Nonpathogenic Simian Immunodeficiency Virus Infections

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The simian immunodeficiency viruses (SIVs) are a diverse group of viruses that naturally infect a wide range of African primates, including African green monkeys (AGMs) and sooty mangabey monkeys (SMs). Although natural infection is widespread in feral populations of AGMs and SMs, this infection generally does not result in immunodeficiency. However, experimental inoculation of Asian macaques results in an immunodeficiency syndrome remarkably similar to human AIDS. Thus, natural nonprogressive SIV infections appear to represent an evolutionary adaptation between these animals and their primate lentiviruses. Curiously, these animals maintain robust virus replication but have evolved strategies to avoid disease progression. Adaptations observed in these primates include phenotypic changes to CD4⁺ T cells, limited chronic immune activation, and altered mucosal immunity. It is probable that these animals have achieved a unique balance between T-cell renewal and proliferation and loss through activation-induced apoptosis, and virus-induced cell death. A clearer understanding of the mechanisms underlying the lack of disease progression in natural hosts for SIV infection should therefore yield insights into the pathogenesis of AIDS and may inform vaccine design.

The simian immunodeficiency viruses (SIVs) are a genetically diverse group of viruses that naturally infect a wide range of African nonhuman primates and are the source of the human immunodeficiency viruses (HIV-1 and HIV-2). The origins of HIV-1 and HIV-2, as well as the SIVcpz and SIVgor strains, are discussed in greater detail in Sharp and Hahn (2011). SIVs first came to the attention of AIDS researchers with the occurrence of immunodeficiency in macaques in the California, New England, and Washington primate centers

(Apetrei et al. 2005). Almost simultaneously, transfer of tissues from sooty mangabeys to macaques resulted in a similar disease at the Tulane Primate Center (Murphey-Corb et al. 1986). The virus isolated from these macaques originated from sooty mangabey monkeys, either by experimental infection at Tulane or through cohousing of African and Asian monkeys earlier in the history of the primate centers (Apetrei et al. 2005). This event represented the birth of a new animal model for HIV infection based on the use of SIVmac and SIVsmm

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infection of rhesus macaques (Johnson and Hirsch 1992). Subsequent studies have determined that SIV infection of macaques, although more rapid than HIV infection in humans, is remarkably similar in terms of pathogenesis, and the model has been used extensively for vaccine development (Haigwood 2009). However, the use of the sooty mangabey–derived SIV as an experimental macaque model for AIDS is only a small aspect of the overall scientific interest in the SIV infection of natural African host species. First, these primate viruses are the source of the HIV-1 (cross-species transmission of SIVcpz) and HIV-2 (cross-species transmission of SIVsmm) epidemics in humans (Sharp and Hahn 2010). Second, these animals present a fascinating enigma: lack of progression to AIDS in the face of active viral replication (Hirsch 2004; Paiardini et al. 2009a; Pandrea and Apetrei 2010). It is hoped that the study of the mechanism(s) underlying their resistance to AIDS will help us understanding the pathogenesis of HIV in humans and to design vaccine and therapeutic strategies (Sodora et al. 2009). This article will focus on the natural hosts of SIVs and their viruses and the lessons they teach us about the pathogenesis of AIDS.

THE PRIMATE LENTIVIRUSES

Origins and Phylogeny of SIVs

There is a wide variety of SIVs in African non-human primates, although only a fraction of them have been molecularly characterized (see Table 1). To date, serological evidence of SIV infection has been reported in 36 different primate species, and partial or full-length viral sequences have been characterized from 30 of these (Apetrei et al. 2004). Primate lentiviruses have been detected in most of the African monkeys of the genus *Cercopithecus*, African green monkeys (*Chlorocebus*), mandrills and drills (*Mandrillus*), the mangabeys (*Cercocebus*), a variety of colobus monkeys (*Colobus*, *Ptilocolobus*), and within the great apes, two subspecies of chimpanzees (*Pan*) and gorillas (*Gorilla*) (Table 1). However, interestingly, infection of Asian monkeys such as macaques (genus

Macaca) and the Asian great apes, orangutans, has not been detected in the wild. This restriction of primate lentiviruses to African monkeys suggests that this is an ancient virus that has coevolved with its primate host. The observation of similar viruses in related species such as the multiple species of African green monkeys (AGMs) that are infected, despite geographic separation, suggests that the ancestor of the current day SIVs may date back to the time of phylogenetic divergence and geographical separation of African and Asian monkeys. A conservative estimate of the age of natural SIV infections based on the phylogeny of SIVs isolated from nonhuman primates at the Bioko island places these infections at least 32,000 years ago, although less conservative analysis suggests a much longer time (Worobey et al. 2010). In contrast, HIV-1 and HIV-2 infections of humans represent relatively recent introductions into human populations by cross-species transmission (Sharp and Hahn 2010).

