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CD4$^+$ T CELL SIGNALING IN THE NATURAL SIV HOST – IMPLICATIONS FOR DISEASE PATHOGENESIS

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1. ABSTRACT

SIV infection of nonhuman primates is widely utilized as a powerful model of human AIDS. The major effort in this field has so far been oriented towards the induction of an AIDS like disease in the disease susceptible species with the aim to elucidate mechanisms of HIV/SIV induced disease. The fact that there exist disease resistant natural SIV infected host species offers a unique opportunity for comparative studies aimed at not only defining of those mechanisms that may be critical in the development of disease but also the mechanisms that are important for the disease resistance in the natural host. The hallmark of pathogenic HIV and SIV infection is generalized immunosuppression due to both a loss and functional impairment of CD4$^+$ T cells. This review summarizes currently available data on CD4$^+$ T cell function in the naturally SIV infected sooty mangabey with potential implications of these characteristics for our understanding of the pathogenesis of SIV infection.

2. INTRODUCTION

Natural SIV infection of nonhuman primates has become in recent years an important model and a useful tool for studies of the pathogenesis of lentivirus induced disease. The fact that naturally infected SIV species do not develop SIV induced disease despite viral loads and virus replication levels comparable to those in SIV infected disease susceptible species makes this model especially attractive for studies aimed at defining the immune response mechanisms important for the "containment" as compared with development of the disease. This model also provides an attractive tool for discriminating between those virus induced mechanisms that lead to the pathogenesis of the disease from those that are deviations from the "normal" physiological state but do not potentially lead to the pathogenic effect observed in AIDS disease.

A number of nonhuman primate species from Africa have been described to exhibit natural "nonpathogenic" SIV infection including sooty mangabeys, African green monkeys, mandrill monkeys, L'hoest monkeys and others. However the most extensively studied to date are the sooty mangabeys and the African green monkeys. Initially these studies were primarily oriented towards defining the basic parameters of the immune system, such as cell counts, viral loads, cell turnover rates etc. It is important to realize that the different outcome of SIV infection in these "resistant" species could be a result of not only virus-host interaction, but also host immune system properties that can be inherent to the host or, most likely, a combination of both. Therefore not only is it important to characterize the nature of SIV specific immune response but, in addition, it is just as important to delineate characteristics of the immune system that may be unique to these naturally infected species. Knowledge gained from such studies may provide important clues as to which of these parameters may be important for the "disease resistant" phenotype. For example HIV/SIV infection is known to induce aberrations in cell cycle of the CD4$^+$ T cells and these aberrations are very likely one of the mechanisms important for virus induced pathogenesis. It is possible that, in the naturally infected hosts, the ability to compensate for such virus induced effects may be contributing to the "disease resistant" status of these species. However, it is also possible that additional parameters or pathways may be operational in these species, irregardless of SIV infection, giving the natural host species an advantage over the susceptible host. This

review will focus on summarizing our current knowledge of $CD4^+$ T cell function in natural SIV host and its potential implications for immune system function in comparison with disease susceptible host. The discussion will focus predominantly on natural SIV infection in the sooty mangabey monkey (Cercocebus atys) (1) and where appropriate, comparisons are made with the SIV infection of rhesus macaques (Macacca mulatta), the most widely used animal model for the study of AIDS disease.

