MAIT Cells Are Highly Enriched in the Bronchoalveolar Lavage Fluid of Patients With TB

Emily B. Wong¹ ², Zuri Sullivan¹, Marielle C. Gold¹ ³, Umesh G. Lalloo¹, Prinita Baijnath², Leon Naidoo³, Thumbi Ndung’u¹ ⁷, William R. Bishai¹ ⁸, David M. Lewinsohn¹ ⁴

¹KwaZulu Natal Research Institute for Tuberculosis and HIV, Durban, South Africa, ²Division of Infectious Diseases, Massachusetts General Hospital, Boston, MA, United States, ³Division of Pulmonary and Critical Care Medicine, Oregon Health & Science University, Portland, OR, United States, ⁴Portland Veterans Administration Medical Center, Portland, OR, United States, ⁵Department Pulmonology and Critical Care, Nelson R. Mandela School of Medicine, Durban, South Africa, ⁶Department of Pulmonology and Critical Care, Nelson R. Mandela School of Medicine, Durban, South Africa, ⁷HIV Pathogenesis Programme, University of KwaZulu Natal, South Africa, ⁸Division of Infectious Diseases, Johns Hopkins School of Medicine, Baltimore, MD, United States

Background: Mucosal Associated Invariant T (MAIT) cells are a class of non-conventional CD8+ lymphocytes that respond to a broad range of bacterial, mycobacterial and fungal pathogens. They have been defined by their usage of a semi-invariant T cell receptor (TRAV1-2 TRAJ33) and can be activated by microbial riboflavin metabolites presented by the evolutionarily conserved MR-1 molecule. Though found in people who have no history of TB exposure, M.tb-reactive MAIT cells are absent in the peripheral blood of those with active TB. This observation led us to hypothesize that during pulmonary TB MAIT cells leave the peripheral circulation to participate in the lung’s mucosal immune response.

Methodology: Bronchoalveolar lavage (BAL) fluid was collected from a cohort of patients undergoing clinically indicated bronchoscopy in Durban, South Africa. Pulmonary TB cases were defined microbiologically (positive M.tb. culture or PCR); controls were defined as having no evidence of inflammatory or infectious lung disease (negative bacterial, fungal and mycobacterial BAL cultures and no eventual diagnosis of sarcoidosis or interstitial lung disease). BAL cells were characterized by flow cytometry to assess the frequency of MAITs (TRAV1-2+) among CD8+ T cells (gated on live, CD14-negative, CD3+ lymphocytes). When sufficient cells were obtained, they were stimulated with CD2/CD3/CD28 beads to assess the production of TNFα and IL-17 by intracellular cytokine staining. When available, matched PBMC were also analyzed for the frequency of peripheral MAIT cells. The Mann-Whitney U test was used to compare frequencies.

Results: In pulmonary TB cases, MAIT cells comprised a significantly higher percentage of lung-resident CD8+ T cells (n=8, median 22.9%, IQR 16.4-33.9%) than in controls (n=11, median 5.0%, IQR 4.3-5.8%, p=0.0005). In contrast, during pulmonary TB, TRAV1-2+ CD8+ T-cells were not expanded in the peripheral blood (n=5, median 5.8%, IQR 5.6-6.2%, p=0.0016). Upon non-specific activation, lung resident MAIT cells in those with pulmonary TB produced very high levels of TNFα and did not produce IL-17 above background.

Conclusions: MAIT cells, an emerging class of innate lymphocytes, are highly enriched in the lungs during pulmonary TB. Interestingly, though it has been shown that HIV severely depletes MAITs in the peripheral blood, here we find MAITs to be comparably enriched in the lungs of both HIV-positive and HIV-negative patients during active tuberculosis. This suggests that MAITs are redistributed to mucosal surfaces rather than destroyed by HIV. Further research the role of MAIT cells in protective immunity against TB is urgently needed; their potential as a novel TB vaccine target should be explored.