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M. tuberculosis antigens under diversifying evolutionary selection induce Th17 responses in human infection

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While CD4 T cells are known to be essential for immunity to M. tuberculosis (Mtb), the effector functions and antigenic targets that provide optimal immunity to Mtb have not been defined. While recent efforts to define protective T cell effector functions have generated interest beyond IFNγ, there have been fewer efforts to define optimal Mtb antigens. Furthermore, it is unclear whether all Mtb antigens induce T cells with the same effector functions, or whether individual antigens might induce T cells with different effector functions. We hypothesized that CD4 T cells that recognize distinct Mtb antigens differ in their functional and phenotypic properties, and compared a set of Mtb antigens that are unusual for their exhibiting evidence of diversifying evolutionary selection (suggesting that their recognition is detrimental to the bacteria) to a set of conserved antigens (representing the majority of Mtb antigens). We termed the former group Rare Variable Mtb Antigens (RVMA). We studied two cohorts of IGRA+ HIV-uninfected adult recent household contacts of an active case of TB in western Kenya and in Addis Ababa, Ethiopia. We stimulated PBMC with overlapping peptides representing the individual antigens in each category and characterized the CD4 T cell responses by intracellular cytokine staining and flow cytometry. We found that RVMA preferentially induce CD4 T cells that express the transcription factor RoRγt, produce IL-17, and express varying levels of the chemokine receptor CCR6. In contrast, 'classical' conserved Mtb antigens induce T cells that produce IFNγ, express the transcription factor Tbet, and chemokine receptor CXCR3. Our results indicate that individual Mtb antigens can induce T cells with different functional responses and suggest that RVMA can be valuable antigens in vaccines for those already infected with Mtb, to amplify existing antigen-specific Th17 responses and prevent progression to TB disease.

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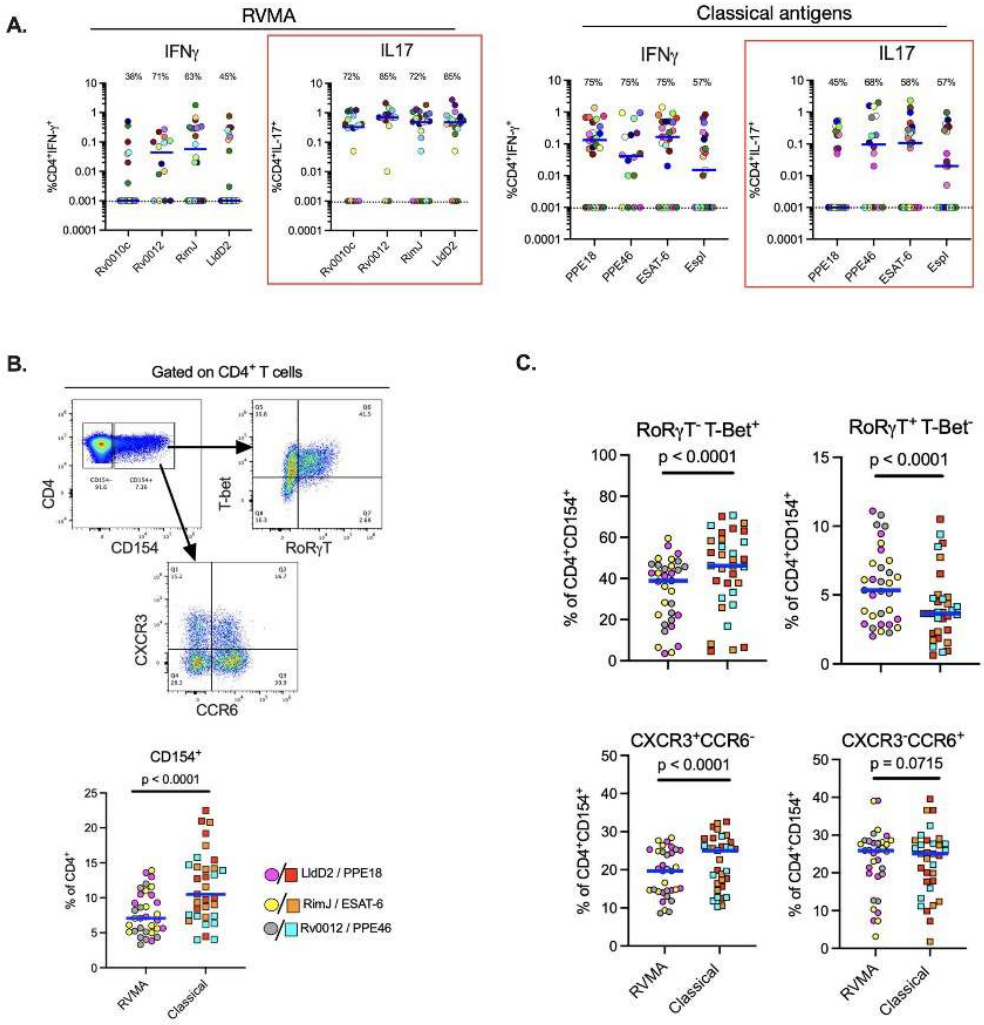
Conflicts of Interest

None



Rare Variable *M. tuberculosis* Antigens (RVMA) induce predominant human Th17 responses. (**A**) Cryopreserved PBMC were stimulated with eight distinct *Mtb* antigens, 4 RVMA and 4 classical (immunodominant), with protein transport inhibitors added followed by detection of IL17 and IFNγ production by CD4 T cells by intracellular cytokine staining. The dotted line indicates the limit of detection after subtraction of cytokine response in no antigen-stimulated cells, the percentage at the top indicates participants with a detectable response, blue horizontal line indicates the median. The identities of the distinct antigens are shown on the x-axis. (**B**) To identify other T cell features beyond cytokine production, PBMC from the same participants in A were stimulated with the 3 RVMA and 3 classical antigens in the absence of protein transport inhibitors then expression of CD154 on CD4 T cells (marker of antigen activation) determined followed by characterization of Th17 (based on RORγT and CCR6 expression) and Th1 (based on Tbet and CXCR3 expression) on antigen-activated cells (**C**). Statistics: Wilcoxon ranked test.