In the past 25 years, over 40 nonhuman primate (NHP) species-specific simian immunodeficiency virus (SIV) strains have been described (3, 6, 7, 13, 15, 28, 30). These viruses naturally infect NHPs in Africa, and these natural host species do not typically manifest AIDS, unlike the progressive immunodeficiency seen in lentiviral infections of humans or Asian macaques. Comparative studies of virological and immunological characteristics of these natural and nonnatural host species may explain how the natural hosts have coevolved with SIV to avoid disease progression and give us a better understanding of how to circumvent the progressive disease in HIV-infected humans.

Similar to progressive HIV and SIV infections, natural hosts maintain high levels of virus replication after SIV infection (21, 25). However, in contrast to pathogenic lentiviral infections, natural hosts have low levels of immune activation, do not develop mucosal dysfunction or the associated microbial translocation (11, 25, 26), and most importantly, do not progress to disease in HIV-infected humans. In the past 25 years, over 40 nonhuman primate (NHP) species-specific simian immunodeficiency virus (SIV) strains have been described (3, 6, 7, 13, 15, 28, 30). These viruses naturally infect NHPs in Africa, and these natural host species do not typically manifest AIDS, unlike the progressive immunodeficiency seen in lentiviral infections of humans or Asian macaques. Comparative studies of virological and immunological characteristics of these natural and nonnatural host species may explain how the natural hosts have coevolved with SIV to avoid disease progression and give us a better understanding of how to circumvent the progressive disease in HIV-infected humans.

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Here we studied 12 different species of African NHPs belonging to four different genera (Table 1) to determine whether maintenance of CD4 function by T cells resistant to SIV infection is a common manifestation of African, natural host, nonhuman primates. Nine of the 13 species studied are known natural hosts for SIV (Cercopithecus atys, Cercopithecus torquatus, Cercopithecus nictitans, Cercopithecus mona, Cercopithecus cephus, Cercopithecus erythropus, Cercopithecus neglectus, Cercopithecus preussi, and Chlorocebus pygerythrus). One species has been reported to harbor SIV (Cercopithecus lundatus) (28), but it is likely this animal was infected via cross-species transmission with SIVagm. Another (Erythrocebus patas) manifests a nonprogressive infection after experimental infection. Indeed, the E. patas monkey is a nonprogressive experimental model of SIV that exhibits infection characteristics similar to those seen in natural hosts, and its habitat range colocalizes with that of AGM (1, 8). For comparison, we also studied animals that manifest progressive disease once infected with SIV (Macaca mulatta).

**MATERIALS AND METHODS**

**Animals.** For this study, blood was collected from wild or captive animals. Wild animals included 30 Cercopithecus spp. (3 C. neglectus, 1 C. cephus, 3 C. erythropus, 12 C. mona, 5 C. nictitans, 1 C. preussi, 3 C. sclateri, and 2 hybrids), and 12 Cercopithecus torquatus. Captive animals included 44 Erythrocebus patas, 22 Cercopithecus atyus, 9 Cercocebus lundatus, 26 Chlorocebus pygerythrus, and 28 Macaca mulatta. Lymphocytes were isolated from blood by Ficoll gradient centrifugation, viably cryopreserved in fetal bovine serum supplemented with 10% dimethyl sulfoxide (Sigma, St. Louis MO), and stored in liquid nitrogen.

**Flow cytometry.** For intracellular cytokine staining (ICS), peripheral blood mononuclear cells (PBMC) were stimulated overnight at 37°C with 1 μg/ml of staphylococcal enterotoxin B (SEB; Sigma), and 1 μg/ml brefeldin A (Sigma), or
negative controls were incubated with only medium and brefeldin A. After stimulation, cells were washed twice and incubated with Live/Dead fixable Aqua Dead cell stain (Invitrogen, Carlsbad, CA). Cells were then stained for surface markers with monoclonal antibodies to CD3 (SP34-2; BD Biosciences, Franklin Lakes, NJ), CD4 (L200 [BD Biosciences] or OKT4 [eBioscience, San Diego, CA]), CD8 (RPA-T8; BD Biosciences), CD28 (CD28.2; Beckman Coulter, Brea, CA), and CD95 (DX2; BD Biosciences). Cells were washed and permeabilized with Cytofix/Cytoperm buffer (BD Biosciences). Cells were then intracellularly stained with fluorescent-conjugated monoclonal antibodies to gamma interferon (4S.B3; BD Biosciences), interleukin-17 (IL-17; eBio64DEC17; eBioscience), IL-2 (M91-17H12; BD Biosciences), CD40 ligand (CD40L; 24-31; eBioscience), or Ki67 (B56; BD Biosciences). For analysis of FoxP3 expression, PBMC were surface stained and then permeabilized using FoxP3 permeabilization solution (eBioscience). Cells were intracellularly stained for FoxP3 (PCH101; eBioscience). Cells were incubated at 4°C for 20 min. Cells were washed and then fixed with a 1% paraformaldehyde solution (Electron Microscopy Sciences, Hatfield, PA).

