrome represents one of the greatest challenges for science and medicine. The purpose of this book is to aid clinicians, provide a source of inspiration for researchers, and serve as a guide for graduate students in their continued search for a cure of HIV. The first part of this book, â€œFrom the laboratory to the clinic,â€ and the second part, â€œFrom the clinic to the patients,â€ represent the unique but intertwined mission of this work: to provide basic and clinical knowledge on HIV/AIDS.

How to reference
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Zachary Ende, Michelle Bonkosky and Mirko Paiardini (2011). HIV Without AIDS: The Immunological Secrets of Natural Hosts, HIV and AIDS - Updates on Biology, Immunology, Epidemiology and Treatment Strategies, Dr. Nancy Dumais (Ed.), ISBN: 978-953-307-665-2, InTech, Available from: http://www.intechopen.com/books/hiv-and-aids-updates-on-biology-immunology-epidemiology-and-treatment-strategies/hiv-without-aids-the-immunological-secrets-of-natural-hosts

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