3. VIRAL LOADS AND $CD4^+$ T CELL DYNAMICS IN NATURAL SIV INFECTION

One of the main areas of research in the pathogenesis of HIV infection of man and SIV infection of nonhuman primates has focused on $CD4^+$ T cells since they represent the primary target cell of these lentiviruses. The immunosuppression – a hallmark of HIV or SIV induced disease - is characterized by a $CD4^+$ T cell response impairment resulting from both declining $CD4^+$ T cell counts and functional impairment of the remaining $CD4^+$ T cells. The progressive $CD4^+$ T cell decline in pathogenic SIV infection is an important marker of disease progression and has not so far been detected in any natural host species so far. Interestingly, several natural host species exhibit markedly lower $CD4^+$ T cell counts regardless of infection when compared to SIV susceptible hosts. These counts are maintained despite a wide range of viral loads/replication found in these species that are comparable to those observed in disease susceptible species that develop AIDS following SIV infection. In the naturally infected AGM, plasma viral loads in the range ~ 10^3 to 10^7 virus copies/ml have been reported. Similar viral loads were detected at viral setpoint when SIV seronegative AGM were experimentally infected with SIVagm (2-4). Although the AGM exhibit a rather low frequency of $CD4^+$ T cells (~10% in the peripheral blood) before seroconversion, this frequency does not decline after seroconversion (5). Seronegative sooty mangabeys exhibit a similar or a somewhat lower $CD4^+$ T cell frequencies when compared with disease susceptible RM (30% vs 35%) (6-8). In SM however, unlike in AGM, $CD4^+$ T cell frequencies exhibit a 20-25% decrease after SIV seroconversion. Plasma viral loads detected in SM are in the range of 10^4-10^7 copies/ml-similar to those observed in SIV infected RM that develop an AIDS like disease. Although these two species – when infected – exhibit similar viral loads, the $CD4^+$ T cell turnover did not increase in SM after seroconversion (7), while it significantly increased in RM after SIV infection (9). Even the cells within the $CD4^+$ compartment in uninfected RM exhibited a higher frequency of proliferating/activated cells compared to seronegative SM as measured by the percentage of Ki-67 positive cells (7). Increased $CD4^+$ T cell proliferation and turnover is one of the central issues of HIV/SIV pathogenesis as it is considered the major mechanism responsible for the massive $CD4^+$ T cell depletion characteristic for progression to disease and AIDS. An increase in the $CD4^+$ T cell turnover in SIV infected RM correlates with decline in the $CD4^+$ T cell counts and increase in viral replication (9). It is therefore intriguing that SM after seroconversion do not experience at least a modest increase in the turnover rate despite the moderate $CD4^+$ T cell decline and continuous sustained high levels of virus replication. One of the parameters that was shown to be linked to lymphocyte proliferation and activation, is telomerase activity. The quantitative level of telomerase activity has been shown to serve as a marker of cell proliferation and telomerase activity in lymphocytes increases with immune activation (10-12). Increased telomerase activity has been shown to correlate with an increase in the replicative potential of T cells (13). Interestingly, in our previous studies we have observed that seronegative SM exhibit higher $CD4^+$ T cell associated baseline levels of telomerase activity as compared with $CD4^+$ T cells from RM or humans (14). The $CD4^+$ T cell associated telomerase activity further increases following SIV seroconversion in SM while it moderately or markedly decreases in SIV infected RM or pigtail macaques, respectively, that exhibit an accelerated disease progression. Thus although measurement of telomerase activity is only an indirect measure of cell activation, these findings suggest that an increase in telomerase activity is characteristic for disease resistance. Indeed, an increase in telomerase activity was observed also in SIV infected RM with slow disease progression equivalent to HIV-1 infected humans classified as long-term non-progressors (LTNP). As both telomerase activity and Ki67 expression are only indirect measures of cellular activation or proliferation, further studies, presumably utilizing in vivo cell labeling will be needed to clarify this issue.

4. $CD4^+$ T CELL SIGNALING IN NATURALLY INFECTED HOST

4.1. TCR signaling

The above mentioned data clearly suggest that it is not the level of virus replication, virus associated cell death and quantitative changes in $CD4^+$ T cell population that dictate the level of immunosuppression and progression of disease in HIV/SIV infected susceptible hosts. It was indeed shown that the generalized impairment of TCR signaling is a marker characteristic of HIV disease progression (15,16). Further analysis of signaling molecules associated with TCR signaling – such as lck, fyn, ZAP70 and TCRzeta chain - by Stefanova et al. suggested, that HIV infection leads to a modification, rather than downregulation of these molecules in T cells isolated from patients at both the asymptomatic and symptomatic stages of HIV infection, but not from LTNP (17). Similarly, experimental SIV infection of rhesus macaques induced pronounced defective responses in both the $CD4^+$ and $CD8^+$ cells from the animals prior to any detectable signs of $CD4^+$ T cell depletion (18). These "dysregulatory" changes have been observed in multiple intracellular signaling pathways induced by and associated with the stimulation of CD3, CD2 and $CD4^+$ in both uninfected and infected cells. These findings suggest that it is an indirect mechanism, rather than a direct effect of virus replication in an individual cell that plays a major role in T cell dysregulation contributing to AIDS pathogenesis. Further in vitro studies have provided a large body of evidence documenting various effects of HIV/SIV viruses or virus derived proteins on various aspects of $CD4^+$ T cell