For in vitro proliferation assays, PBMC were stained with 0.0625 μM carboxyfluorescein succinimidyl ester (CFSE; Invitrogen) and then stimulated with 1 μg/ml SEB (Sigma) for 6 days. Cells were then labeled with fluorescent antibodies directed against CD3, CD4, and CD8 (BD Biosciences).

All flow cytometry samples were run on a FACSFortessa or FACSArria apparatus (BD Biosciences) using FACSData software (BD Biosciences), and data were analyzed using the FlowJo program (Tree Star, Ashland, OR). CD8α and CD8β were distinguished by “bright” (CD8αβ) versus “dim” (CD8α+β) expression of CD8α as previously characterized (4).

Quantitative real-time PCR. Cell populations were sorted by flow cytometry and were lysed using 25 μl of a 1:100 dilution of protease K (Roche, Indianapolis, IN) in 10 mM Tris buffer. Quantitative PCR was performed using 5 μl of cell lysate per reaction mixture. Reaction conditions were as follows: 95°C holding stage for 5 min and 40 cycles of 95°C for 15 s followed by 60°C for 1 min. The Taq DNA polymerase kit (Invitrogen) was used. The sequence of the forward primer for SIVsmm was GGGAGGAAAATCTCCAGCA. The reverse primer sequence is GCCCTTACCTGCTTCATAC. The probe sequence is AGTCCCCGTTCRGGCGCCAA. For cell number quantitation, monkey albu-

### RESULTS

Frequencies of CD4, CD8αα, CD8αβ, and double-negative (DN) T cells in different species of African nonhuman primates. We previously showed that adult AGM have lower frequencies of CD4+ T cells than humans or Asian macaques but that these animals have high frequencies of T cells that express the α-chain of CD8 (4). We therefore studied the phenotypes of T cells based upon expression patterns of CD4 and CD8α from multiple species of African nonhuman primates known to manifest a nonprogressive disease after SIV infection. We studied the frequencies of CD4+ T cells, CD8ααbright CD4− T cells, CD8ααdim CD4− T cells, and CD8− CD4+ (DN) T cells in Asian macaques (RM) and African species of mangabeys (Cercopithecus), AGM (Chlorocebus), patas monkeys (Erythrocebus), and Cercopithecus (see the details in Table 1 and Fig. 1; see also Fig. S1 in the supplemental material for a representative analysis). We then only knew the infection status of AGM and mangabey animals (open symbols represent infected animals). We found that all species of African species of nonhuman primates known to manifest a nonprogressive SIV infection had lower frequencies of CD4+ T cells than uninfected RM (Fig. 1A). This low frequency of CD4+ T cells in natural hosts of SIV was not simply attributed to expansion of CD8ααbright CD4− T cells, as no natural host species of nonhuman primates had higher frequencies of these cells than RM. In fact, both patas and Cercopithecus animals had lower frequencies of CD8ααbright CD4− T cells than RM (Fig. 1B). We next examined the frequencies of CD8ααdim CD4− T cells, cells we have previously seen to have functions normally associated with CD4+ T cells and to be expanded in AGM (Fig. 1C). Consistent with previous studies, these cells were expanded in AGM regardless of infection status, but these cells were also present at high frequencies in patas monkeys and mangabeys. Cercopithecus animals had low frequencies of these cells, similar to RM (Fig. 1C). Finally, we also studied the frequency of T cells that lacked expression of both CD4 and the alpha-chain of CD8 (DN T cells) in each group of animals (Fig. 1D). Interestingly, all groups of natural host animals exhibited higher frequencies of these DN T cells than RM.

Given that CD4 is downregulated only as AGM CD4+ T cells are stimulated in vivo (4), we examined the memory phenotype of each subset of T cells in our cohort of animals based upon characteristic expression patterns of CCR7, CD28, and CD95 (23). Not surprisingly, CD4+ T cells and CD8ααbright CD4− T cells were comprised of both memory and naïve T cells in all species of animals we studied (Fig. 1E and F). However, both the CD8ααdim CD4− T cells and DN T cells were predominately of a memory phenotype (Fig. 1G and H).

