FALL 2021

Biochemistry and Molecular Biology Brown Bag Series

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"Effects of Lipin1 Upregulation in the Diaphragm of the mdx Mouse"

Tuesday, November 23, 2021

11:00 AM

135 Oelman Hall

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https://science-math.wright.edu/biochemistry-and-molecular-biology

Abstract

Effects of Lipin1 Upregulation in the Diaphragm of the *mdx* Mouse

Duchenne Muscular Dystrophy (DMD) is an X-linked recessive disorder that is characterized by severe and progressive muscle wasting. This disease is caused by a mutation in the largest known human gene which encodes the protein, dystrophin. Dystrophin connects the inner cytoskeleton to the extracellular matrix and is critical for maintaining the structural stability of muscle cells during contraction. Mutations to the dystrophin gene result in myocyte membrane instability, contributing to the structural deterioration of the muscle tissue. Progressive muscle degeneration and the replacement of muscle fibers with fibrotic tissue negatively impacts muscle contractility and is particularly detrimental to health when essential muscles such as the diaphragm are affected. Respiratory failure is a hallmark of DMD and is one of the leading causes of mortality associated with this disease.

Currently there is no cure for Duchenne Muscular Dystrophy, and gene therapy approaches are limited by the sheer size of the dystrophin gene which spans across 2,200 kb. Previous data generated from the laboratory has shown that the *mdx* mouse (used to model DMD) displays a reduced expression of Lipin1. Additionally, other works have shown that skeletal muscle specific Lipin1 knockout mice present muscle membrane instability. Collectively, these findings suggest the potential for Lipin1 to serve as an alternative therapeutic target in the dystrophic diaphragm by stabilizing membrane integrity. Lipin1 is a phosphatidic acid phosphatase (PAP), which catalyzes the conversion of phosphatidic acid (PA) to diacylglycerol (DAG), a reaction important for membrane phospholipid and triacylglycerol synthesis. Preliminary data suggests overexpression of Lipin1 in the dystrophic diaphragm reduces inflammation, fibrosis, and degeneration/regeneration cycling of muscle fibers. Further knockdown of Lipin1 in the dystrophic diaphragm has been found to increase fibrosis and muscle fiber degeneration/regeneration cycling. Continued investigation is required to better understand the role of Lipin1 in maintaining muscle membrane stability and its effect on respiratory function in the *mdx* mouse model.