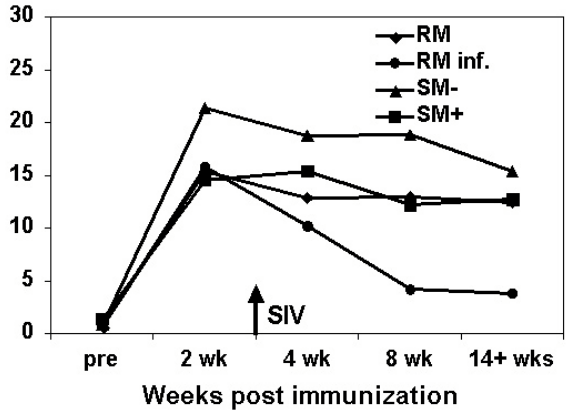

Figure 1. Antigen specific recall responses are maintained in SM. Six adult rhesus macaques (RM), 3 SIV sero-negative (SM-) and 3 SIV sero-positive (SM+) mangabeys were hyperimmunized with tetanus toxoid (T.T). Three of the 6 rhesus macaques (RMinf) were then infected with 100 TCID50 of SIVmac239 (at two weeks, indicated by arrow). PBMC samples were co-cultured with autologous herpes papio transformed cell lines which had been pulsed overnight with ovalbumin (control) or T.T., washed and irradiated. The co-cultures were incubated for 48 hrs and each culture pulsed with 3H-thymidine and harvested 16 hrs later. Cultures were performed in triplicate and the mean cpm of triplicate co-cultures with T.T. pulsed APC's was divided by the mean cpm of the triplicate co-cultures with ovalbumin pulsed APC's to derive stimulation indices (S.I.).

signaling machinery. It was shown that while under physiological conditions engagement of CD4 by its ligands leads to the generation of activation signals and protein kinase lck activation, binding of HIV gp120 to this receptor failed to elicit lck phosphorylation leading to the abrogation of both Ca^{2+} and protein kinase dependent downstream signaling which is important for antigen mediated cell activation (19). Kanner et al showed that HIV-1 infection selectively affects CD4 signaling by uncoupling the CD4-lck signal transduction pathway, while leaving other pathways – such as TCR induced PLC-gamma1 stimulation intact (20). In addition HIV derived gp120 was shown to downmodulate lck expression along with CD4 (21) and to inhibit CD4-lck-CD3 interaction and signaling (20,22). However, other studies reported that in vitro HIV infection leads to the activation, rather than inhibition of TCR and CD4 associated downstream pathways (23,24). Similarly, HIV-2 and SIV derived nef proteins were shown to associate directly with lck and TCR-zeta chain (25), the adaptor protein vav and to exhibit complex effects on TCR interaction with lck leading to suppression of both the proximal and distal lck signaling (26). Other in vitro studies however, showed that SIV nef associates with ZAP70 leading to the activation of NFAT and that select nef variants of highly pathogenic SIV strains even contain ITAM motifs capable of direct activation of NFAT (27). These and other studies demonstrate a rather complex effect(s) that HIV or SIV infection exhibits on TCR signaling within $CD4^+$ T cells.

