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Reduced Activation of CD4+ Regulatory T Cells is Associated With Preserved HIV- Specific CD8+ T Cells in Cohort of Indian Long Term Non Progressors (LTNPs)

Abstract

Background: Regulatory T cells (Treg) are CD4+ T cell with suppressive function and play a critical role in controlling immune activation and inflammation but its role in HIV infection is not well understood. The present study is aimed to determine the interplay between the Tregs, HIV specific CD8+ CTLs and the immune activation in HIV infected individuals with non-progressive disease.

Methodology: CD4+CD25+highFoxP3+ Tregs cells were characterized for their frequency and activation status in 20 long term non Progressors (LTNPs), 40 Progressors and 30 HIV-1 negative healthy controls whereas the HIV-1 Env C-specific CD8+ CTL frequencies were measured in 19 LTNPs using multicolour flow cytometry. The levels of lipopolysaccharide (LPS) and sCD14 were measured in plasma samples by enzyme linked immunosorbent assay.

Results: The frequencies of total and activated (CD39+) Tregs were significantly lower in LTNPs as compared to those seen in Progressors and were associated with higher CD4 counts ($p<0.0001$ for both). The total Treg percentage were associated with higher lower plasma viral loads ($p=0.005$). No association between the LPS and sCD14 levels and Tregs or HIV specific CD8+ T cells was observed. The activated CD4+ and CD8+ T cells were significantly associated with higher Treg frequencies and lower plasma viral load (PVL). Lower frequencies of CD39+ activated Tregs were associated with higher CD8+ CTL response ($p=0.01$) in LTNPs.

Conclusion: Lower activation of Tregs might have an influence on HIV-specific CTL response. Additionally understanding the interplay between the activation of cellular compartment and HIV-specific CTL response is critical to plan the focused intervention.

Keywords: CTLs; CD39; immune activation; LTNP; Treg cells

Research Article

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Abbreviations: CTL: Cytotoxic T Lymphocytes; ELISA: Enzyme-Linked Immunosorbent Assay; HIV: Human Immunodeficiency Viruses; LTNPs: Long Term Non Progressors; LPS: Lipopolysaccharide PVL: Plasma Viral Load

Introduction

Understanding the immune correlates of non-progressive HIV infection is utmost important in planning immune protection strategies like vaccine and also efficient immune therapies. HIV infected Long term Non Progressors (LTNPs) maintain CD4 counts for more than 7-10 years of HIV infection and may or may not have detectable viral load whereas the elite controllers (ECs) limit the viral load below undetectable level (<50 copies/ml) and also have normal CD4 count [1-3]. Since both these populations are known to be infected with replication competent HIV, these populations are thus could be used as a model for understanding immune correlates of absence of disease progression. Presence of HIV-specific CD8+ CTL responses is known to be important factor contributing in control over disease progression [4-6]. The Regulatory T cells (Tregs) have an immuno regulatory function and known to control immune activation and inflammation [7-9] and could also play a role in the HIV disease progression.

The Tregs may suppress the chronic immune activation in HIV infection reducing the immune mediated damage and however in the process they also may suppress the CTL responses contributing to viral multiplication and disease progression [10,11]. We have previously shown that the LTNPs from our cohort have lower cellular immune activation [12] however their association with Treg frequencies was not studied. Also the influence of Tregs on the CD8+ T cell responses in non-progressive HIV infection has not been studied. This study aimed at determining the relationship between the *ex vivo* frequencies of Treg and HIV-specific CD8+ CTLs and the impact of immune activation on these cell population in LTNPs.

Materials and Methods

Twenty (07M/13F) LTNPs (ART naive, asymptomatic HIV infected individuals with a stable CD4 count of ≥500 cells/mm^3 for a period of 7 or more years), forty (18M/22F) Progressors

(ART naive HIV infected patients with CD4 count ≤500 cells/mm^3) and thirty (19M/11F) HIV seronegative healthy controls (with self-reported history of no fever in last two weeks and no major systemic disease) were enrolled in the study. All enrolled LTNPs fulfilled the inclusion criteria for LTNP even at one year after enrolment in the present study. The demographic and clinical details of the study participants are given in (Table 1). There was no significant difference in age of the enrolled participants from all study groups. The CD4 counts were significantly lower in Progressors (median 326; range 75-486 cells/mm3) as compared with the healthy controls (Median 960; range 673-1772 cells/mm3, p<0.0001), and LTNPs (Median 748; range 531-1540 cells/mm3, p=0.001), whereas the log plasma viral load (PVL) was significantly higher in Progressors (median 4.8; range 2.8-6.1 $\log_{10}$ copies/ml) as compared to LTNPs (median 3.5; range 1.6-5.1 $\log_{10}$ copies/ml, p=0.002). Twenty ml whole blood sample was collected from each study participants. The plasma and peripheral blood mononuclear cells (PBMCs) were separated as previously described [13] and stored at -80 ^{0}C and -196 ^{0}C respectively until tested. The study was approved by institutional ethics committee, and all subjects gave written informed consent before participation.

