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YOU ARE INVITED TO ATTEND THE DEFENSE OF THE DOCTORAL DISSERTATION

"Uncovering mechanisms leading to differences in host response and disease outcome in epidemiologically characterized high and low transmission strains of Mycobacterium tuberculosis"

by
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Friday, March 13th, 2020
3:00 P.M.
ICPH Auditorium

ABSTRACT

In a recent household contact study conducted in Vitória, Brazil, clinical Mtb strains with both high (Mtb-HT) and low (Mtb-LT) transmission phenotypes were identified. Infection of C3HeB/FeJ mice with the Mtb strains showed that mice infected with Mtb-LT strains exhibited significantly higher bacterial burden compared to Mtb-HT strains and also developed diffuse inflammatory pathology. In stark contrast, a significant number of mice infected with Mtb-HT strains developed caseating granulomas.

In this study, we examine the mechanistic basis for the differential trajectory in response to Mtb-HT and Mtb-LT infections. We found that following aerosol infection, Mtb-HT rapidly activates alveolar macrophages (AMs) which then migrate, in an IL-1R dependent manner, from the alveolar space into the lung interstitum. This rapid translocation of AMs into the interstitium results in early activation of T cells in the lymph node and recruitment of Th1 cells to the lungs. Mtb-LT is less immunogenic early on in infection leading to delayed T cell activation in the lymph node and a Th17 skewed T cell response. Adoptive transfer of T cells from Mtb-HT, but not Mtb-LT mice, into Mtb-LT infected mice led to significant reduction in bacterial burden compared to control animals. Interestingly, the reduced bacterial burden was not associated with a reduction in diffuse immunopathology associated with Mtb-LT infections. This suggests that the high bacterial burden present in Mtb-LT infection is delinked from the pathological response observed in these mice. Together, these results indicate that the early innate alveolar macrophage response may be regulating the subsequent divergent T cell and granulomatous response in Mtb-HT and Mtb-LT infected mice