Polyfunctionality of TB-specific CD4+ T cells in HIV-TB co-infection in Latent and Pulmonary TB

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INTRODUCTION

HIV infected persons with latent tuberculosis infection (LTBI) have a 10% ***annual*** risk of developing active tuberculosis (TB) compared to a 10% ***lifetime*** risk in HIV-uninfected individuals.

Mean CD4+ T cell counts of HIV+ patients with pulmonary TB (PTB) are higher than seen with other opportunistic infections suggesting that progression to active TB in the setting of HIV infection may be partly related to functional impairment of CD4+ T cells.

Here we compare CD4+ T cell cytokine profiles and polyfunctionality in response to *M. tuberculosis* (MTB) antigens between TB uninfected, LTBI and PTB in HIV+ adults.

METHODS

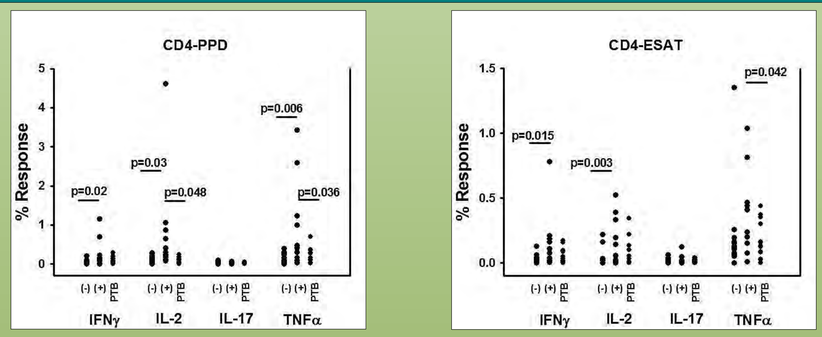
- ❑ HIV+ adults recruited in Kampala, Uganda were differentiated into 3 groups:
  1. PTB (positive sputum smear and/or culture for MTB)
  2. LTBI (>5mm response to the tuberculin skin test (TST) and negative chest x-ray)
  3. TST- (negative TST and chest x-ray)
- ❑ Multicolor flow analysis was performed on PBMC stimulated with either PPD, ESAT+CFP10, or SEB, and frequencies of IL-2, IFN-γ and TNF-α secreting cells were determined within the memory subset of CD4+ T cells.
- ❑ Polyfunctionality was determined using FlowJo and analysis was performed using SPICE software.

STUDY POPULATION

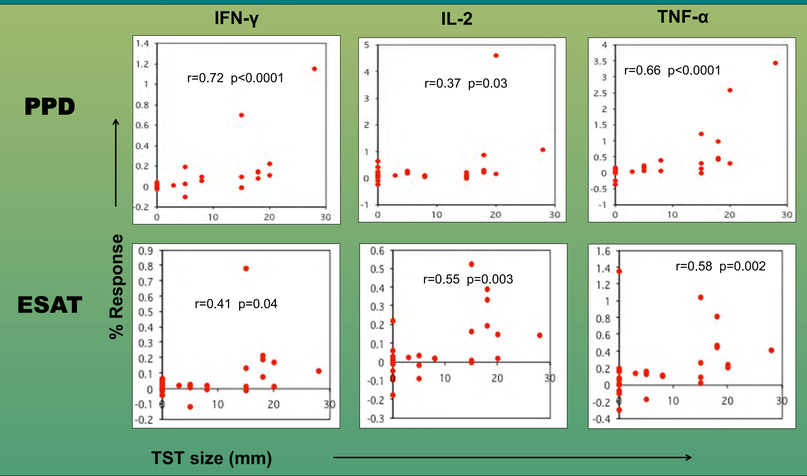
	TST-	LTBI	PTB	Significant P values
N	15	15	15	-
Median age (range)	33 (26-42)	30 (25-49)	34 (25-56)	-
Sex	F9, M6	F12, M3	F10, M5	-
TST in mm	0 (0-3)	15 (5-28)	-	-
Log 10 HIV-RNA (copies/ml)	4.3 (2.6-5.9)	4.1 (2.6-5.5)	5.7 (3.2-6.7)	-
CD4 count (cells/mm^3)	230 (34-502)	300 (221-646)	359 (168-724)	p=0.03 (TST- vs. LTBI)