Table 1: Demographic characteristics of study participants.

Cohort			
HIV status Median (Range)	HCs (n=30)	LTNPs (n=20)	Progressors (n=40)
Age (Years)	33 (26-48)	36 (30-54)	35 (30-48)
Viral Load (log10)	NA	3.5 (1.6-5.1)	4.81 (2.8-6.1)
CD4T cell (cells/mm^3)	960 (673-1772)	748 (531-1540)	326 (75-486)
% CD4 T cells	62 (39-81)	54 (30-74)	32 (12-61)

Abbreviations: HIV: Human Immunodeficiency Virus; ND: Not Done; HCS: Healthy Controls; LTNPs: Long Term Non Progressors.

CD4 count and viral load estimation

CD4 T cell counts were quantified by Flow cytometry (FACS Cali bur, Becton-Dickinson, CA) using Tru Count kit (Becton-Dickinson, San Jose, CA) described previously [13] and plasma viral load was measured as RNA copies/ml by Abbott m200rt HIV-1 Real time PCR according to the manufacturer's instruction. The Treg frequencies were determined using multicolour flow cytometry. Briefly, 1X10^6 PBMCs were permeabilized with Perm 2 (BD Biosciences, San Jose, CA) and incubated with a cocktail of antibodies [anti FoxP3 PerCpCy5.5, anti CD4 PECy7, anti CD25 APCCy7, anti CD39 APC (all from BD Pharmingen San Jose, CA), and anti CD3 PETR (Invitrogen, Carlsbad, CA) for 30 min at room temperature in the dark. After washing, the cells were fixed with 3% para formaldehyde and acquired on FACSA ria-I using FACSDiva software version 6.1.3 (BD Biosciences, USA).

The data was analysed using Flow Jo software version 7.6.5 (Tree star, Ashland, or USA). At least 1,00,000 events of lymphocytes were acquired using appropriate cells and isotope controls. Treg were identified as CD4+CD25+^{high} FoxP3+ cells and the activated Treg as CD39 expression. The gating strategy is shown in (Figure 1a). The HIV-specific CTLs were identified as CD8+ T cells secreting IFN-γ, and/or expressing CD107a in response to HIV Env stimulation using multicolour flow cytometry as described previously [14]. Briefly, the PBMCs were stimulated for 2 hrs with or without overlapping HIV-1 C Env peptides (catalogue No. 9499, NIH AIDS Reagent program, USA) (5 µg/ml final concentration) at 37 °C in 5% CO2, followed by incubation with Brefeldin A (10 µg/ml; Sigma Aldrich, USA) for 4 hrs. The Staphylococcal Enterotoxin B (SEB) (1µg/ml final concentration) was used as positive control, while unstimulated cells were kept as background control. After washing, the cells were incubated with anti CD3 PECy7 and anti CD8 APCCy7 antibodies for 30 min in dark at room temperature.

After washing, the cells were fixed and permeabilized with Perm2 (BD Biosciences, San Jose CA) and incubated with anti IFN-γ APC, anti CD107a PECy5.5 (Becton Dickinson, San Jose, CA) for 30 min at room temperature in the dark. The cells were fixed in 3% para formaldehyde, acquired on FACSAria-I using FACSDiva software version 6.1.3 (BD Biosciences, USA). Minimum 1,00,000 events of CD3+ T lymphocytes were acquired using appropriate cell and isotope controls. The gating strategy to identify HIV specific CD8+ CTLs is mentioned in (Figure 2a). The magnitude of Env-specific CD8+ CTL response was expressed as sum of % of either or both IFN-γ secreting or CD107a expressing Env stimulated CD8+ T cells after subtracting the background response.

Estimation of soluble markers of immune activation

The LPS and sCD14 levels were measured in the thawed plasma samples using a commercially available enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions [sCD14: Quantikine Immunoassay kit, (R&D system, Minneapolis, MN) and LPS: Shanghai Blue Gene Biotech co ltd, China]. The concentrations were estimated using a standard curve generated by the standards included in the kit and expressed as pg/ml.