Studies focused on the delineation of $CD4^+$ T cell signaling pathways in the natural SIV infected "disease resistant" host in comparison with studies of corresponding pathways in experimentally infected "disease susceptible" host provide an ideal tool for the select identification of those SIV associated signaling defects that correlate with disease resistance and susceptibility. Analysis of recall responses indeed showed that while SIV infected rhesus macaques much alike HIV-1 infected humans (28-31) demonstrate an accelerated loss of their antigen specific $CD4^+$ T cell responses (see Figure 1), SIV seropositive sooty mangabeys failed to show such loss in memory T cell responses. The decreased responses of SIV infected rhesus macaques were not secondary to loss of $CD4^+$ T cells and could not be ascribed to dysfunction of the APC (32). However, further comparative analysis failed to reveal significant differences related to the SIV status in TCR associated membrane proximal signaling (summarized in Figure 2). We have previously published that lck expression or phosphorylation did not show any significant difference in PBMCs from SIV infected RM and SM (33). Previous in vitro experiments showed that one of the mechanisms leading to cellular activation induced by the HIV/SIV protein nef is the association with and activation of vav and its downstream targets leading to cytoskeletal rearrangements and activation of the JNK pathway (34,35). When we analyzed the expression and phosphorylation patterns of vav in $CD4^+$ T cells from SIV infected RM and SM, there was no detectable difference related to the SIV status of the animals (Figure 3). $CD4^+$ T cells from SM exhibited consistently higher levels of vav expression regardless of the SIV status when compared to cells from RM. However, the levels of phosphorylation of vav in both the nonstimulated and the anti-CD3 stimulated $CD4^+$ T cells from both species were comparable. Interestingly though, anti-CD3 stimulation with anti-CD28 co-stimulation induced detectable increase in vav phosphorylation selectively in SM. This is an interesting finding, because it was previously proposed that vav plays an important role in the regulation of TCR and TCR/CD28 stimulation (36). It was indeed shown, that mice defective in Cbl-b, a negative regulator of T cell activation, show an increase in the baseline and TCR stimulation induced vav phosphorylation while Cbl-b wt mice required both TCR stimulation and CD28 co-stimulation for full vav activation (37,38). Our data therefore seem to suggest that although $CD4^+$ T cells from SM and RM exhibit similar parameters of vav activation in TCR only stimulated cells, the TCR/CD28 co-stimulation induces a faster response, as measured by vav phosphorylation, in the $CD4^+$ T cells from SM. However – as stated above – no differences in vav expression or phosphorylation were detected in either species with regards to the SIV status suggesting that the differences observed are more likely intrinsic to the SM species rather than specific for non-pathogenic SIV infection.

Analysis of LAT, ZAP70 and ERK did not show any significant difference in expression between $CD4^+$ T cells from SIV infected animals from both species (data not shown). It should be noted however that there was a difference in the requirements for TCR stimulation and co-

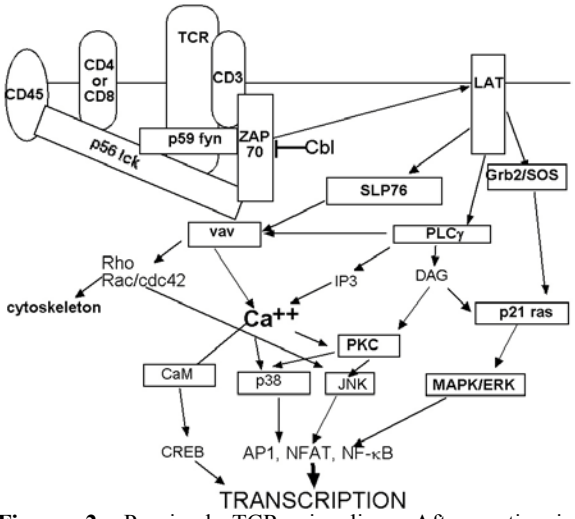

Figure 2. Proximal TCR signaling. After antigenic stimulation, intracellular ITAMs of TCR/CD3 are phosphorylated by src kinases (TCR associated p59 fyn, CD4 and CD8 associated p56 lck) and form an activation complex (AC) recruiting PTK ZAP70. ZAP-70 (phosphorylated by src kinases) in turn activates (phosphorylates) downstream linker/adapter proteins, such as LAT (linker for activation of T cells), that connect TCR signaling to downstream effectors. CD45 possesses phosphatase activity and can stimulate p56 lck. Cbl protein is a negative regulator of AC through ZAP70. Activated LAT assembles several complexes crucial for downstream signaling: p21 ras/MAPK/ERK pathway signaling is elicited either through the association of LAT with the GTP exchange factor (GEF) SOS/Grb2 complex, directly through SOS (during partial agonist T cell activation) or independently through PLCgamma and DAG (see below). Activation of phospholipase C (PLCgamma) by LAT regulates phosphatidylinositol (IP3) and diacylglycerol (DAG) metabolism, thus regulating Ca^{2+} and protein kinase C (PKC) pathways. Association of LAT with vav and the adapter protein SLP76 has a direct effect on Ca^{2+} mediated signaling and which also activates Rac/cdc42/Rho factors linking AC signaling to rearrangements within the cytoskeleton/actin . The nuclear targets of each of these signaling pathways are the transcription factors (such as CREB, AP1, NF-kB, NFATp). PKC and Ca^{2+} regulate the downstream mitogen activated protein kinase (MAPK)/stress activated protein kinase pathways ERK/JNK/p38. SAPK (JNK/p38) pathways are also regulated by activated Rac1/cdc42. Calcium levels also regulate the calmodulin cascade (CaM) leading to the activation of CREB.