### Functionality among different T cell subsets of African nonhuman primates. Having shown lower frequencies of CD4+ T cells and higher frequencies of DN T cells in all natural host species compared to RM (Fig. 1), we next sought to determine if functions normally associated with CD4+ T cells could be observed among non-CD4+ T cells. Initially, we examined expression of FoxP3 in each subset of cells. We examined the frequency of each T cell subset that expressed FoxP3 in our cohort of animals (Fig. 2). As expected, we were routinely able to find FoxP3-expressing CD4+ T cells, and the frequency of FoxP3-expressing CD4+ T cells was significantly higher than

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
<th>Common name</th>
<th>SIV subtype</th>
<th>No. analyzed</th>
</tr>
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<tr>
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<td>Sooty mangabey</td>
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<td>SIVsnp</td>
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<td>Rhesus macaque</td>
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the frequency of canonical CD8\textsuperscript{bright} CD4\textsuperscript{−} T cells expressing FoxP3 in all nonhuman primate species. However, we were also able to routinely identify FoxP3-expressing DN T cells in all animals studied. The frequency of DN T cells expressing FoxP3 was similar, or even higher, than the frequency of CD4\textsuperscript{+} T cells expressing FoxP3 (Fig. 2). Consistent with our previous data, CD8\textsuperscript{dull} CD4\textsuperscript{+} T cells from AGM had frequencies of FoxP3 expression similar to the frequencies among CD4\textsuperscript{+} T cells. Given that the frequencies of each individual subset of T cells were different in each species of nonhuman primate, we also calculated the relative number of T cells for each T cell subset (Fig. 2, lower panel). For RM it was clear that the vast majority of FoxP3\textsuperscript{+} cells reside within the CD4\textsuperscript{+} T cell subset. However, for the majority of the natural host species of nonhuman primates, there were an equivalent number, or more, of FoxP3\textsuperscript{+} T cells residing within either the DN T cell fraction and/or the CD8\textsuperscript{dull} CD4\textsuperscript{−} T cell fraction.

We performed similar analysis of functionalities generally attributed to CD4\textsuperscript{+} T cells by mitogenically stimulating PBMC and examining expression of IL-2 (Fig. 3), IL-17 (Fig. 4), and CD40L (Fig. 5). Unfortunately, PBMC were very limited from the wild-born Cercopithecus animals, and we were unable to...
analyze their PBMC after mitogenic stimulation. Similar to what we observed for expression of FoxP3, CD4+ T cells more frequently expressed IL-2 (Fig. 3), IL-17 (Fig. 4), or CD40L (Fig. 5) than any other subset of T cells for all species of natural hosts. However, relatively high frequencies of DN T cells in all natural host species and CD8<sup>+</sup> CD4<sup>+</sup> T cells in both mangabeys and patas monkeys were capable of expressing FoxP3, IL-2, IL-17, and/or CD40L. Given that these T cell subsets were present at higher frequencies in natural host species than in RM, preservation of these cells may impart these animals with immunological functions, normally attributed to CD4<sup>+</sup> T cells, that render them resistant to infection in vivo.

Low level of infection among DN T cells in mangabeys. We next sought to determine if the DN T cells, which were present at high frequencies in all natural host species and maintained CD4<sup>+</sup> T cell function, were putative targets for SIV in vivo. Our hypothesis is that preservation of immunological function among T cells resistant to infection is an important aspect of the nonprogressive nature of natural SIV infection. Unfortunately, we do not know the infection status of the Cercopithecus animals, nor do we have species-specific SIV PCR conditions for these animals; thus, we were unable to perform quantitative PCR for each of the species-specific SIV strains, and all of the patas animals we studied were SIV uninfected. Therefore, we sorted by flow cytometry the naïve (CD28<sup>dull</sup> CCR7<sup>+</sup> CD95<sup>-</sup>), central memory (CCR7<sup>+</sup> CD95<sup>-</sup>), and effector memory (CCR7<sup>-</sup> CD95<sup>+</sup>/dull) CD4<sup>+</sup> T cells as well as DN T cells from our cohort of known SIVsmm-infected sooty mangabeys (SM; Cercopithecus atys). We then performed quantitative real-time PCR.
PCR for SIVsmm to quantify viral infectivity of each cell subset in vivo (Fig. 6). We were able to routinely identify SIVsmm-infected cells among all subsets of CD4+ T cells. However, in some of the DN T cells we found no viral DNA (with results for 2/8 animals reported as at the limit of detection [LOD]), and when viral DNA was detected, there were lower frequencies of infected DN T cells than memory CD4+ T cells (Fig. 6).