As detailed in Table 1 and Figure 1, there are at least seven distinct lineages of primate lentiviruses: (1) SIVsm from sooty mangabeys (Hirsch et al. 1989), including HIV-2; (2) SIVagm from the four different species of AGMs (Allan et al. 1991; Hirsch 2004); (3) SIV from monkeys of the genus *Cercopithecus*, commonly called guenons (e.g., SIVgsn, SIVdeb, SIVmus) (Courgnaud et al. 2002, 2003); (4) SIVcpz from two species of chimpanzees (Keele et al. 2006) and SIVgor from gorillas; (5) SIVlho and SIVsun from the related L'Hoest and suntailed monkeys (Beer et al. 1999, 2000); (6) SIVcol from black and white colobus monkeys (Courgnaud et al. 2001); and (7) SIVrcm from red capped mangabeys (Beer et al. 2001) and SIVmnd and drl from mandrills and drill monkeys (Clewley et al. 1998; Hu et al. 2003). Each of the various lineages are approximately equidistant from any other lineage, sharing 40%–50% identity in the most conserved Gag and Pol proteins (Hirsch et al. 1995a). The phylogenetic relationship between many of these various SIVs, with distinct species-specific lineages, is shown in Figure 1. The primate lentiviruses all share a common genomic organization encoding the structural and enzymatic proteins Gag, Pol,

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Table 1. Natural host species harboring simian immunodeficiency viruses (SIVs)

Genus	Common name	Species	SIV
<i>Pan</i>	Chimpanzees	<i>troglodytes troglodytes</i> <i>troglodytes schweinfurthi</i>	SIVcpzPtt SIVcpzPts
<i>Gorilla</i>	Gorilla	<i>gorilla</i>	SIVgor
<i>Cercocebus</i>	Sooty mangabey	<i>atys</i>	SIVsmm
	Redcapped mangabey	<i>torquatus</i>	SIVrcm
<i>Mandrillus</i>	Mandrill	<i>sphinx</i>	SIVmnd-1, mnd-2
	Drill	<i>leucophaeus</i>	SIVdrl
<i>Miopithecus</i>	Talapoin	<i>talapoin</i>	SIVtal
<i>Colobus</i>	Black and white colobus	<i>guerza</i>	SIVcol
<i>Procolobus</i>	Olive colobus	<i>verus</i>	SIVolc
<i>Ptilocolobus</i>	Western red colobus	<i>badius</i>	SIVwrc
<i>Chlorocebus</i>	African green monkeys		
	Sabaeus	<i>sabaeus</i>	SIVagmSab
	Vervet	<i>pygerythrus</i>	SIVagmVer
	Tantalus	<i>tantalus</i>	SIVagmTan
	Grivet	<i>aethiops</i>	SIVagmGri
<i>Cercopithecus</i>	The guenons		
	Greater spot-nosed	<i>nictitans</i>	SIVgsn
	Blue monkey	<i>mitis</i>	SIVblu
	Mona monkey	<i>mona</i>	SIVmon
	Dents' monkey	<i>denti</i>	SIVden
	Moustached monkey	<i>cephus</i>	SIVmus
	Red-eared monkey	<i>erythrotis</i>	SIVery
	Redtailed monkey	<i>ascanius</i>	SIVasc
	DeBrazza	<i>neglectus</i>	SIVdeb
	Sykes monkey	<i>albogularis</i>	SIVsyk
	L'Hoests monkey	<i>l'hoesti</i>	SIVlho
	Suntailed monkey	<i>solatus</i>	SIVsun
	Preussis monkey	<i>preussi</i>	SIVpre

and Env but also a variety of accessory proteins. All SIV and HIV strains share open reading frames for *tat*, *rev*, *vif*, *vpr*, and *nef* genes. However, the *vpu* gene is unique to HIV-1, SIVcpz, and a variety of SIV strains from *Cercopithecus* monkeys including SIVgsn (greater spot nosed monkey) (Courgnaud et al. 2003), consistent with an ancestral relationship between these viruses. In contrast, the *vpx* gene is unique to SIVs from mangabeys, SIVsmm and SIVrcm; in these two viruses, some of the various functions of the *vpr* gene have been segregated to *vpx*. Recent studies suggest that some of the functions attributed to *vpu* gene were acquired by the *nef* or the *env* genes in viruses that lack *vpu* (Sauter et al. 2009) suggesting that they played a role in overcoming intrinsic host

restriction factors on cross-species transmission as discussed in Sharp and Hahn (2010).

