RUTGERS
School of Graduate Studies

Office of Student Affairs and Admissions
SGS at New Jersey Medical School
Rutgers, The State University of New Jersey
185 South Orange Avenue, MSB C-696
Newark, NJ 07103

http://njms.rutgers.edu/gsbs/
p. 973-972-4511
f. 973-972-7148

YOU ARE INVITED TO ATTEND THE DEFENSE OF THE DOCTORAL DISSERTATION

"Study of three distinct host factors in regulating susceptibility to *Mycobacterium tuberculosis* infection: TLR2, Sex bias and Autophagy"

by

Madhuri Bhagavathula

Molecular Biology, Genetics, and Cancer Program

MS, 2012, University of Pennsylvania, Philadelphia

B.Tech., 2010, SRM University, India

Thesis Advisor: Padmini Salgame, Ph.D.
Professor
Department of Medicine

Tuesday, May 31st, 2022
1:00 PM

Join Zoom Presentation:
https://rutgers.zoom.us/j/91433690255?pwd=ZnpSd25ucXo0OStEZzFLUzducVlTZz09

Meeting ID: 914 3369 0255
Password: 723473

ABSTRACT

Tuberculosis caused by *Mycobacterium tuberculosis* (Mtb) is a heterogeneous disease with clinical presentations ranging from latent infection to incipient and subclinical disease and subsequent progression to active tuberculosis (TB). Considering most of the individuals infected with Mtb do not develop active TB disease, one can argue that host factors must play a crucial role in maintaining the integrity of the granuloma and in controlling bacterial replication. Therefore, it is necessary to understand how host factors maintain the integrity of the granuloma, control bacterial burden, and thereby dictate the outcome of Mtb infection. Here, we examined three factors that control bacterial replication and immunopathology: 1. TLR2; 2. Sex Bias; 3. Autophagy.

1. Role of TLR2 in immunoregulation: TLR2 is an innate immune receptor that recognizes Mtb ligands. Previously, we reported that TLR2 controls bacterial burden and pathology by regulating neutrophil recruitment early on during infection with the clinical Mtb Beijing strain. So, the main aim of this study was to identify pathways by which TLR2 controlled this exuberant neutrophil recruitment into lung. Here, we found that expression of CXCL5, a neutrophil chemoattractant, was significantly higher in lung epithelial cells of Toll like receptor 2 knock out (TLR2KO) mice than WT during Mtb infection. So, we neutralized CXCL5 in TLR2KO mice and observed a reduction in bacterial burden and neutrophil recruitment compared to control mice. Next, we explored the role of IL-17A at various stages of infection as IL-17A signaling leads to the secretion of chemokines mediating neutrophil recruitment. In TLR2KO mice, IL-17A plays a protective role early on, while IL-17A contributes to bacterial burden and neutrophil recruitment later during infection. In addition, we also observed that IFN-β was down regulated in the absence of TLR2 which could contribute to dysregulation of IL-17A at the later stage of infection. Overall, from this study, we concluded that TLR2 mediated IFN-β is likely restricting IL-17A and neutrophilic inflammation during Mtb HN878 infection.

2. **Sex differences:** We explored the role of sex differences during Mtb infection and observed that C57BL6/J, C3HeB/FeJ, and TLR2KO males were more susceptible to TB infection than females. Gene expression analysis of infected lungs showed that expression of several genes regulating innate immunity, including IL-1α and IL-1β were significantly lower in the lungs of males than females. *IL-1* is necessary for the induction of early-phase *protective* immunity against Mtb infection. The findings thus indicate that enhanced innate immune activation comprising the IL-1 signaling pathway likely contributes to the enhanced resistance observed in female mice.

3. Host-directed therapy (HDT) for curtailing immunopathology: One of the main goals of HDT against TB is to dampen aberrant lung inflammation and preserve lung function in TB patients. In this section, we evaluated the potential of rapamycin, an autophagy inducer, as a host-directed therapeutic strategy against tuberculosis. We observed that adjunct treatment with rapamycin led to a significant reduction in lung pathology during moxifloxacin monotherapy and thereby supporting the use of rapamycin or its analogs as HDT against TB.

Overall, the thesis has provided new information regarding host factors that regulate bacterial burden and immunopathology during Mtb infection. Future studies will aim at translating the murine findings to humans.