stimulation for the activation of ERK pathways between cells from uninfected RM vs SM. Thus the $CD4^+$ T cells from RM required both TCR and CD28 co-stimulation to increase ERK phosphorylation while SM derived CD4 T cells showed moderate ERK phosphorylation with TCR stimulation only (32). These "species" specific differences – e.g differences in $CD4^+$ T cell observed in SIV negative animals are further discussed under section 5. The lack of significant differences observed in the proximal TCR signaling pathways in $CD4^+$ T cells from SIV infected animals from the two species (RM and SM) led subsequently to the complex screening and comparative analysis of protein kinase expression patterns in $CD4^+$ T cells from the pathogenically infected RM (33). This analysis yielded identification of a variety of cellular protein kinases that were differentially regulated in the natural vs pathogenically infected hosts (Table 1). These kinases represent a diverse group of enzymes involved in Ca^{2+} signaling (CaMKKbeta), MAPK activation pathways (MLK3, MLK2 and MKK3), cell cycle regulation (Plk3) and other pathways (GSK3, ROR2). These data indicate that there are significant differences in the expression of a number of signal transduction molecules that are characteristic for pathogenic but not natural SIV infection. Further studies aimed at defining the importance of these observed differences are therefore fully warranted.

4.2. STAT signaling

While the TCR signaling plays a critical role in antigen recognition and antigen specific T cell activation, stimulation of cytokine receptors by their cognate ligands plays an equally important role in the modulation of these responses. Defects and dysregulation of these important immuno-modulatory pathways can therefore have profound qualitative and quantitative effects on the nature of $CD4^+$ T cell response. One of the products of $CD4^+$ T cell response are cytokines and it is now generally accepted that HIV/SIV infection leads to the alterations in T lymphocyte associated cytokine expression. In HIV infected patients, a cytokine "shift" from the Th1 to Th2 type cytokines is detected during disease progression. It is characterized by defective production of interferon gamma (IFN gamma), IL-2 and IL-12 accompained by increased production of IL-4, IL-5, IL-6, and IL-10 (Reviewed in (39). Similarly in RM a dominant Th1 profile changes into the Th0 specific response after SIV infection. Interestingly however, SM continuously demonstrate a predominant Th2 specific T cell response irregardless of SIV status (40).

Although complex signaling mechanisms are involved in cytokine elicited T cell signaling, arguably, one of the most important signaling mechanisms of cytokine mediated response is represented by the JAK-STAT pathway. This pathway consists of the cytokine receptor associated Janus kinase (JAK) that is activated upon receptor engagement. This JAK activation leads to the phosphorylation of JAK substrates resulting in the recruitment and phosphorylation of STAT molecules. Phosphorylated STATs then localize into the nucleus where they exert transcriptional regulatory functions at various promoters. The STAT family of proteins consists of STAT 1, STAT 2, STAT 3, STAT 4, STAT 5A, STAT 5B and STAT 6. Different members of STAT family interact and are phosphorylated with various JAK kinases associated with particular cytokine receptors (reviewed in (41,42). Studies conducted with cells from HIV infected patients have shown that the STAT expression and activation is dysregulated. Pericle et al reported that purified T cells from HIV-infected patients at various stages of the disease consistently showed decreases in STAT 5A, STAT 5B, and STAT 1 (43). Bovolenta et al reported that ~75% of the patients with progressive HIV disease show constitutive