This family of primate lentiviruses has also been the source of two separate epidemics in humans. HIV-1 arose from multiple cross-species transmissions events with HIV-1 Groups M and N arising from SIVcpzPtt and SIVcpzPts, and HIV-1 Group O from SIVgor (Fig. 1, red lines) (reviewed in Sharp and Hahn 2010). Similarly, SIVsmm (Hirsch et al. 1989) was the source of the HIV-2 epidemic in West Africa (Fig. 1, red lines). Although SIVs are generally not pathogenic in their natural host species, the infection of humans by these animals, and evolution as HIV-1 and -2, was associated with the acquisition of virulence.

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Figure 1. SIV and HIV lineages. Phylogenetic tree of a region of polymerase showing the relationship between the various primate lentiviruses. HIV strains are shown in red. The nonhuman primate natural hosts for are shown for each cluster. (Adapted from Peeters et al. 2008 and reprinted with permission from EDP Science © 2008.)

Epidemiology, Cross-Species Transmission, and Recombination

Serologic surveys and evaluation of bushmeat in Africa reveal that infection of nonhuman primates is widespread, although the prevalence may vary, depending on species and geographic location (Aghokeng et al. 2006, 2010). SIV infection has been detected in nearly all species of African nonhuman primates with the possible exception of one species of chimpanzee (*Pan troglodytes vellerosus*), baboons, and patas monkeys. In some species of monkeys, there is serological evidence of infection, but viruses have not yet been isolated or characterized. The prevalence of infection increases with age, with fairly uniform lack of infection in infants and juveniles suggesting that sexual routes as well as aggression may play a role in transmission. Furthermore, mother to infant transmission appears to be somewhat rare based on the lack of infection in infants and juveniles. This notion is also supported by studies of the colony

of sooty mangabeys housed at the Yerkes primate center, in which only ~5% of infants born to SIV-infected mothers appear to have contracted the infection vertically (Chahroudi et al. 2011). However, the route of transmission in wild populations has not been clearly defined.

SIVs generally appear to be species-specific, and with each species showing only one virus except for mandrills that are infected with two viruses (SIVmnd-1 and SIVmnd-2). This pattern is consistent with coevolution during the speciation and migration of the different primate species throughout Africa. For example, SIVagm strains are present within all species of AGM (vervet, grivet, tantalus, and sabaeus) throughout sub-Saharan Africa, but each of the species harbor a distinct, but related virus (70% identity). In at least two cases, the species of AGM have been geographically isolated from one another for thousands of years, ruling out contemporaneous spread of the virus (Muller and Barre-Sinoussi 2003; Hirsch 2004).

However, with more extensive characterization, the picture has become increasingly complex with evidence of multiple cross-species transmissions and recombination events. There is evidence for present-day natural transmission occurring in the wild, for example SIVagm infection of baboons and patas monkeys (Jin et al. 1994a; Bibollet-Ruche et al. 1996). However, there is also evidence of a long history of cross-species transmission, coinfections, and apparent recombination. Many of the SIV strains appear to be recombinant and often the parental strains are difficult to define because of genetic divergence from representative strains. The most notable recombinant is HIV-1 and its ancestor SIVcpz. SIVcpz appears to be a recombinant between ancestral viruses that gave rise to SIVrcm from red-capped mangabeys, and the clade of viruses found that infect species of *Cercopithecus* monkeys or guenons that includes greater spot-nosed, mona, and mustached monkeys (Bailes et al. 2003; Courgnaud et al. 2003). Other obvious recombinants are (1) SIVagmSab from the West African sabaeus species of AGM that is a recombinant of an ancestral form of SIVagm and SIVrcm (Jin et al. 1994b); (2) SIVrcm from red-capped mangabeys (Beer et al. 2001); and (3) SIVdrl and SIVmnd-2 from drills and mandrills, respectively, that are recombinants between SIVrcm and SIVmnd-1 (Hu et al. 2003). These latter viruses share a common breakpoint, suggesting a common origin and another example of cross-species transmission. Presumably, there has been a long history of cross-species transmission events and recombination within the primate lentiviruses. However, it is still evident from the species specificity of many of these strains that these viruses are ancient and have coevolved with their host species over long periods of time.

manipulation. Essential elements for such studies are a molecularly characterized SIV strain that can reproduce the kinetics of viral replication seen in natural infection and availability of the correct species from which this virus was initially derived. Animal models that satisfy these criteria are (1) SIVsmm infection of sooty mangabeys (SMs); (2) SIVagm infection of AGMs; and (3) SIVmnd infection of mandrills (Pandrea et al. 2003; Onanga et al. 2006). Two lineages of SIVagm have been evaluated in vivo, SIVagmVer and SIVagmSab from vervet and sabaeus AGM, respectively (Goldstein et al. 2006; Pandrea et al. 2006a,b). Initial studies with SIVagmSab were performed using sabaeus AGMs of African origin but a model has now been established using the same species of AGM of Caribbean origin, as these animals were imported from Africa more than 300 years earlier and are more readily available for experimental manipulations (Pandrea et al. 2006b). Initial studies of various strains of SIVagm in different species of AGMs revealed that these viruses are adapted for their specific host species (Goldstein et al. 2006). Thus, SIVagmVer strains are restricted in terms of replication in sabaeus AGMs relative to replication in their matched host, vervet AGMs. Because of cost and ethical issues, SIVcpz infection of chimpanzees has only been studied on a small scale or in terms of its impact in wild, habituated chimpanzee populations (Keele et al. 2009) and is discussed in more detail in article by Hahn and Sharp (2011). Infection of mandrills with SIVmnd has also been studied to a limited degree, because of restricted availability of these animals in captivity (Pandrea et al. 2003; Onanga et al. 2006). Therefore, much of what we know about natural hosts has been gleaned from studies of SMs and AGMs.

