Mia Farrah Tazi
PhD Candidate

“Improving Autophagy in Cystic Fibrosis: The Effects of Epigenetic Regulation”

April 13, 2015
Davis Heart and Lung Research Institute Room 165
12:00
VITA

Sept. 27, 1987 . . . . . . . . . . . . . . . . . . . Born – Pompton Plains, New Jersey

Mar. 2010 . . . . . . . . . . . . . . . . . . . . . . B.S. Microbiology, The Ohio State University

July 2010 – Present . . . . . . . . . . . . . . . PhD Candidate, Biomedical Sciences The Ohio State University

COMMITTEE MEMBERS

Amal Amer, MD, PhD, Advisor

Patrick Nana-Sinkam, MD

William Lafuse, PhD

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ABSTRACT

Cystic Fibrosis (CF) is a fatal, genetic disorder that critically affects the lungs and is directly caused by mutations in the CF transmembrane conductance regulator (CFTR) gene, resulting in defective CFTR protein function. Autophagy is a highly-regulated biological process that provides energy during periods of stress and starvation. Normally, it functions to clear pathogens and dysfunctional protein aggregates within macrophages. This process is impaired in CF patients and CF mice, as their macrophages exhibit limited autophagy activity. The low expression of autophagy genes, characteristic of CF cells, promoted us to examine transcriptional and translational regulation of autophagy molecules that result from microRNA (miRNA, miR) and epigenetic variations.

The study of microRNAs (miRNAs, miRs) continues to offer novel therapeutic targets. The objective of this study was to elucidate the role miRNAs play in the dysregulation of autophagy in CF macrophages and target them to restore this process and improve CFTR function. We identified the miR-17~92 cluster as a potential negative regulator of autophagy since CF macrophages exhibit increased cluster expression compared to WT. The absence of the cluster increased autophagy protein expression, suggesting the canonical inverse relationship between miR-17~92 expression and autophagy gene expression which was further validated by luciferase assays. Downregulation of miR-17 and miR-20a restored autophagy expression in the lungs of CF mice. Notably, downregulation of these inherently elevated miRNAs in vitro improved CFTR function, the fundamental cause of CF and its symptoms, via restoration of autophagy in macrophages.

We also investigated the role of epigenetic regulation on dysfunctional autophagy in CF. Epigenetic regulation, characterized by the alteration of gene functions that occur independently of changes in the DNA, may be the result of four different mechanisms. One of which, DNA methylation, results in the decrease of gene expression as the addition of methyl groups
by DNA methyltransferases (DNMTs) interrupts transcriptional read-through. We demonstrated that DNA methylation significantly reduces autophagy function in CF macrophages. Given this effect occurs at DNA sites exhibiting cytosine-phosphate-guanine (CpG) repeats, and autophagy genes exhibit several CpG islands, we hypothesized that DNA methylation contributes to dysfunctional autophagy. Our data reveal that the autophagy genes of CF macrophages are significantly hypermethylated compared to WT macrophages at a basal level. Elevated mRNA levels of DNMT-1 expressed by CF macrophages suggest its role as the predominate DNMT mediating this effect. Addition of methylation inhibitor epigallocatechin gallate (EGCG), a potent tea extract, restored autophagy expression at both the mRNA and protein level. Burkholderia cenocepacia, a lethal CF pathogen harboring innate antibacterial resistance to the majority of therapies, decreases autophagy mRNA and protein expression in CF macrophages by unknown mechanisms. Here, we find that B. cenocepacia infection significantly methylates autophagy genes thereby contributing to further reduction of autophagy expression in CF. EGCG treatment during infection with this pathogen partially restored autophagy protein expression compared to infection alone.

Together, these data advance our understanding of mechanisms underlying the pathobiology of CF and provide new therapeutic platforms for restoring CFTR function and autophagy by targeting specific miRNAs or methylation machinery in CF.
**RECENT ABSTRACTS AND PRESENTATION**


RECENT PUBLICATIONS


AWARDS AND HONORS


American Association of Immunologists Travel Award to attend the Immunology Conference for poster and oral presentation in New Orleans, Louisiana. May 2015.

American Society for Biochemistry and Molecular Biology Travel Award to attend the Experimental Biology Conference in Boston, Massachusetts. March 2015.

The Ohio State University Sigma Xi Chapter Grants-In-Aid of Research Fund. November, 2014.

The Ohio State University Jane Addams Award for Civic Engagement. September 2014.


Public Health Preparedness for Infectious Diseases Travel Award. June 2014.


St. Jude National Graduate Student Symposium Travel Award to attend the St. Jude NGSS in Memphis, Tennessee. March 2014.

Center for Microbial Interface Biology Training Grant supported by the College of Medicine and the Graduate School at The Ohio State University. March 2013 – March 2014

Midwest Microbial Pathogenesis Travel Award to attend the Midwest Microbial Pathogenesis Conference in Columbus, Ohio. August 2013.

Immunology Round Table Travel Award for Best Research Presentation. December 2012.

FUTURE PLANS

I will be pursuing post-doctoral opportunities in industry upon graduation. I aspire to continue making impactful discoveries regarding disease mechanisms in an effort to significantly improve patients’ lives.