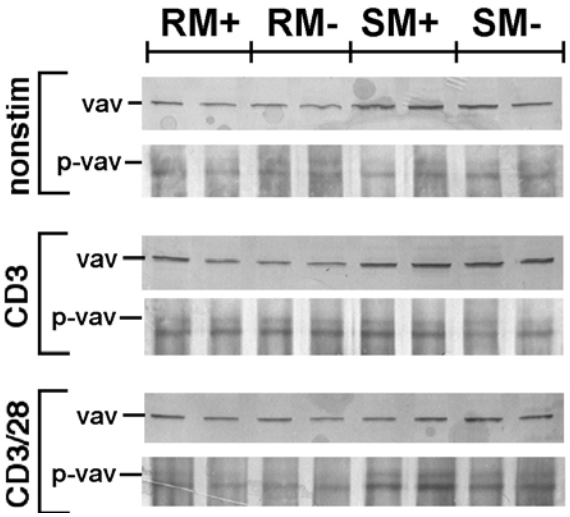

Figure 3. Vav expression and phosphorylation in RM and SM derived $CD4^+$ T cells is unaffected by SIV infection. Lysates from cells from SIV seronegative (-) or seropositive (+) sooty mangabeys and SIV naïve (-) or SIV infected (+) rhesus macaques were mock stimulated (nonstim), stimulated with anti-CD3 (CD3) or anti-CD3/anti-CD28 (CD3/CD28) coated beads and assayed for the presence of vav or phospho-tyrosine- vav (p-vav) by Western blot. Phospho-tyrosine vav detection was perfomed by first immunoprecipitating the lysates with anti-vav antibody with subsequent detection with anti-phospho-tyrosine antibody. Representative data from each group containing at least three monkeys are shown.

Table 1. Summary of the differences in protein kinase expression in $CD4^+$ T cells from sooty mangabeys and rhesus macaques

	Sooty mangabey	Rhesus macaque
MLK3	No change	Decrease
MKK3	No change	Decrease
GSK3	No change	Decrease (stimulated cells)
PLK3	No change	Decrease (>10 fold)
ROR2	Decrease (stimulated cells)	Increase (>10 fold)

Differences are listed as comparative levels of expression between SIV positive and SIV negative animals within each species

activation of a CD4 associated C-terminal truncated STAT 5 and STAT 1alpha (44). Further in vitro studies showed that HIV virions, env or nef proteins induce dysregulation of STAT 1, STAT 3 and STAT 5 (45,46). However to this date there is no evidence of the potential effect of SIV infection on STAT signaling in lymphoid cells from the non-human primate model of AIDS. It was therefore deemed important to determine whether SIV infection leads to perturbations of the JAK-STAT pathway within $CD4^+$ T cells from SIV disease susceptible RM and, if yes, whether similar perturbations also occurr in $CD4^+$ T cells from disease resistant SM. We analyzed STAT expression in $CD4^+$ T cells from uninfected and SIV infected RM and seronegative and seropositive SM by Western blot (Figure 4). The expression of STAT 1, STAT 2, STAT 3, STAT 4 and STAT 5 was consistently increased in the $CD4^+$ T cells obtained ex-vivo from infected animals from both species (Figure 4A). These higher levels of STAT expression in $CD4^+$ T cells from infected animals were maintained even when the cells were stimulated with either anti-CD3 antibody or anti-CD3/CD28 (data not shown). Interestingly, however the expression of STAT 6 was clearly increased in $CD4^+$ T cells from SM compared to RM, regardless of SIV status (Figure 4B). The increased expression of STAT 6 in SM may be a reflection of the presence of predominantly Th2 type of T cells. The STAT6 pathway has been identified as an important signaling mechanism for IL-4 mediated signaling and Th2 type response development (47). Clearly, further studies assessing the activation status of STATs will be required to characterize any potential differences in JAK-STAT signaling in detail. However, the data presented herein seem to suggest that the SIV infection has similar effects on the STAT expression in both pathogenically and naturally/apathogenically infected nonhuman primate hosts.