Statistical analysis

Graph Pad Prism (version 5.01) was used to perform nonparametric statistical tests. Mann-Whitney t test was used to estimate differences in various parameters within study groups. The association of total and activated Treg frequencies with the markers of disease progression and *ex vivo* frequencies of HIV-specific CD8+ CTLs was assessed using the Spearman correlation coefficient. P-values less than 0.05 were considered as significant.

Results

Treg frequencies in LTNPs were unaltered

The CD4+ Treg frequencies (median 2.8%, range 1.4%-4%) in LTNPs were similar to those seen in healthy controls (median 3.1%, range 1.6%-4.5%) (p>0.05), however significantly higher in Progressors (median 4%, range 3%-8.7%) as compared to those observed in LTNPs (p=0.001) and in healthy controls (p=0.003) (Figure 1b). The frequencies of activated (CD39+) Tregs were also found to be significantly increased in HIV infection (p<0.005), as compared to those in healthy controls, whereas, with in HIV infected groups the frequencies were significantly higher in Progressors (p=0.02) (Figure 1e). The Treg frequencies correlated inversely with CD4+ T cell counts (r=-0.55, p<0.0001) (Figure 1c) and positively with PVL (r=0.36; p=0.005) (Figure 1d). The CD39+ activated Tregs were also associated with lower CD4 counts (r=-.42; p<0.0001) (Figure 1f) but not with PVL, although showed a trend of positive association (r=0.23; p=0.06) (Figure 1g).

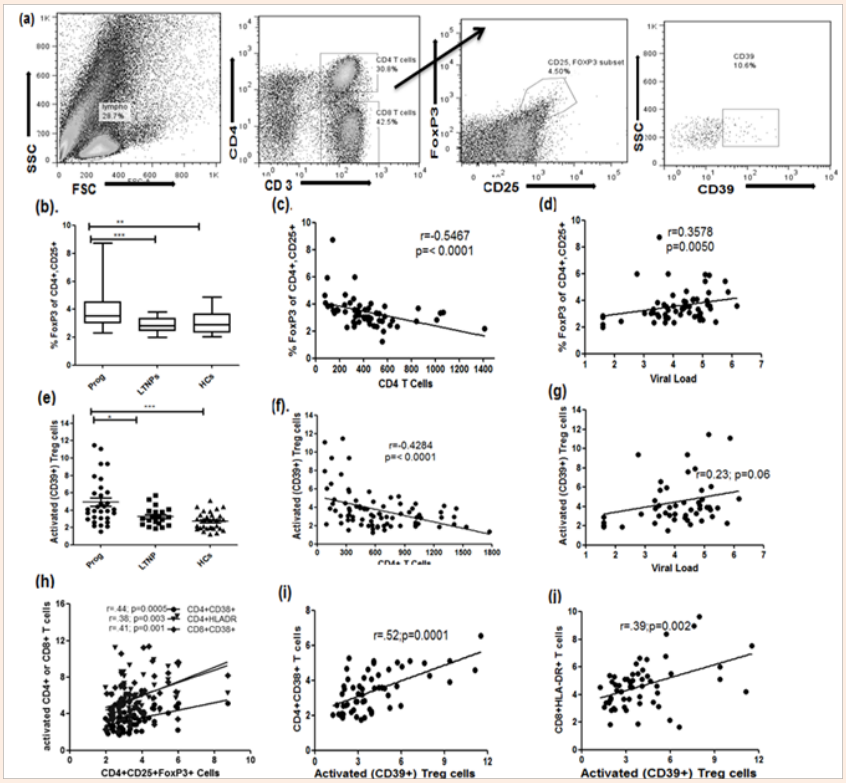

Figure 1: Identification of regulatory T cells (Treg) in PBMCs by flow cytometry. Treg cells were identified as CD4+CD25^{high}+FoxP3+ and activated Treg as CD4+CD25^{high}+FoxP3+ CD39+ cells (extreme right plot) in a representative HIV-1 infected subject.

a. The lymphocyte were first gated on the basis of forward and side-scatter and second gate was set on CD4+ T cell population, CD4+ T cells were further gated to identify Treg cells (CD25+FoxP3+) and Treg cells were further gated to quantify activated Treg (CD39+) cells.

b. The dot plots representing the frequencies of Treg cells in different study groups.

c. The scatter diagram represent the correlation between the frequencies of Treg cells on (Y-axis) with corresponding CD4 counts (on X-axis),

d. And plasma viral load (RNA copies/ml) on (X-axis).

e. The scatter diagram represents the frequencies of activated Treg (CD39+) cells in different study groups. (f) The scatter diagram represents correlation between activated Treg (CD39+) cells on (Y-axis) with CD4 counts on (X-axis),

f. And plasma viral load (RNA copies/ml on (X-axis).

g. The analysis of association is shown between the frequencies of CD4+CD38+, CD4+HLA-DR+, and CD8+CD38+ cells on (Y-axis) with the corresponding Treg cells on (X-axis).

h. The analysis of association is shown between the frequencies of CD4+CD38+, CD4+HLA-DR+, and CD8+CD38+ cells on (Y-axis) with the corresponding Treg cells on (X-axis).

i. The analysis of association is shown between the frequencies of activated Treg cells on (X-axis) with CD4+CD38+ T cells on (Y-axis), and

j. CD8+HLA-DR+ T cells on (X-axis).