PATHOGENESIS STUDIES IN ANIMAL MODELS

Experimental Animal Models

Despite the wide range of SIV-infected African nonhuman primates in the wild, there are only three available models for experimental

General Characteristics of Natural Infection

The lack of virulence of SIV isolates for their homologous natural host species is intriguing when contrasted with their effect in Asian macaques, and with the typically pathogenic effect of HIV-1 in humans. Natural SIV hosts, such as SMs infected with SIVsmm or AGMs infected

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with SIVagm, generally show no evidence of immunodeficiency. There have been sporadic reports of the development of immunodeficiency, as defined by opportunistic infection or neoplasms normally associated with AIDS. Indeed, CD4⁺ T-cell depletion was observed in one naturally infected mandrill, and immunodeficiency was observed in a SM that had been naturally SIV-infected for more than 18 years (Ling et al. 2004; Pandrea et al. 2009). AIDS has also been observed in at least one chimpanzee inoculated with HIV-1 and progressive infection seen in a subset of HIV-infected chimpanzees (Novembre et al. 1997; O'Neil et al. 2000). Although HIV-1 is only a close relative of SIVcpz, this study suggests that these African primates are not immune to the pathogenic effects of primate lentiviruses under specific circumstances. Indeed, recent studies in wild habituated chimpanzee populations show a significantly greater mortality rate associated with SIVcpz infection (Keele et al. 2009). This is in agreement with the idea that SIVcpz is perhaps less adapted to chimpanzees than SIV in such hosts as SMs, consistent with a more recent introduction into chimpanzees from the monkeys on which they prey. The conclusion is that SIV infection of most natural host species is generally asymptomatic within the time frame of the lifespan of the animal. This lack of pathogenicity has been postulated to be the result of an evolutionary adaptation that, in AGMs and SMs, allows for a mutual coexistence between the host and the virus.

Despite their general lack of pathogenicity in their matched host species, SIVs clearly do not lack the intrinsic potential to cause AIDS, revealed by the either accidental or experimental introduction of SIVsmm into rhesus macaques (RMs) (Apetrei et al. 2005). In addition, experimental infection of macaque species with SIVsmm, SIVagm, and SIVlho results in a syndrome remarkably similar in pathogenesis of AIDS in humans. Interestingly, uncloned/unpassaged SIVsmm in RMs results in levels of virus replication that are lower than in SIV-infected SMs (Bosinger et al. 2009); however, when SIVsmm becomes adapted to RM cells through in vitro and/or in vivo passage,

the level of virus replication become even higher than in SMs (Johnson et al. 1990; Hirsch et al. 1995b). In the case of SIVagm and SIVlho, infection of pigtail macaques (*Macaca nemestrina*) was required to achieve efficient replication and subsequent disease (Hirsch et al. 1995b; Beer et al. 2005). The majority of pathogenesis and vaccine studies have focused on SIVmac infection of RMs because of its more uniform course of infection. Interestingly, recent studies revealed that allelic variation in the rhesus macaque TRIM5 α gene results in differences in susceptibility to infection and viral replication in the early stages of cross-species transmission of SIVsmm and that emergence of pathogenic SIVmac in RMs required adaptations in the viral capsid protein (CA) to overcome suppression by two distinct types of TRIM5 α allele (Kirmaier et al. 2010). Presumably similar types of adaptations occurred for both HIV-1 and HIV-2.

