Examination of the role of ZIP8 and cadmium in the development of Chronic Obstructive Pulmonary Disease

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165 Davis Heart and Lung Research Institute
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VITA

March 13, 1987 . . . . . . . . . . . . . . . . . . . . . . . Born – New York, NY

May 2009 . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . B.A. Biology
College of the Holy Cross, Worcester MA

July 2009 - present . . . . . . . . . . . . . . . . . . . . . . . Ph.D. Biomedical Science,
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COMMITTEE MEMBERS

Dr. Daren Knoell, Pharm.D., Advisor

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a complex respiratory disease primarily caused by cigarette smoking. Cadmium, a toxic metal abundantly present in cigarette smoke, has been implicated in the development of disease, and accumulates in the bodies of smokers. It was recently discovered that a zinc transporter, SLC39A8 (ZIP8), is responsible for the import of cadmium into mammalian cells. Our lab discovered that ZIP8 is under the transcriptional regulation of the NF-κB pathway. Based on this we hypothesize that inflammation in the lung created by smoke exposure increases the expression of ZIP8 thereby facilitating cadmium uptake and pathology associated with COPD.

The first aim of our work addressed the role of ZIP8 in Cd-mediated epithelial cell toxicity using the alveolar epithelial A549 cell line. Cadmium-induced toxicity was enhanced by TNFα in an NF-κB-dependent manner, which induced the expression of ZIP8. Use of an NF-κB (p65) inhibitor (Bay11-7082) or ZIP8 siRNA resulted in a significant decrease in cell toxicity. Cell death was also reversible with increasing concentrations of the micronutrient zinc. Immunohistochemical analysis of primary human upper airway epithelial cells revealed preferential ZIP8 expression on the apical membrane. Analysis of lung tissue from GOLD stage 0 cigarette smokers and non-smoking controls revealed that ZIP8 mRNA and protein is significantly increased in the lungs of smokers.

We translated these findings into a mouse model of chronic cigarette smoke exposure using a transgenic ZIP8 overexpressing mouse line. ZIP8 overexpression significantly increased emphysema-like pathology, compared to smoke exposed C57/Bl6 control mice. In line with previous studies, epidemiologic analysis of the 2011-2012 National Health and Nutrition Examination Survey revealed that blood cadmium levels of smokers correlated with lower zinc serum levels. Based on our findings, we contend that ZIP8 is a potential mediator of COPD pathogenesis and more so, when Cd content is in relative abundance in the lung compared to Zn. Lastly, we investigated the contribution of cadmium to macrophage dysfunction in the context of COPD. We observed
that cadmium significantly reduced macrophage capacity to respond to an endotoxin challenge, specifically by inhibiting NF-κB activity, an effect not observed in monocytes, a precursor cell type. Atomic absorption spectroscopy revealed a greater accumulation of cadmium within macrophages than monocytes, suggesting fundamental differences in cadmium metabolism. We postulate that this may be an important mechanism by which cadmium contributes to impaired immune responses observed in COPD patients. Taken together, this novel body of work suggests that a transporter primarily responsible for zinc metabolism and regulation of immune function, may inadvertently contribute to COPD pathogenesis by facilitating cadmium import thereby causing lung dysfunction in multiple ways.
RECENT ABSTRACTS AND PRESENTATION

Oral Presentations

- *The Role of ZIP8 and Cadmium in the Development of COPD.* Biomedical Sciences Graduate Program Annual Retreat, Columbus OH, December 2012

Poster Presentations

- Ohio State College of Pharmacy Research Day, Columbus OH, April 2014
- Davis Heart and Lung Research Institute Research Day, Columbus OH, October 2014
- American Association of Immunologists Annual Meeting, Honolulu HI, May 2013
- 12th Annual OSUWMC Trainee Research Day, Columbus OH, April 2013
- Regenerative Medicine Wound Care Conference, Columbus OH, March 2013
RECENT PUBLICATIONS


AWARDS AND HONORS

2012  2nd Place Student Speaker Travel Award Winner, Biomedical Sciences Graduate Program Annual Retreat

2012  1st Place Graduate Student Division Travel Award Winner Ohio State College of Pharmacy Research Day

2011  Outstanding Poster Travel Award Winner The Ohio State University Medical Center Research Day

2007-2008  Deans List – Second Honors, College of the Holy Cross

2005-2009  Ignatian Scholar, College of the Holy Cross

2005-2009  Michael Lynch Memorial Scholar College of the Holy Cross

FUTURE PLANS

I have accepted a post-doctoral fellowship at Columbia University in the laboratory of Dr. Mary Gamble, where I will investigate nutritional influences on arsenic toxicity and metabolism. I will be supported by the Columbia Institute of Human Nutrition’s Post-doctoral Training Program in Nutrition and Human Health, which will provide me with funding to cross-train as an epidemiologist. In the future, I hope to pursue a translational research career focused on nutrition and environmental exposures.