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University Grant Program – Final report

Project title: Epigenetic biomarkers for MWCNT exposure and DHA diet modification

Yoon Hee Cho, Ph.D., Associate Professor

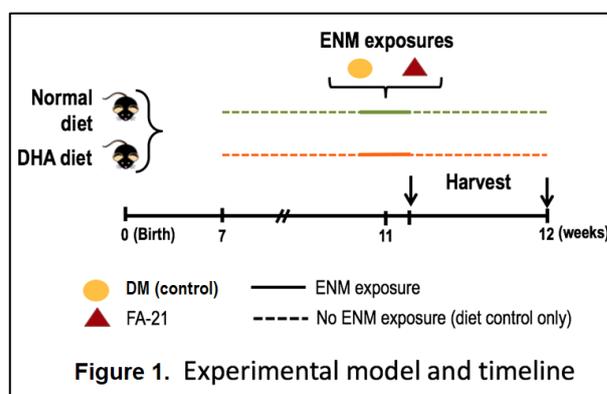
Department of Biomedical & Pharmaceutical Sciences

Background: Engineered nanomaterials (ENM) are a technological innovation with a rapidly expanding societal presence; but their bioactivities have not yet been thoroughly characterized. While the benefits have been attributed, in part, to their unique physico-chemical properties at the nanoscale, these same characteristics have been identified as contributors to adverse pro-inflammatory consequences, particularly in the context of human occupational exposures and respiratory disease risk [1]. Many airborne exposures to ENM, particularly multi-walled carbon nanotubes (MWCNT)—which are widely produced—have been shown to cause significant pathological changes in animal models [2, 3]; thus, possible adverse health effects resulting from human exposure to MWCNT are of great concern.

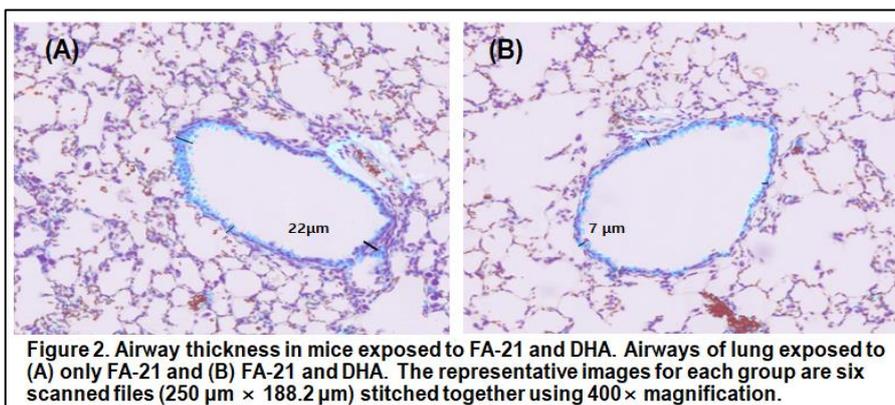
Diet changes are simple to incorporate into one's lifestyle and provide an easy method for reducing susceptibility to disease. Docosahexaenoic acid (DHA), an omega-3 fatty acid is the most commonly consumed dietary supplement in children and adults in the United States [4, 5]. DHA can inhibit NLRP3-inflammasome mediated inflammation; thus, it is reported to prevent adverse particle-induced pathologies and contribute to respiratory health via modification of the pro-inflammatory progression of respiratory diseases [6, 7].

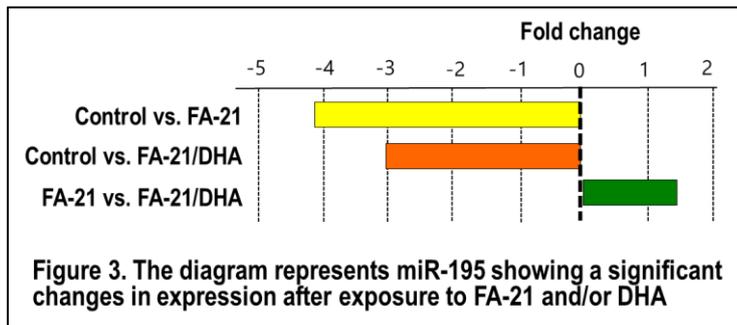
Comprehensive studies of ENM toxicity and bioactivity remain challenging, despite their growing use for industrial and biomedical applications. Furthermore, mechanistic predictive models and data necessary to understand the factors contributing to their pathology are largely lacking. Epigenetic alterations are known to hold substantial potential as biomarkers for environmental exposures; this, in turn, may provide insight into mechanisms of environmentally related diseases and allow for a better understanding of disease etiology. The primary goal of this study is to determine epigenetic alterations associated with a DHA-supplemented diet and MWCNT exposure, and the relationship to decreased inflammation and development of lung disease.

Methods: Balb/c mice were fed with normal diet or 50uM DHA-SD for 4 weeks, then both normal and DHA diet-mice were exposed to either dispersion media or 50 ug FA-21 (high Ni-MWCNT) via oropharyngeal instillation. 24 hours and one week post-exposure to FA-21, lung and blood were harvested for analyses of epigenetic alterations and lung pathology as illustrated in Figure 1. Laser Scanning Cytometry and nCounter miRNA expression assay (NanoString Technologies) were used to measure airway thickness in lung tissues and profile expression of 600 miRNAs, respectively.



Results: FA-21 induced significant airway thickness in lung tissues, and these thicknesses were decreased when DHA was treated to mice (Figure 2). Differential expression of miRNAs in response to FA-21 exposure and/or DHA diet modification were simultaneously measured. Comparisons within the control (DM





exposure and normal diet) identified 42 and 30 significant miRNAs abnormally expressed in response to FA-21 and FA-21/DHA exposures, respectively. In comparing DHA diet modification in the response to FA-21 (FA-21 vs. FA-21/DHA), only one miRNAs, miR-195 was significantly overexpressed as shown in Figure 3. Notably, miR-195 upregulation has been demonstrated to target lung

related proteins in the context of lung cancer and COPD and as a regulator of cell proliferation in the NF- κ B pathway [8, 9].

Future direction and Impact of study: miRNA-mRNA potential pathways will be determined, particularly for miR-195 using *in silico* approaches to further a mechanistic understanding of the complex influences of over-expressed miRNAs on dysregulated gene expression in the context of MWCNT lung exposure and disease. Furthermore, this direction will provide a better understanding of a potential role of anti-inflammatory omega-3 fatty acid diet supplementation on preventing lung disease.

The funding obtained from the UGP provided great opportunities to generate preliminary data for external grant application and support my graduate student, Beth Cole's Ph.D. dissertation. I am currently writing a manuscript to submit for peer-reviewed journal publication.

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