Mechanisms regulating granuloma development and heterogeneity in high- and low-transmission *Mycobacterium tuberculosis* infections

Vaishnavi Kaipilyawar[1], Sheetal Verma[1], Heidi Risman[1], Jerrold J Ellner[1], Reynaldo Dietze[2], Rodrigo Ribeiro-Rodrigues[2] and Padmini Salgame[1]

[1]Center for Emerging Pathogens, Rutgers-New Jersey Medical School, Newark, NJ, USA
[2]Núcleo de Doenças Infecciosas, Universidade Federal do Espírito Santo, Vitória, Brazil

Background: Granuloma formation is the histopathological hallmark of Tuberculosis (TB). The host and bacterial mechanisms that dictate granuloma formation and *Mycobacterium tuberculosis* (Mtb) containment and those that subsequently induce granuloma necrosis and Mtb transmission remain poorly understood.

Methods: In a household contact (HHC) study of TB cases from Brazil, Mtb strains were isolated from the index cases of households and categorized into High transmission (Mtb-HT) and Low transmission (Mtb-LT) based on the number of Tuberculin skin test-positive HHCs in the household. To investigate the host-pathogen interactions underlying Mtb transmission heterogeneity, these strains were studied in C3HeB/FeJ mice that develop caseating necrotic lesions as observed in human TB.

Results: We previously reported that mice infected with the Mtb-HT strain develop discrete caseating granulomas. In these mice, rapid IL-1-receptor-dependent alveolar macrophage migration from the alveolar space into the interstitium led to early dissemination of bacteria to the lymph nodes and T-helper type 1 cell priming. In contrast, the alveolar macrophage migration and early bacterial dissemination was significantly impeded in Mtb-LT infection, promoting a T-helper type 17 cell response, diffused inflammatory lung pathology, and significantly increased bacterial burden. To further examine the lung immune cell populations that shape the distinct immune responses in Mtb-HT and Mtb-LT infections, we conducted single cell RNA-sequencing of lung cell infiltrates at 2-, 4- and 6-weeks post-infection. Of note, there was a striking increase in the neutrophil cell cluster by weeks 4 and 6 post-infection in the Mtb-LT-infected mice. Transcriptomic analysis demonstrated that in comparison to Mtb-HT-infected mice, neutrophils from Mtb-LT-infected mice upregulated pathways associated with IL-17 signaling. Our ongoing studies are focused on characterizing the early impact of IL-17 on neutrophil recruitment, bacterial replication, and the granulomatous response to these Mtb strains.

Conclusions: Defining these mechanisms may offer substantial opportunities for therapeutic interventions to mitigate Mtb transmission.