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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 interstitium. 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.