SIV infections of SMs, AGMs, and mandrills share many similar features with pathogenic infections such as SIVmac infection of macaques and HIV infection of humans (Johnson and Hirsch 1991; Paiardini et al. 2009b). The general features of SIV infection of AGM and SM are compared with pathogenic infection in with differences highlighted (Table 2). Common features include the kinetics of primary viremia with robust peak viremia and persistence of viremia into the chronic phase of infection in both models (Pandrea et al. 2006a). Infection is associated with the development of adaptive and innate immune responses that are similar or lower in kinetics and magnitude, and fail to control virus replication. Based on the rapidity of viral clearance following treatment with antiviral drugs, SIV infection targets cells whose lifespan is short (i.e., 1–2 d) (Gordon et al. 2008; Pandrea et al. 2008a) and even acute depletion/loss of mucosal CD4⁺ T cells, once thought to be pathognomonic for pathogenic primate lentivirus infections, is observed in both models. The most obvious difference is the clinical course of disease in natural hosts, which is typically nonprogressive. Other distinguishing features of natural host infections are (1) the maintenance of peripheral CD4⁺ T cells

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Table 2. Comparisons of the characteristics of primate lentivirus infection of natural SIV hosts versus macaques and humans

Characteristics	Host species	
	Sooty mangabeys and African green monkeys	Humans and Asian macaques
Clinical outcome	Depletion of peripheral CD4 ⁺ T cells rare Progression to AIDS is very rare. Survival for up to 20–30 yr Generally no evidence of AIDS	Progressive depletion of CD4 ⁺ T cells Progression to AIDS is common. Median survival 1.5 yr Opportunistic infections, neoplasia, encephalitis
Viremia	Vertical transmission is rare. High peak viremia in 1–2 wk (10 ⁶ –10 ⁸ /mL) Post-peak decline of viral load High to moderate set point virus load (10 ³ –10 ⁶ /mL) Stable setpoint	Vertical transmission is more common. High peak viremia in 1–2 wk (10 ⁶ –10 ⁸ /mL) Variable post peak decline in viral load High set point of virus replication (10 ⁵ –10 ⁸ /mL) Increasing viral load over time
Immune responses	Adaptive immune responses Marked acute type I interferon response Resolution of type I interferon responses Variable bystander T-cell activation and apoptosis Establishment of an anti-inflammatory milieu Limited immune activation and T-cell apoptosis Preservation of mucosal TH17 cells	Adaptive immune responses Marked acute type I interferon response Persistence of type I interferon responses High levels of bystander T-cell activation and apoptosis Establishment of a proinflammatory milieu Generalized immune activation and significant T-cell apoptosis Preferential loss of mucosal TH17 cells
Target cells	Absence of microbial translocation Short-lived, activated CD4 ⁺ T cells Early depletion of mucosal CD4 ⁺ T cells Healthy CD4 ⁺ T-cell counts in most animals CD4 depletion is not associated with AIDS.	Microbial translocation is prominent. Short-lived, activated CD4 ⁺ T cells Early depletion of mucosal CD4 ⁺ T cells Progressive depletion of circulating and mucosal CD4 ⁺ T cells CD4 depletion of <100/ μ L is associated with AIDS.

levels in the majority of animals; (2) the lack of chronic immune activation following resolution of primary infection; (3) the absence of microbial translocation; and (4) the preferential sparing of CD4⁺ central memory T cells from infection.

Targets Cells for SIV Replication

Similar to pathogenic models of HIV/SIV infection, SIV expression is primarily observed in lymphoid tissues and the gastrointestinal tract by polymerase chain reaction or in situ hybridization (Goldstein et al. 2006). The vast

majority (i.e., >90%) of SIVsmm replication in naturally SIV-infected SMs and AGMs occurs in short-lived cells (Perelson et al. 1993; Ho et al. 1995; Wei et al. 1995; Nowak et al. 1997), suggesting that activated CD4⁺ T cells are the major site for viral replication (Gordon et al. 2008; Pandrea et al. 2008a). This finding was shown by treating SMs and AGMs with reverse transcriptase inhibitors, and the lifespan of productively infected cells was calculated based on the slope of the decline of SIV plasma viremia after initiation of ART using a widely accepted mathematical model (Perelson et al. 1997; Gordon et al. 2008; Pandrea et al. 2008a). In

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addition, in situ hybridization studies have shown that SIVsmm and SIVagm colocalizes with CD3⁺ lymphocytes in lymph nodes and mucosal tissues of SMs and AGMs, respectively (Pandrea et al. 2008a; Sodora et al. 2009). Further evidence that SIVsmm infected activated CD4⁺ T cells in vivo was shown by depletion of CD4⁺ T cells in SIV-infected SMs; the subsequent levels of viremia correlated directly with the number of activated CD4⁺ T cells (Klatt et al. 2008). The rapid depletion of mucosal CD4⁺ T cells during acute SIVsmm and SIVagm infection also suggested that CD4⁺ T cells are the main targets of SIV replication in SM and AGM (Gordon et al. 2007; Pandrea et al. 2007a). However, despite destruction of mucosal CD4⁺ T cells during acute infection and concomitant development of chronic viremia, these animals maintain relatively normal mucosal immune function, with preserved levels of Th17 cells and a lack of microbial translocation (Brenchley et al. 2006, 2008; Sumpter et al. 2007). Although maintenance of peripheral CD4⁺ T cells in natural hosts is a striking feature of natural SIV infection, this model also shows that loss of CD4⁺ T cells alone is not sufficient to cause AIDS (Kosub et al. 2008). Indeed, naturally and experimentally SIV-infected SMs exist that are depleted of peripheral CD4⁺ T cells during infection, but remain AIDS-free (Sumpter et al. 2007; Milush et al. 2007). Furthermore, experimental CD4⁺ lymphocyte depletion in SIV-infected SMs does not result in AIDS (Klatt et al. 2008), nor does CD4⁺ depletion in either uninfected SMs or RMs result in an AIDS-like phenomenon (Engram et al. 2010). Thus, preservation of peripheral CD4⁺ T cells during natural SIV infection does not by itself explain the lack of disease progression in natural hosts.