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Activated Tregs correlated inversely with HIV-specific CD8+ CTL frequencies

The frequencies HIV-specific CD8+ CTLs were estimated as CD8+ T cells expressing CD107a and secreting IFN-γ upon HIV-1C Env stimulation in 19 LTNPs. The Env-specific CD8+ CTLs (median 3.01; range 0.67%-17.47%) correlated inversely with PVL (r=-0.51; p=0.02) and positively with CD4 counts (r=0.57; p=0.01). The inverse correlation was observed between activated CD39+ Treg frequencies and Env specific CTL response (r=-0.58; p=0.01) (Figure 2b). The total Treg frequencies although showed a trend of negative correlation with the Env specific CD8+ CTLs, the correlation was not statistically significant (r=-.42; p=0.07) (Figure 2c). We could not determine the CD8 frequencies in Progressors due to the unavailability of sufficient PBMCs from these patients.

Plasma levels of sCD14 and LPS did not correlate with Treg frequencies

The levels of both LPS and sCD14 were similar in LTNPs and Progressors [LPS: median: 38.24 ng/ml (range 16.64-157.70 ng/ml) in LTNPs versus median: 57.09 ng/ml (range 23.76-172.03 ng/ml) in Progressors and sCD14: median 1703 ng/ml (range 674-7167 ng/ml) in LTNPs versus median: 1836 ng/ml (range 1191-4611 ng/ml) in Progressors] and significantly higher than the levels in healthy controls [LPS; median 36.72 (range 8.1-84.37 ng/ml) and sCD14: median 1496 (range 569-2620)] (p<0.005 for all). Neither LPS nor sCD14 levels correlated with the *ex-vivo* frequencies of Treg cells (LPS: p=0.07, sCD14: p=0.8) (Figures 2d & 2e), activated Treg cells (LPS: p=0.37, sCD14: p=0.54) (Figures 2f & 2g) and with the Env specific CD8+ CTLs (LPS: p=0.1, sCD14: p=0.2) (Figures 2h & 2i).

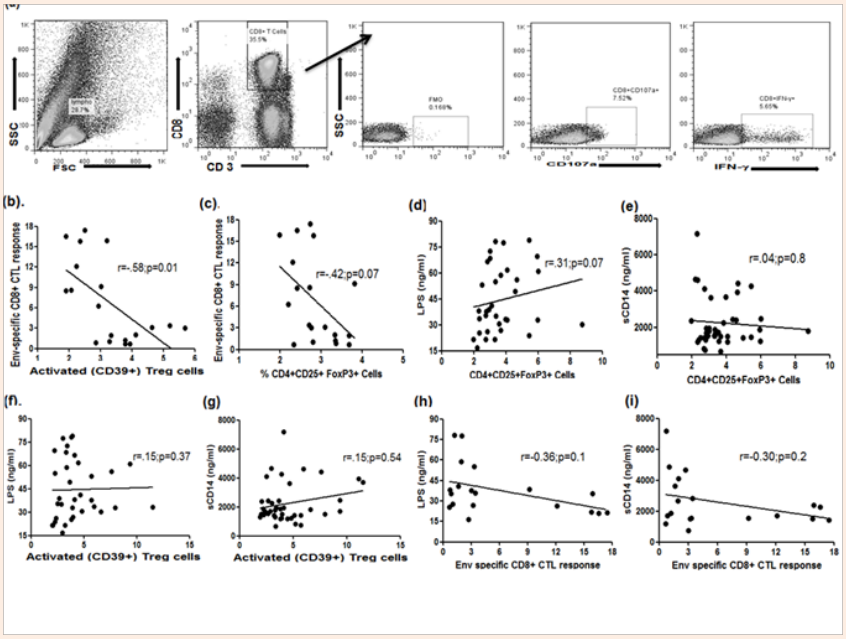

Figure 2: The gating strategy for quantification of CD8+ CTLs response in terms of CD107a and IFN-γ secreting CD8+ T cells upon HIV Env stimulation.

