THE GRADUATE COLLEGE OF THE
UNIVERSITY OF OKLAHOMA HEALTH SCIENCES CENTER

ANNOUNCES THE FINAL EXAMINATION OF

Md Huzzatul Mursalin

FOR THE DEFENSE OF THE DOCTOR OF
PHILOSOPHY DEGREE GRADUATE COLLEGE

Department of Microbiology and Immunology
Tuesday, April 21, 2020 | 1.30 pm.
Location: https://ouhsc.zoom.us/j/267175845
Password: 005007

BACILLUS S-LAYER CONTRIBUTES TO THE PATHOGENESIS OF ENDOPHTHALMITIS BY TRIGGERING TLR2/4-DRIVEN INFLAMMATORY RESPONSES

COMMITTEE IN CHARGE: Michelle Callegan, PhD, Chair, Allison F. Gillaspy, PhD, Zachary D. Dalebroux, PhD, Darren J. Lee, PhD, Michael H. Elliott, PhD

ABSTRACT: *Bacillus* causes a blinding infection of the posterior segment of the eye. Hallmarks of *Bacillus* endophthalmitis include robust inflammation and rapid vision loss. The robust inflammatory response in this disease is likely activated via host innate receptor interactions with the cell wall components of *Bacillus*. S-layer protein (SLP) is the outermost layer of some bacteria and *Archaea* and contributes to the pathogenesis of several infections. The potential role of *Bacillus* SLP in endophthalmitis had not been considered. Here, we explored how *Bacillus* SLP (SlpA) contributes to the pathogenesis of endophthalmitis. This study demonstrated that intraocular infection with a Δ*slpA Bacillus* mutant resulted in improved retinal function retention and clinical outcome relative to infection with wild type *Bacillus*. *Bacillus* SLP was also an activator of the NF-κB pathway which induced expression of inflammatory mediators from retinal cells. SLP impacted bacterial adherence to retinal cells and protected the pathogen from internalization by phagocytic cells. Using a reporter assay, we determined that B*acillus* SLP activated Toll-like receptors TLR2 and TLR4. Chemical inhibition of TLR2 and TLR4 activation during *Bacillus* endophthalmitis resulted in retained retinal function and an improved clinical outcome similar to that observed in eyes infected with the Δ*slpA Bacillus* mutant. Our final study on therapeutic interference of TLR pathways revealed that inhibition of TLR2 and TLR4 resulted in blunted inflammatory responses in the eye, similar to that observed in eyes infected with the Δ*slpA Bacillus* mutant. We identified several key inflammatory genes whose expression was significantly reduced in this scenario, including genes involved in complement, innate immunity, cytokine, and chemokine pathways. Taken together, our results suggest that *Bacillus* SLP impacts the pathogenesis of endophthalmitis potentially by triggering TLR2/4-driven inflammatory responses in the eye. Blocking inflammatory responses by targeting these pathways may be a viable anti-inflammatory strategy for this disease. Thus, this dissertation work provides a deeper understanding of the host-pathogen interactions and the therapeutic potentials of innate inhibition in *Bacillus* endophthalmitis.