Adaptive Immune Responses

The fact that natural hosts maintain high viral load (Rey-Cuille et al. 1998; Chakrabarti et al. 2000; Silvestri et al. 2003) indicates that the disease resistance of these animals is unlikely to be because of particularly effective SIV-specific immune responses. This hypothesis is

supported by the observations of lower levels of virus-specific T-cell responses in SIV-infected SMs than HIV-infected individuals (Dunham et al. 2006). In addition, depletion of CD8⁺ T cells results in minimal increase in virus replication in either chronically SIV-infected SMs or during primary infection of AGMs (Schmitz et al. 1999; Barry et al. 2007). In contrast, CD8⁺ lymphocyte depletion in SIV-infected rhesus macaques or pigtail macaques results in increased virus replication and rapid disease progression (Schmitz et al. 1999, 2009; Klatt et al. 2010). Furthermore, lack of disease progression cannot be accounted for by humoral responses. Depletion of CD20⁺ B cells in AGMs significantly delays seroconversion but does not result in significant changes in viremia (Schmitz et al. 1999; Gaufin et al. 2009). Moreover, autologous neutralizing antibody levels in SIV infection of SMs are much lower than those observed in HIV-infected humans (Li et al. 2010). Thus, immune control during chronic SIV infection of natural hosts likely does not account for the nonpathogenic nature of the infection.

Innate Immune Responses

Despite the lack of immune control of SIV replication in natural hosts, there is a rapid and robust innate immune response to SIV during acute infection. Similar to pathogenic SIV infection (Table 2), acute SIV infection of SMs and AGMs results in a rapid increase in proliferating T cells (Bosinger et al. 2009; Jacquelin et al. 2009). Activation of an innate immune response was observed as an induction and massive up-regulation of interferon responsive genes measured by gene expression during acute SIV infection of both SMs and AGMs (Bosinger et al. 2009; Jacquelin et al. 2009; Lederer et al. 2009). This is associated with the production of type I interferons by plasmacytoid dendritic cells (pDCs) as measured by immunohistochemical staining in tissues during acute SIVsmm infection (Harris et al. 2010). Moreover, during acute SIV infection, in vitro production of type I interferons by SIV-stimulated pDCs was enhanced in AGMs

compared to RMs (Jacquelin et al. 2009). However, in stark contrast to pathogenic SIV infection of RMs or HIV infection of humans, this robust innate immune response to the virus is rapidly attenuated after acute SIV infection of both SMs and AGMs (Bosinger et al. 2009; Jacquelin et al. 2009; Harris et al. 2010). Consistent with this, a similar phenomena is observed in a minor subset of HIV-infected individuals who are highly viremic but maintain high CD4⁺ T cell counts (Rotger et al. 2011). The genetic profile of T cells isolated from these viremic nonprogressors is similar to that of natural hosts, and, furthermore, interferon-stimulated gene expression was decreased compared to progressive infection, but similar to chronically infected natural hosts (Rotger et al. 2011). Indeed, many reports indicate that a striking and consistent feature of SIV infection of natural hosts is the lack of chronic, generalized immune activation (Silvestri et al. 2003; Paiardini et al. 2006; Sumpter et al. 2007), which is one of the major correlates of disease progression in pathogenic models (McCune 2001; Picker 2006; Fauci 2008).

Chronic Immune Activation and Microbial Translocation

Systemic immune activation, characterized by increased cell proliferation, high rates of lymphocyte apoptosis, cell cycle dysregulation, and increased levels of proinflammatory cytokines (Paiardini et al. 2004, 2006; Hurtrel et al. 2005; Hunt et al. 2008) is a very strong predictor of disease progression during pathogenic HIV/SIV infections. Massive infection of CD4⁺ T cells in MALT early in HIV/SIV infections is proposed to be associated with breakdown of mucosal integrity, which allows microbial products to translocate from the lumen of the gastrointestinal (GI) tract into peripheral circulation (Brenchley et al. 2006). Translocation of microbial products during pathogenic HIV/SIV infections, can be shown by an increase in plasma lipopolysaccharide (LPS) and bacterial DNA levels and is significantly correlated with systemic immune activation (Brenchley et al. 2006). A consistent feature of natural infection