a. The lymphocytes were first gated on the basis of forward and side-scatter and second gate was set on CD8+ T cells, CD8+ T cells were further gated to quantify the CD8+ CTLs response in terms of CD107a and IFN-γ secreting CD8+ T cells in study participants.

b. The scatter diagram represents the analysis of association between the Env- specific CD8+ CTL response was expressed as percentage of IFN-γ secreting or CD107a expressing or both CD8+ T cells on (Y-axis) with activated (CD39+) Treg cells on (X-axis), and

c. Frequencies of Treg cells on (X-axis).

d. (d) The scatter diagram represents correlation between Treg cells on (X-axis) with soluble activation marker LPS ng/ml on (Y-axis), and

e. sCD14 on (Y-axis).

f. The analysis of association is shown between the frequencies of activated (CD39+) Treg cells on (X-axis) with LPS ng/ml on (Y-axis), and

g. sCD14 on (Y-axis).

h. The analysis of association is shown between the frequencies of Env specific CD8+ CTL response on (X-axis) with LPS ng/ml on (Y-axis), and

i. sCD14 on (Y-axis).

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Discussion

Understanding the interplay between the immune activation, regulatory immune cells such as Tregs and effector immune cells such as HIV-specific CTLs is important for understanding the correlates of disease control and for devising strategies for the same. We used LTNPs as a model of disease control to understand this interplay. We observed unaltered frequencies of total and activated CD4+ Tregs in Indian LTNPs confirming previous findings [15-17]. The activated CD39 expressing Treg frequencies correlated with HIV-1 higher viral load supports the earlier observation [18-19]. Further we determined whether the immune activation markers correlate with *ex vivo* frequencies of Tregs.

Although the levels of activation markers, sCD14 and LPS were considerably higher in both LTNPs and Progressors, the levels were not associated with either Treg frequencies/PVL/CD4 counts/HIV Env-specific CTL response. An absence of association of these levels with HIV disease progression have been reported previously [20] and similar observation in our study indicate that although LTNPs from our cohort show presence of immune activation however, it's role in either disease progression or the increase in Treg frequencies might be questionable. We further wanted to assess whether the Tregs have any association with cellular immune activation in study participants. Our previous study on the same study participants have reported that the cellular immune activation (frequencies of CD38+ and HLA-DR+ CD4+ and CD8+ T cells) in LTNPs was lower as compared to that observed in Progressors and the activation was associated with higher PVL and lower CD4 count as well as with the lower frequencies of central memory T cells [12]. The lower frequency of activated Treg observed in these LTNPs in the present study adds to the previous findings indicating probable presence of uncompromised cellular immune compartment in LTNPs.

Also we observed that the total and activated (CD39+) Treg cell frequencies were associated with higher percentages of activated (CD38 and HLA-DR expressing) CD4 and CD8+ T cells (Figures1h-1j). These analysis indicate that the lower cellular immune activation in LTNPs extended to Tregs might be collectively responsible for reduced virus multiplication and thus might be one of the important factors contributing to the control over the disease progression. Further it is known that the Treg cells negatively influence the CD8+ CTL response [21-23]. The inverse association between the *ex vivo* frequencies of activated Tregs and Env specific CD8+CTLs in LTNPs probably indicate that the activated Tregs might be responsible for the compromised CD8+ CTL responses and thus favoring virus multiplication. The presence of CD4+ CD25+ cells during in vitro HIV-specific stimulation has been shown to decrease HIV-specific CD4 and CD8 responses [9,21,23-27]. A study by Jiao et al. has shown that the absolute counts of circulating Tregs from individuals with the progressive HIV infection but not from LTNPs were inversely correlated with the activation and apoptosis of CD8+ T cells [17]. These differences could be attributed to the different study population with different genetic background. Also, recently, Elahi and coworkers reported that epitope-specific CD8+ CTLs restricted to the protective HLA allele groups HLA-B*27 and HLA-B*57 are not susceptible to Treg mediated suppression [28].

Conclusion

In our population however the LTNPs do not show presence of HLA-B*27 and HLA-B*57 alleles (unpublished observation). Hence it might be possible that the Tregs from our LTNP cohort may not have differential suppression. Considering all these observations we can predict that the lesser activation of cellular compartment of innate and adaptive immune response including Tregs observed in LTNPs might have a positive influence on HIV-specific CD8+ CTL response and thus might have a role in reduced virus multiplication and absence of disease progression. It would be important to assess the importance of this finding in a prospective study to understand the influence of Treg on HIV and vice versa in HIV disease progression which might improve our understanding of HIV immune pathogenesis and might lead to the development of effective strategies for immune prevention of disease progression.

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Conflict of Interest

The authors declare no conflict of interest.

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