5. INTRINSIC PARAMETERS OF $CD4^+$ T CELL RESPONSE IN NATURAL SIV HOST

5.1. $CD4^+$ T cell anergy

Data from several studies showed that SIV infected rhesus macaques much alike HIV-1 infected humans (28-32) demonstrate an accelerated loss of their antigen specific $CD4^+$ T cell responses and exhibit T cell anergy. T cell anergy is characterized by nonresponsiveness of the T cell upon interaction with its cognate antigen presented in association with MHC molecules. It is brought about by an insufficient level of T cell stimulation through the TCR alone (signal 1) in the absence of co-stimulatory signal II (e.g. stimulation via CD28) that is delivered by other cells, such as APCs (48,49). Alternatively anergy can be induced by other pathogenic mechanisms, such as those that are operational in HIV and SIV infection, where the lentiviruses directly target $CD4^+$ T cells and APCs by affecting their signaling and functions. Anergic cells are characterized by their inability to proliferate and express IL-2 following TCR specific stimulation by their cognate antigen even in the presence of adequate co-stimulation (50,51). Indeed, $CD4^+$ T cells from HIV infected patients also exhibit defective IL-2 production and these defects were shown to be reversed following HAART (52-55). Similarly, initially "anergic" p24 specific $CD4^+$ T cells from HIV infected individuals exhibited increased specific activation after additional co-stimulation with Th1 specific cytokines or CD28 ligands (56).

It was therefore interesting to find that sooty mangabey $CD4^+$ T cells exhibit an increased resistance to the development of anergy (32). This study suggested that, regardless of SIV status, the $CD4^+$ T cells from sooty mangabey synthesize IL-2 upon signal 1 activation alone which prevents anergy induction. This "anergy resistant" phenotype was further characterized by a substantial increase in ERK phosphorylation in $CD4^+$ T cells from sooty mangabey after stimulation with signal 1 alone. Interestingly, there were no differences in ERK stimulation in seropositive vs. seronegative sooty mangabeys, although

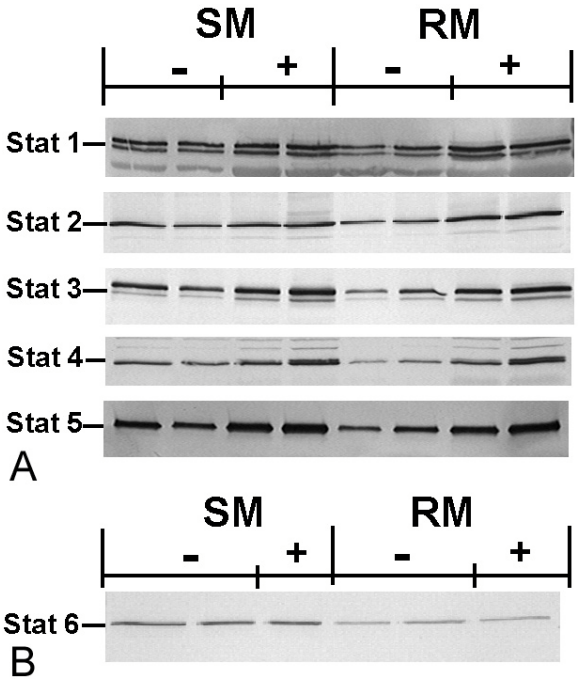

Figure 4. STAT expression in CD4 T^+ cells from RM and SM. Lysates from cells from SIV seronegative (-) or seropositive (+) sooty mangabeys and SIV naïve (-) or SIV.

Table 2. Comparison of the proximal promoter sequences of select cytokines.

	TNFalpha	IFNgamma	IL12alpha	IL2
Rhesus macaque	96.4%	99.7%	94%	98.6%
Human	88.1%	97.9%	96.6%	95.3%

Numbers indicate percent identity of the sooty mangabey sequence to the corresponding sequence in the species indicated

it has been reported that ligation of CD4 by HIV derived gp160 inhibits ERK stimulation (57,58) and seropositive sooty mangabeys harbor high viral loads and therefore abundance of SIV derived gp160.

This data would indicate that the potential differences in T cell signaling within $CD4^+$ T cells from sooty mangabey are likely to be intrinsic and may contribute to the SIV disease free phenotype of this species.