is the absence of generalized chronic immune activation that is characteristically associated with disease progression in pathogenic SIV and HIV infection. Indeed, SIV-infected SMs have low levels of immune activation, T-cell turnover and cell cycle perturbation as compared to SIV-infected RMs or HIV-infected humans, and more comparable levels in uninfected animals (Silvestri et al. 2003; Paiardini et al. 2006; Sumpter et al. 2007). Moreover, SIV infection of natural hosts does not result in microbial translocation, as shown by lack of LPS or sCD14 in the plasma of SIV-infected RMs or AGM (Brenchley et al. 2006; Pandrea et al. 2007a). Furthermore, experimentally induced immune activation with LPS in natural hosts results in significantly increased virus replication and CD4⁺ T-cell depletion (Pandrea et al. 2008b), which indicates that lack of chronic, systemic immune activation, and microbial translocation may play a role in the lack of disease progression observed in natural hosts.

POTENTIAL MECHANISMS UNDERLYING LACK OF DISEASE PROGRESSION

The key to understanding the benign nature of SIV infection in natural hosts likely lies in understanding the differences between pathogenic and nonpathogenic infections. The most notable differences between SIV-infected natural hosts and SIV-infected macaques and HIV-infected humans are the lack of CD4⁺ T-cell depletion and attenuation of immune activation.

Attenuated Chronic Immune Activation

As mentioned above, natural hosts have the ability to dampen acute innate immune responses to SIV after a few weeks of infection. This feature contrasts with pathogenic SIV and HIV infections in which immune activation persists throughout the course of infection (Fig. 2). The precise mechanisms underlying resolution of acute immune activation in SIV-infected SMs and AGMs remain poorly understood and are likely quite complex. Several hypotheses have been proposed, including (1) rapid up-regulation of the membrane

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Figure 2. Pathophysiology of natural SIV infections.

receptor programmed death 1 (PD-1); (2) lack of up-regulation of genes such as TRAIL (tumor necrosis factor-related apoptosis-inducing ligand/Apo-2 ligand) and other associated death receptors that trigger apoptosis after pathogenic HIV/SIV infections of human and RMs (Kim et al. 2007); (3) early enhanced Treg responses; (4) reduced response to TLR ligands by pDCs during chronic infection (Mandl et al. 2008); and (5) the ability of Nef alleles to down-modulate the CD3-TCR complex from the surface of infected cells. Additional studies addressing genetic regulation of immune activation after acute SIV infection of natural hosts compared to nonnatural hosts will be crucial in determining a precise mechanism in which natural hosts resolve acute immune activation.

Lack of Microbial Translocation

One potentially important mechanism that underlies the lack of immune activation in SIV-infected natural hosts is absence of

significant microbial translocation in these animals (Fig. 2). During SIV infection of RMs, damage to the mucosal barrier of the GI tract is associated with microbial translocation and ensuing immune activation (Estes et al. 2010). In natural infection, preservation of mucosal immune function and of the tight epithelial barrier of the GI tract appears to prevent microbial translocation from occurring. The absence of microbial translocation is associated with preservation of cell subsets integral to mucosal health, including γ - δ T cells and Th17 cells. γ - δ T cells, which are important for mucosal immunity and response to bacterial antigens, are dysregulated during HIV infection but preserved during SIV infection of SMs (Kosub et al. 2008). Th17 cells are specialized CD4⁺ T cells that produce IL-17 as a signature cytokine in response to bacterial and fungal antigens, that are preferentially depleted from mucosal tissues during pathogenic HIV/SIV infections (Brenchley et al. 2008; Klatt and Brenchley 2010) but are maintained in natural hosts (Klatt and Brenchley 2010). Thus, despite loss of mucosal CD4⁺ T cells

after SIV infection of natural hosts, particular subsets important for mucosal immunity such as γ - δ and Th17 cells are maintained. The retention of such cells may underlie the lack of damage to the GI tract and ensuing microbial translocation and immune activation in natural SIV hosts (Brenchley et al. 2008; Favre et al. 2009; Paiardini 2010).

