WRIGHT STATE UNIVERSITY | BIOMEDICAL SCIENCES PhD PROGRAM

Dr. Mill W. Miller, Director
937-775-2504

DISSERTATION DEFENSE

JAMES READLER

PhD Candidate

"ADENOVIRUS CO-OPTS NEUTROPHILIC INFLAMMATION IN ORDER TO ENHANCE ENTRY INTO EPITHELIAL CELLS"

Monday, March 4th, 2019

1:00 p.m.

NEC Auditorium (101)

Advisor: Katherine Excoffon, PhD
Department of Biological Sciences

Readler, James, Biomedical Sciences PhD Program
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Human adenoviruses (AdV) are double-stranded DNA viruses that can cause a range of diseases. While AdV respiratory infections are often mild and self-limited, severe manifestations such as fulminant pneumonia and acute respiratory distress syndrome (ARDS) are not uncommon. Severe infections are more likely to occur in immunosuppressed patients, such as those undergoing chemotherapy or organ transplantation. Despite the threat they pose, there are currently no specific anti-AdV therapeutics available. In contrast to their pathogenic nature, AdV have been widely investigated as vector systems to treat human diseases. Recent advances in oncolytic virotherapy and vaccine production using AdV vectors show great clinical potential. In order to identify potential modalities to treat AdV infections and potentially enhance the effectiveness of AdV vector delivery, a thorough mechanistic understanding of how AdV enters host cells is needed. Previous studies have revealed polarized epithelia, one of the primary targets for AdV respiratory infections, are highly resistant to AdV entry from the apical (luminal) surface. However, upon exposure to interleukin 8 (IL-8), the 8-exon encoded isoform of the Coxsackie and Adenovirus receptor (CAR^{Ex8}) localizes to the apical surface of airway epithelial cells where it is able to mediate AdV entry. Furthermore, neutrophils, or polymorphonuclear leukocytes (PMN), that migrate to the epithelium as a result of the IL-8 stimulus have been shown to further enhance AdV infection of the epithelium through an uncharacterized mechanism. I *hypothesized* that neutrophilic factors alter epithelial physiology in such a way that renders them more susceptible to AdV infection. Furthermore, I *hypothesized* that a combination of enhanced apical CAR^{Ex8} expression and PMN factor signaling drastically enhances epithelial susceptibility to AdV5 infection. Consistent with these hypotheses, I demonstrate that neutrophil elastase (NE), a PMN serine protease with diverse functions, is a major neutrophilic factor that drives PMN-mediated enhancement of epithelial AdV5 infection. Furthermore, I show that NE activates autophagic flux in epithelial cells and that this process is indirectly related to PMN enhancement of epithelial AdV5 transduction. Finally, using newly emerged CRISPR/Cas9 techniques, three epithelial model systems were generated and data suggest that NE mediated enhancement of epithelial AdV5 transduction is largely independent of CAR^{Ex8} expression. Taken together, this dissertation shows data that implicates NE as a key regulator of AdV5 infection of the airway epithelium and presents new tools for the field of adenovirology. Future research will focus on establishing the role of NE in AdV5 entry *in vivo*.