Julia Scordo
PhD Candidate

“Impact of the Human Lung Mucosa on Mycobacterium tuberculosis Infection of Alveolar Epithelial Cells”

Friday, November 9, 2018
DHLRI Room 170
9:00 AM
VITA

1988 ........................................... Born – Fairfax, VA

2011 ........................................... B.S. – James Madison University

COMMITTEE MEMBERS

Jordi Torrelles, PhD, Advisor

Ian Davis, DVM, PhD

Mark Peeples, PhD

Virginia Sanders, PhD

Larry Schlesinger, MD
ABSTRACT

Tuberculosis (TB) is the leading cause of death due to an infectious disease. It is estimated that two nearly billion people worldwide are currently infected with *Mycobacterium tuberculosis* (*M.tbc*), the causative agent of TB. During aerosol transmission of *M.tbc*, the bacterium is deposited into the alveolar space of the lung where it encounters host cells and soluble factors present in the alveolar lining fluid, or ALF. It is in this first environment that the early innate immune response develops, potentially altering the course of infection. Previous work from our lab has demonstrated a critical role for human ALF in modifying the *M.tbc* cell wall surface. Importantly, ALF-induced *M.tbc* cell wall modifications impact *M.tbc*-phagocyte interactions by enhancing phagocyte-*M.tbc* killing and dampening host inflammatory responses during infection. These findings suggest that early ALF-*M.tbc*-host cell interactions may influence infection outcome.

Alveolar epithelial cells (ATs) are non-professional phagocytes that are believed to play an important role in different stages of *M.tbc* infection, including establishment of infection and progression to active TB disease. In this work we investigate the impact of human ALF-induced *M.tbc* modifications on *M.tbc*-AT infection. In contrast to our previous studies with human phagocytes, our results presented here elucidate a unique role for ALF in driving differential *M.tbc*-AT infection outcome. We observe significant heterogeneity among ALFs, with each ALF obtained from a different human adult donor, that allows for identification of two subsets of ALFs: Low(L) ALF and High(H) ALF, based on the low and high *M.tbc* intracellular growth rate in ATs that is induced following *M.tbc*-ALF exposure. Through examination of L- and H-ALF exposed-*M.tbc* phenotypes, we observe that H-ALF drives enhanced active *M.tbc* replication during AT infection. Moreover, ATs infected with H-ALF exposed-*M.tbc* have decreased immune mediator production, less cytotoxicity, and decreased surface adhesion molecule expression. H-ALF impacts *M.tbc*-infected AT cellular crosstalk with macrophages through both direct and indirect mechanisms, resulting in decreased
macrophage pro-inflammatory cytokine production and less macrophage activation marker expression. When we examine the composition of L- and H-ALF subsets, we find that H-ALF has more protein nitrosylation, indicative of nitric oxide-induced oxidative stress, and less functional ALF- innate proteins, which results in less binding of these innate proteins to the \textit{M.tb} surface. Furthermore, by replenishing H-ALF with functional ALF-proteins, specifically complement C3, mannose binding lectin, and surfactant proteins A and D (alone or in combination), we can reverse the \textit{M.tb} growth rate to the levels observed in ATs infected with L-ALF-\textit{M.tb}. These findings suggest that together H-ALF and ATs may promote \textit{M.tb} growth and subsequent establishment of \textit{M.tb} infection, with ATs serving as a cellular reservoir during latent infection. Alternatively, by enhancing phagocyte activation L-ALF-\textit{M.tb}-infected ATs may promote clearance of \textit{M.tb} infection. Importantly, by modulating levels and function of ALF innate proteins we can drive decreased \textit{M.tb} growth in ATs, suggesting that ALF-innate proteins may be therapeutic targets to modulate early events in \textit{M.tb} infection and subsequent infection outcome.

Collectively, the work presented here reveals a unique role for variability in human ALF in influencing \textit{M.tb} infection outcome within ATs, suggesting that accounting for soluble host factors present in ALF is critical for our understanding of early events in host-\textit{M.tb} interactions in the alveolar space.
ABSTRACTS AND PRESENTATIONS

Selected Speaker, ‘Human Lung Mucosa Modulates Mycobacterium tuberculosis Infection of Alveolar Epithelial Cells’ 2018 UT-Health San Antonio Spring Retreat, San Antonio, TX.

Selected Abstract, ‘Human Lung Mucosa Heterogeneity Drives Mycobacterium tuberculosis Infection of Alveolar Epithelial Cells’ 2018 Texas Tuberculosis Research Symposium, El Paso, TX.


Selected Speaker, ‘Human Alveolar Lining Fluid Drives Mycobacterium tuberculosis Infection in the Alveolar Epithelium’ Immunology 2017 AAI Meeting, Washington, DC.


Selected Speaker, ‘A New Take on an Old Disease: Studying TB in the Lung Microenvironment’ 2016 Discovery Themes-TEDx Event at the Ohio State University, Columbus, OH.

Selected Speaker, ‘Mycobacterium tuberculosis Infection of Alveolar Epithelial Cells is Driven by the Human Lung Mucosa’ 2016 Center for Microbial Interface Biology Symposium at The Ohio State University, Columbus, OH.

Selected Speaker, ‘Human Lung Modulation of Mycobacterium tuberculosis Infection of the Alveolar Epithelium’ 2015 Biomedical Sciences Graduate Program Retreat at The Ohio State University, Columbus, OH.
PUBLICATIONS


AWARDS AND HONORS

Winner, Second Place for Best Poster Presentation at the 2017 Vaccine, Infection and Immunity Conference, San Antonio, TX.

Finalist, Public Health and Preparedness for Infectious Diseases Graduate Training Scholarship; 2016.

Winner, Travel Fellowship for Best Poster Presentation at the 2016 Public Health and Preparedness for Infectious Diseases Annual Meeting at the Ohio State University, Columbus, OH.

Winner, First Place for Best Poster Presentation at the 2016 Center for Microbial Interface Biology Symposium at the Ohio State University, Columbus, OH.


Recipient, College of Medicine Systems and Integrative Biology (SIB) Training Program Fellowship NIH/NIGMS T32-GM068412; 2014-2016.

University Fellow, The Ohio State University Graduate School; 2013-2017.

FUTURE PLANS

For my post-doctoral training I will be working with Dr. Joanne Turner studying aging and tuberculosis at Texas Biomedical Research Institute in San Antonio, Texas. My long-term career goals are to perform research to improve public health. Additionally, I hope to be in a position where I am able to educate and mentor young scientists.