Target Cell Restriction

Low levels of mucosal CCR5⁺CD4⁺ T-cell targets appears to be a common characteristic of natural hosts (Pandrea et al. 2007b). Indeed, recent studies suggest additional mechanisms used by these hosts to restrict access of SIV to crucial central memory (TCM) CD4⁺ T cells, “the target restriction” hypothesis (Fig. 2) (Brenchley et al. 2010). CD4⁺ TCMs are a subset of antigen-experienced T cells that serve as a self-renewing source, whereas CD4⁺ effector memory (TEM) are more “expendable” and activated than CD4⁺ TCM cells, and produce the most virus (Grossman et al. 2006). These cells play a central role in AIDS pathogenesis as shown in the pathogenic model of SIV infection of rhesus macaques (RMs), in which depletion of CD4⁺ TCM cells is crucial for progression to AIDS and, conversely, preservation of these cells is a correlate of vaccine efficacy (Letvin et al. 2006; Mattapallil et al. 2006; Okoye et al. 2007). Protection of CD4⁺ TCM in natural SIV hosts appears to occur, at least in part, at the entry level. In AGMs, protection of memory CD4⁺ T cells from SIVagm infection is achieved through down-regulation of the expression of the CD4 molecule as these cells enter the memory pool (Beaumier et al. 2009). AGM “helper” T cells that have down-modulated CD4 expression maintain functions that are typical of CD4⁺ T cells, including production of IL-2 and IL-17, expression of FOXP3 and CD40 ligand, and restriction by major histocompatibility complex class II molecules (Beaumier et al. 2009). In the case of SIV-infected SMs, expression of CD4 is maintained as these cells enter the memory pool. However, CD4⁺ TCMs of SM express significantly lower levels of CCR5 both while resting and when

undergoing in vivo and in vitro activation (Pandrea et al. 2007b; Paiardini et al. 2011). Thus, purified CD4⁺ TCM show on average >10-fold lower levels of cell-associated SIV-DNA when compared to either CD4⁺ TEM of SMs or CD4⁺ TCM of SIV-infected rhesus macaques, RMs (Paiardini et al. 2011). It is not clear whether this is a common mechanism observed in all natural hosts of SIV because samples are not readily available for this analysis. Although regulation of CCR5 expression is central in determining the level of SIV infection of CD4⁺ TCM in SMs, other mechanisms must also play a role. For example, 6% of SIV-infected SMs are homozygous for a 2 bp deletion in CCR5 (Δ 2) that abrogates surface expression of CCR5 (Riddick et al. 2010). These animals show $\sim$ 0.5 log lower viral load than CCR5 wild-type SMs and slightly elevated levels of CD4⁺ T cells. In addition, SMs infected with an CXCR4-tropic SIVsmm that depletes most CD4⁺ TCM may be protected by CD3⁺CD4[−]CD8[−] cells that produce “helper” cytokines and show a TCM-like phenotype (Milush et al. 2011).

In terms of pathophysiology, sparing of the CD4⁺ TCM subset may limit the homeostatic strain on the pool of CD4⁺ TCMs and may help preserve a normal total pool of CD4⁺ T cells that maintains the low level of immune activation observed in natural hosts. Taken together with other mechanisms of attenuated immune activation, including down-regulation of acute immune responses, lack of microbial translocation, and preservation of mucosal immune cells, natural hosts have evolved efficient mechanisms by which they remain free of disease after SIV infection.

CONCLUSION

Although these hypotheses are quite intriguing, more work needs to be performed to ascertain whether the degree to which lack of microbial translocation, low immune activation, and protection of CD4⁺ TCM are essential to determine the nonprogressive course of infection observed in natural SIV hosts. Future research goals include the identification of the cellular and

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molecular mechanisms responsible for the rapid down-modulation of the immune activation in natural SIV hosts as well as the discovery of major cellular and viral factors that may protect CD4⁺ TCM from SIV in natural hosts. Furthermore, a more complete understanding of the pathophysiologic link between microbial translocation, virus replication in CD4⁺ TCM cells and immune activation is needed. Indeed, a more complete understanding of other potential mechanisms by which natural hosts attenuate immune activation would help to define the basis for reduced pathogenicity of these natural infections. Elucidation of how natural hosts prevent microbial translocation will also benefit from a definition of the mechanism of mucosal protection that preserves mucosal barrier function and prevents damage to the gut epithelium and microbial translocation during nonpathogenic SIV infection. Furthermore, an assessment of the degree of pathogenicity in natural and nonnatural hosts of SIV molecular clones that express accessory gene products (i.e., Nef, Vpu, etc.) that have lost specific functions will establish the role of specific viral factors in the pathophysiology of natural SIV infections. Finally, the development of a model in which AIDS is induced in natural hosts by increasing their immune activation and/or expanding their target cell tropism, or, conversely, SIV-infected macaques are rendered AIDS-free by reducing the immune activation in the chronic phase of infection and/or by protecting their CD4⁺ TCM resistant from infection would provide substantial insight into HIV infection.

There are clearly major lessons to be learned from the natural hosts of SIV, who have spent thousands of years coevolving with the virus, and in fact it is quite possible that a full understanding of the reasons why HIV causes AIDS in humans will not be possible until the mechanisms by which SIVs do not cause disease in natural hosts are fully clarified. In this view, studies of natural SIV hosts have a tremendous impact in AIDS research as a better understanding of HIV pathogenesis will likely result in novel therapeutic and vaccination strategies to delay or prevent HIV transmission and/or disease progression in humans.

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