Kyle Caution
PhD Candidate

“Legionella and caspases: modulation of the actin cytoskeleton”

November 12, 2015
Biomedical Research Tower, 105
10:00 am
VITA
June 19, 1982 . . . . . . . . . . . . . . . . . . . . . . . . Born – Columbus, OH
May 2004 . . . . . . . . . . . . . . . . . . . . . . . . . . BS, Biochemistry/
Molecular Biology, Minor: French
Wittenberg University, Springfield OH

COMMITTEE MEMBERS
Amal Amer, MD, PhD
Mark Wewers, MD
Susheela Tridandapani, PhD
Beth Lee, PhD
Legionella pneumophila (L. pneumophila) is the causative agent of Legionellosis, two forms of respiratory illness: Pontiac Fever, an influenza-like self-limiting, febrile sickness that presents in healthy individual and Legionnaires’ disease (LD), a potentially fatal pneumonia that affects immunocompromised individuals (HIV+, transplant, cancer, and COPD patients). Approximately, 18,000 people each year in the United States are hospitalized due to LD. Humans are prone to infection as the pathogen is ubiquitous in aquatic environments and has evolved a wide array of strategies to subvert and evade host cell immunity.

Clearance of L. pneumophila requires efficient phagolysosomal fusion. This allows for host cells to employ non-cell death-mediated defenses to destroy the intracellular organism by eliminating its replicative niche. Regulation of the host actin cytoskeleton is crucial for proper vesicle trafficking and fusion events. In this work, it was determined that activation of caspases-1 and -11 are required for trafficking and fusion during infection. The molecular mechanisms of caspase-mediated clearance are unknown. The objective of this study was to decipher the effects of caspase-1 and -11 on actin dynamics to promote phagolysosomal fusion and restriction of the bacteria.

Upon infection, Casp-1/− and Casp-11/− bone marrow-derived macrophages (BMDMs) were found to be permissive to L. pneumophila as these cells exhibited significantly lower amounts of colocalization of L. pneumophila-containing phagosomes and lysosomes compared to restrictive C57BL/6 (WT) cells. It was also determined that Casp-1/− and Casp-11/− macrophages exhibited diminished F/G-actin ratios compared to WT counterparts, while also failing to polymerize actin in the vicinity of L. pneumophila during infection. In elucidating the molecular mechanism, it was found that caspase-1 and -11 converge on an upstream regulator of actin dynamics: cofilin. During infection, caspase-1 promoted dephosphorylation (activation) of cofilin, while caspase-11 regulated its phosphorylation (inactivation). In addition, it was determined that upstream signaling molecules, RhoA and
Slingshot, affected the activation of cofilin. The absence of caspase-11 resulted in significantly decreased RhoA GTPase activation, thereby keeping cofilin unphosphorylated. Also, caspase-1-deficient cells inhibited Slingshot phosphatase activity during infection, blocking cofilin dephosphorylation. Together, these molecules differentially modulated cofilin activation, affecting actin dynamics during *L. pneumophila* infection.

These data establish for the first time that inflammasome caspases differentially regulate actin polymerization during *L. pneumophila* infection by modulating F-actin assembly via the activation of cofilin. Understanding the novel molecular mechanisms of caspase-mediated regulation of the host cytoskeletal network will provide novel targets to develop therapeutic interventions for numerous infectious diseases.


AWARDS AND HONORS

2015  Best Graduate Student Poster Presentation at Midwest Microbial Pathogenesis Conference (Indianapolis IN)

2014  Travel Award to American Association of Immunologists (AAI) annual meeting (New Orleans LA)

Best Graduate Student Oral Presentation at annual Center for Microbial Interface Biology Symposium (OSU – Columbus OH)

Travel Award & Oral Presentation at American Society of Microbiologists 2014 General Meeting (Boston MA)

Accepted to St. Jude’s National Graduate Student Symposium (Memphis TN)

Accepted to present at The Hayes Graduate Research Forum (1 of 15 posters selected from all graduate fields on campus – OSU Columbus OH)

Travel Award to the American Society of Biochemistry and Molecular Biology annual meeting (San Diego – CA)

Best Graduate Student Poster Presentation – Cell Signaling at American Society of Biochemistry and Molecular Biology annual meeting (San Diego – CA)

2011  Best Graduate Student Poster Presentation at Davis Heart & Lung Research Day

2010  Best Graduate Student Poster Presentation at Center for Microbial Interface Biology (CMIB) retreat

FUTURE PLANS

I will continue my training as a post-doctoral trainee in Dr. Amal Amer’s lab working on elucidating the link between epigenetic changes of autophagy genes during <i>Burkholderia cenocepacia</i> infection
Biomedical Sciences Graduate Program
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