Interestingly, unlike HIV-infected humans and SIV-infected RM, effector memory CD4+ T cells from SM were as frequently infected as central memory CD4+ T cells (P = 0.1455) (data not shown). As the DN T cells are present at high frequencies in all species of natural hosts, are capable of eliciting CD4-like functions, and are infrequently infected by SIV in vivo, preservation of this subset may be an important common mechanism underlying the nonprogressive nature of SIV infection in natural hosts.

**CD4 downregulation in patas monkeys.** We have previously shown that memory CD4+ T cells from AGM are capable of CD4 downregulation and that these cells concomitantly up-regulate CD8a (4). Indeed, adult AGM have low frequencies of CD4+ T cells and high frequencies of CD8a null CD4- T cells (Fig. 1) (4). However, this phenomenon does not appear to occur, universally, in all natural host species (Fig. 1). Aside from AGM, the only other animals which had significantly higher frequencies of CD8a null CD4- T cells than RM were the patas monkeys (Fig. 1). Based on our previous observations in AGM, we sought to determine if CD4 could be downregulated by memory CD4+ T cells after mitogenic stimulation in patas monkeys. Initially, we compared CD4+ T cell counts in peripheral blood of adult and juvenile (less than 5 years old) patas and RM animals (Fig. 7A), as younger animals routinely have lower frequencies of memory T cells than older animals. Consistent with our premise that CD4 is downregulated by patas monkey CD4+ T cells, younger animals had significantly higher numbers of CD4+ T cells than older patas monkeys. However, younger RM also had higher numbers of CD4+ T cells in peripheral blood than older RM (Fig. 7A). Indeed, consistent with data from humans, this phenomenon was clearly attributed to older macaques having significantly lower lymphocyte counts in peripheral blood than younger animals (data not shown) (16). Therefore, we compared the frequency of CD4+ T cells in each group of animals (Fig. 7B). While both old and young RM maintained high frequencies of CD4+ T cells compared to patas monkeys, young patas monkeys had significantly higher frequencies of CD4+ T cells than older animals. To determine whether CD4 could be downregulated from patas monkey CD4+ T cells upon mitogenic stimulation, we examined CFSE-labeled and mitogenically stimulated cells from 3 patas monkeys and measured CD4 expression levels with respect to cell division (Fig. 7C). In all cases it was clear that CD4 expression was lower with each successive round of

![FIG. 5. CD40L expression by each T cell subset. (Upper panel) Frequencies of CD40L+ cells within each T cell subset for each nonhuman primate genus. (Lower panel) Relative numbers of CD40L+ cells within each T cell subset for each nonhuman primate genus. Open symbols represent SIV-infected animals. Horizontal bars represent the median frequencies.](http://jvi.asm.org/)

![FIG. 6. Infection frequencies, determined by quantitative real-time PCR, of flow cytometry-sorted T cell subsets from SIVsmm-infected sooty mangabeys. Each square represents the number of copies of Gag per 100 flow cytometry-sorted cells for each corresponding cell type. In the DN sorted cells, 2 of the 8 animals reported <0.01% infection, which corresponds to one-half the lower LOD.](http://jvi.asm.org/)
cell division (Fig. 7D). These data indicate, that similar to AGM, patas monkeys have evolved the ability to downregulate CD4 expression to protect CD4<sup>+</sup> T cells from being infected.

**DISCUSSION**

Here we showed that (i) all species of natural hosts we studied had significantly lower frequencies of CD4<sup>+</sup> T cells than Asian macaques; (ii) AGM and patas monkeys had significantly elevated frequencies of CD4<sup>+</sup>CD8<sup>+</sup>dull T cells compared to rhesus macaques; (iii) all species of natural hosts had significantly higher frequencies of DN T cells than rhesus macaques; (iv) these high frequencies of DN T cells elicited effector functions normally attributed to CD4<sup>+</sup> T cells; and (v) these DN T cells were less frequently infected by SIV than were memory CD4<sup>+</sup> T cells. These data suggest that maintenance of immunological function among subsets of T cells resistant to SIV infection in vivo is an important mechanism underlying the nonprogressive nature of SIV infection that is common to multiple species of natural hosts of SIV.