RESULTS

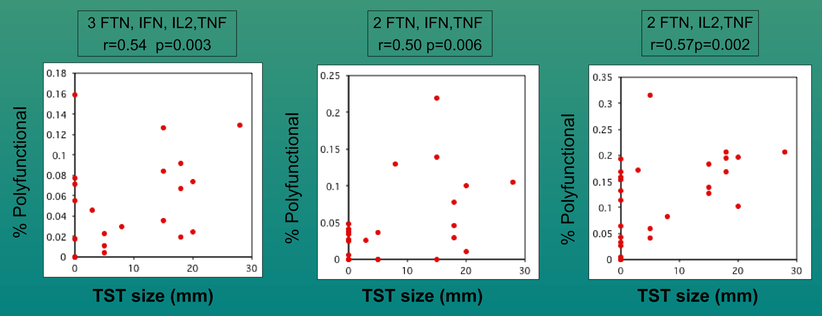
MTB specific CD4+ T cell secretion of cytokines is higher in LTBI compared with TST- group



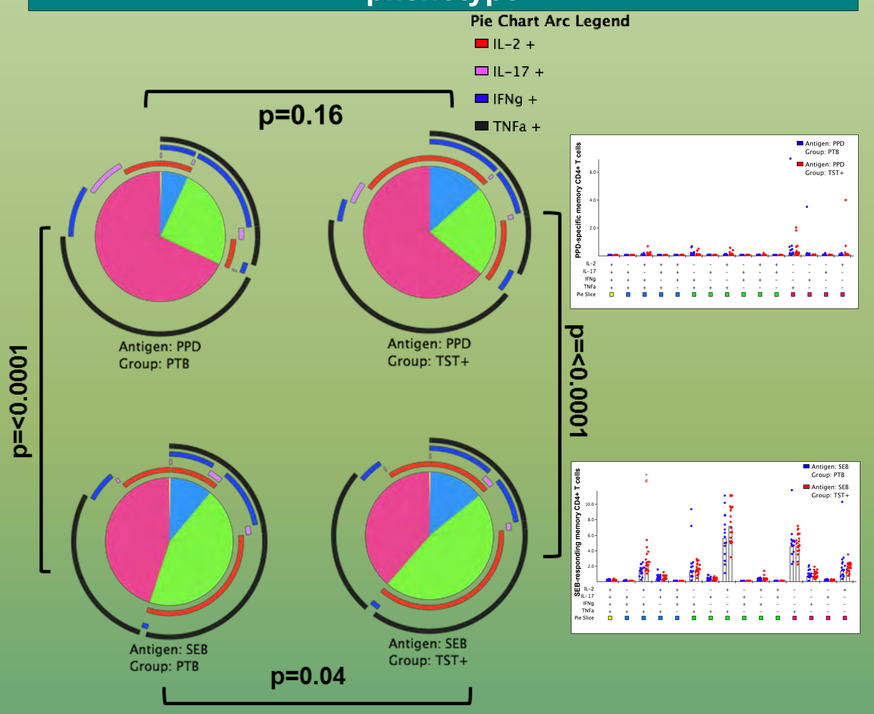
Cytokine responses to both PPD and ESAT stimulation correlate positively with TST measured in millimeters (mm)



Polyfunctional response groups that contain TNF-α correlate with size of TST suggesting TNF is the major cytokine response in LTBI



Polyfunctional profile of MTB-specific CD4+ T cell responses were similar in LTBI and PTB groups with the TNF-α-only secreting cells being the most abundant phenotype



CONCLUSIONS

- ❑ MTB specific CD4+ T cell cytokine responses were higher in LTBI compared to TST- HIV+ adults. TNF-α responses were greater in the LTBI group compared to PTB.
- ❑ ESAT-specific CD4+ T cell responses correlated positively with TST in mm suggesting that TST response in Ugandans is reflective of TB-specific antigen infection with MTB rather than BCG vaccination.
- ❑ Polyfunctional CD4+ T cell profiles differ between LTBI and PTB among HIV-uninfected individuals. The fact that we did not observe such a difference in MTB antigen responses in HIV+ subjects suggests that LTBI may represent a more “smoldering” active TB state. This may help explain the significantly increased risk of progression to active TB in this population.

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