Title: Immune mechanisms of protection against *Mycobacterium tuberculosis* infection.

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Background: The global Tuberculosis (TB) epidemic has been sustained due to a lack of robust, host-directed therapeutic strategies against *Mycobacterium tuberculosis*. In endemic TB settings, despite frequent exposure to *M. tuberculosis*, some individuals remain asymptomatic and persistently negative for the Tuberculin Skin Test (TST) and Interferon Gamma Release Assay (IGRA) screening tests, suggesting that they remain uninfected or rapidly clear their infection early on following exposure. Currently, it is unclear why these 'infection resistant' individuals remain uninfected despite repeated exposure to *M. tuberculosis*.

Methods: A household contact (HHC) study conducted in Vitória, Brazil between 2008 and 2013 evaluated TB patients and their HHCs and identified them as 'infection susceptible' (IS) and 'infection resistant' (IR) based on serial TST and IGRA testing. Peripheral Blood Mononuclear Cells (PBMC) from HHCs were infected *in-vitro* with *M. tuberculosis Beijing-HN878*, followed by RNA-sequencing. Ingenuity Pathway Analysis (IPA) was then used to identify differentially expressed genes and pathways in IR and IS PBMC following infection. Since macrophages are the primary niche for intracellular *M. tuberculosis* survival, we also assessed early mycobacterial growth restriction in monocyte-derived macrophages (MDMs) from the HHC groups.

Results: IPA indicated the upregulation of anti-mycobacterial innate immune response genes including IL-1 and IL-17 family cytokines as the dominant pathway activated in IR PBMC. In contrast, IS PBMC demonstrated an upregulation of pro-inflammatory cytokine genes and Th1/Th2 adaptive immune response pathways. Interestingly, we observed a comparatively greater mycobacterial growth restriction by IR MDMs.
Conclusions: Our findings suggest that distinct protective immune pathways are activated in IR HHC that might modulate the establishment of mycobacterial infection resistance. Our ongoing studies focus on characterizing the mechanistic basis of IL-1 and IL-17-mediated protective immune pathways, allowing for the identification of correlates of protection for the development of novel therapeutics.