5.2. Cytokine expression and promoter polymorphisms

One of the pathogenic mechanisms of the immune deficiency observed in patients and nonhuman primates with AIDS is the role of alterations in the secretion patterns of cytokines and expression of cytokine receptors. As noted above, peripheral blood cells from HIV infected patients exhibit decreased IL-2 production that is restored by HAART therapy (52-55). Disease progression in both HIV infected humans and SIV infected RM leads to a "shift" in the cytokine expression profile from a Th1 to Th2 prototype or Th1 to Th0 prototype, respectively (39,40). On the contrary, maintaining the Th1 type cytokine secretion pattern was found characteristic for slow disease progression in LTNP HIV infected humans (59). One of the investigated mechanisms underlying the potential resistance to the lentivirus induced perturbations in cytokine expression is the effect of sequence variations – polymorphisms - in the regulatory regions of these cytokines or cytokine receptors. Thus certain CCR5 promoter polymorphisms were associated with rapid disease progression in HIV infected humans (60,61) and negatively associated with LTNP status (62). Specifically, for example G/G homozygosity at position 59029 within the CCR5 promoter region was shown to be associated with lower CCR5 expression and slower disease progression (63). Polymorphism within the RANTES promoter (RANTES-28G) increased RANTES expression and was associated with delayed progression (64). TNF-alpha promoter polymorphism at position –308 has been extensively studied and Quasney et al showed a link between the presence of the A allele and AIDS dementia (65). However, other reports failed to establish a link between this polymorphism and disease progression (66,67). Similarly no evidence was found for a link between IFNgamma promoter polymorphism and AIDS progression (68). Polymorphism 589T in the regulatory region of IL-4 (a Th2 type cytokine) was found to be associated with an accelerated HIV phenotypic switch from NSI to SI phenotype and potentially with faster disease progression (69). From this point of view the predominantly Th2 response observed in sooty mangabeys irregardless of SIV status represents an interesting phenomenon since it is associated with disease resistance rather than with accelerated disease progression. Similarly interesting is the fact that the resistance to the SIV disease in SM is associated with an anergy resistant phenotype of $CD4^+$ T cells and their concurrent differential regulation of IL-2 response (discussed in 5.1). To investigate whether these differential patterns of cytokine expression in SM may be a result of gross differences in regulatory sequences we initiated studies aimed at the comparison of the proximal promoter sequences of select cytokines. As can be seen in Table 2 proximal (600-800 bp) sequences of TNF-alpha, IL-2, IFN-gamma and IL-12-alpha from SM were found highly homologous to the corresponding sequences from RM or human. We did not detect any significant deletions or substitutions within these cytokine promoter regions known to be transcription factor binding sites that would be specific for SM. Interestingly, in sooty mangabeys we detected a single nucleotide substitution within the IL-2 promoter region (32) that was shown to be essential for the down regulation of IL-2 transcription in anergic cells and anergy induction (70). Further analysis will be required to assess the importance of this substitution in anergy and in the disease resistant phenotype of SM. Similarly, although there were no apparent significant differences in other cytokine promoters listed it cannot be ruled out that the few 1-2 nucleotide substitutions observed may play a role in the observed differences in cytokine expression.

6. SUMMARY AND PERSPECTIVE

The purpose of this review was to summarize our current knowledge of signaling and regulatory events specific for $CD4^+$ T cells from natural SIV host sooty mangabey with a special emphasis on those events that may

be associated with the SIV disease resistance. It is clear that the utilization of the two models of SIV infection – natural/apathogenic and experimental/pathogenic – is a powerful tool for defining those pathogenic mechanisms that are critical for the development of progressive immune dysfunction in HIV/SIV infection. This experimental model therefore provides a means for defining those SIV induced effects that although significantly pronounced in vivo may not be crucial in the development of immune dysfunction since they are equally pronounced in the naturally infected asymptomatic host. It also offers an insight into the potential inherent parameters of the immune system that may prove important for the development of resistance to SIV disease. The data available so far indicate that the SIV disease resistance in this nonhuman primate species is a result of both adaptational mechanisms involved in the virus-host interaction and some intrinsic, species specific features of the immune system. Such differential studies (currently in progress) can provide important clues not only on the mechanisms of $CD4^+$ T cell dysregulation in AIDS, but also may lead to the identification of strategies for immune reconstitution.

7.ACKNOWLEDGEMENTS

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Abbreviations: AGM, African green monkeys; SM, sooty mangabey (Cercocebus atys); RM, Rhesus macaque (Macacca mulatta); TCR, T cell antigen receptor; STAT, Signal Transducer and Activator of Transcription; JAK, Janus Kinase; MAPK, Mitogen Activated Protein Kinase; ITAM, immunoreceptor tyrosine-based activation motif; LTNP, Long Term Non-Progressor; SI, syncytia inducing; NSI, non-syncytia inducing

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