While it is not entirely clear that such a mechanism could occur in humans, it is clear that these cells are only rarely infected by HIV in vivo (12). Bolassel et al. recently showed that slow-progressing HIV-1-infected individuals have a significantly higher frequency of CD4<sup>+</sup>CD8<sup>+</sup>dull T cells than chronically HIV-infected individuals (9). This finding suggests that a phenomenon similar to what we have described here could slow disease progression in HIV-infected humans.

The ontogeny of the DN T cells, which are present at high frequencies and are capable of eliciting CD4-like effector function in the natural host species, is unclear. In humans and mice, the DN T cells are thought to be thymically derived and to negatively regulate other T cells in an antigen-specific fashion (reviewed in reference 27). While we did not directly measure the regulatory function of this T cell subset, we clearly found expression of FoxP3 within the DN T cells. However, we also observed CD4-like functions within the DN T cells. Whether some of these cells originated from the CD4<sup>+</sup> T cell pool, like the CD8<sup>+</sup>dullCD4<sup>+</sup> T cells in AGM (4), and maintained major histocompatibility complex class II restriction remains unclear, but further experimentation is clearly warranted. Indeed, recent data from humans have suggested that, under inflammatory conditions, DN T cells are fairly plastic and are capable of producing IL-17 (14).

Some of the DN T cells in primates belong to the subset of NK T cells (10). These T cells with rearranged, but invariant, T cell receptors respond quickly after infection and have evolved to recognize CD1d-presented lipid antigens. These cells are thought to play important roles during infection with bacterial, viral, protozoan, and fungal pathogens (10). Indeed, DN T cells are expanded in AIDS patients with disseminated *Mycobacterium avium* infections (20). Moreover, recent studies of sooty mangabeys have shown that the NK T cells can be divided into two subsets based upon expression of CD8α. CD8α<sup>+</sup> NK T cells tend to have a more cytolytic function, while DN NK T cells tend to produce effector cytokines typically expressed by CD4<sup>+</sup> T cells (24).

Of all African NHPs we studied, the only animals other than AGM which appeared capable of CD4 downregulation were patas monkeys. Patas monkeys are widespread in sub-Saharan Africa.
Africa, their habitat overlapping with that of AGM. While they are not a known natural host of SIV, cross-species transmission of SIVagm from sympatric AGM species has been reported to occur in the wild (7, 29). Moreover, recent studies have shown that patas monkeys manifest a nonprogressive infection when infected experimentally with SIVagm (1). Indeed, one patas animal with very low numbers of CD4+ T cells appeared to be resistant to infection with SIVagm (1). Hence, patas monkeys may have adapted similar mechanisms to avoid infection completely. Indeed, the patas animals had very high frequencies of DN T cells and maintained significantly high frequencies of cells capable of CD4-like functions. Whether some of these cells were originally CD4+ T cells that did not upregulate CD8α is unclear.

The potential biological relevance of the DN T cells in natural host species has been highlighted by recent studies which demonstrated that sooty mangabeys infected with CXCR4/CCR5 dual-tropic SIVsmm lost the vast majority of all CD4+ T cells in peripheral blood and tissues, yet these animals did not succumb to simian AIDS (19). While these animals were massively depleted of CD4+ T cells, the DN T cells persisted (19), and recent studies suggest that DN T cells in SIV-infected, CD4-depleted, sooty mangabeys may elicit functions generally attributed to CD4+ T cells (18). Indeed, we have shown that DN T cells are present at high frequencies in many species of mangabeys, that these cells are capable of eliciting CD4-like functions, and that these cells are rarely infected by SIVsmm in vivo. Hence, it is tempting to speculate that maintenance of immunological function by subsets of cells resistant to viral infection in vivo is an important mechanism underlying the nonprogressive nature of natural SIV infection. Moreover, the tendency of African nonhuman primates to have lower numbers of CD4+ T cells in vivo may help explain why these animals tend to have lower plasma viral loads than SIV-infected Asian macaques.

Natural hosts have coevolved with SIV to avoid disease progression, although the mechanisms by which this occurs may diverge, since most SM maintain healthy frequencies of CD4+ T cells. This coevolution may have occurred, in part, via the development of T cell subsets that maintain immunological functions without susceptibility to SIV infection. Once the mechanisms by which CD4 downregulation and DN T cell development are understood, interventions, such as gene therapy, aimed at mimicking this phenomenon could be developed for preventative and therapeutic trials.

ACKNOWLEDGMENTS

These studies were supported by the intramural NIAID, NIH program and by R01 AI064066 (I.P.), R01 AI065325 (C.A.), R01 AI66998 (G.S.), and RR-00168 (Tulane National Primate Research Center). We thank the Bad Boys of Cleveland for helpful discussions.

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