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DISSERTATION

**“Cholesterol Metabolism and mTOR: Driving Diversity of
Oligodendrocytes and Myelin Composition Throughout the
Central Nervous System”**

by

Marie Mather

Molecular Biology, Genetics, and Cancer Program
B.Sc., 2016, University of Connecticut, Storrs, CT

Thesis Advisor: Teresa Wood, Ph.D.
Distinguished Professor
Department of Pharmacology, Physiology, & Neuroscience

Tuesday, June 11th, 2024
12:00 PM
Cancer Center, G1196

Join Zoom Presentation:

<https://rutgers.zoom.us/j/96989527100?pwd=Y0VzazIzeTdoc0tPbXRHZHJbUdBZz09>

Meeting ID: 969 8952 7100

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Abstract

Cholesterol comprises approximately 40% of myelin lipids and is often dysregulated in neurodegenerative diseases affecting myelin integrity. Despite the prominence of promyelinating drugs targeting sterol synthesis and our increasing knowledge of oligodendrocyte heterogeneity, few studies have explored lipid metabolism in both the brain and spinal cord. Therefore, understanding how cholesterol metabolism is regulated in different oligodendrocyte populations is essential to developing effective promyelinating therapies. Our previous study revealed that spinal cord oligodendrocyte precursor cells (OPCs) have higher rates of cholesterol synthesis compared to brain OPCs. Further analyses presented in this dissertation show higher expression of lipoprotein receptors in brain oligodendroglia compared to spinal cord oligodendroglia throughout rapid myelin development (postnatal days 10-18). Subsequently, treatment of primary OPCs with lipoproteins increased myelin gene expression in cultured brain OPCs while spinal cord OPCs showed no response. These data suggest that brain OPCs have a greater capacity for cholesterol uptake rather than cholesterol synthesis.

We also explored whether lower rates of cholesterol synthesis in brain oligodendrocytes could be due to lower lipid requirements to produce myelin. Analysis of myelin composition revealed that brain myelin has lower lipid concentrations compared to spinal cord myelin. Further comparisons between spinal cord and subregions of the brain revealed that myelin lipid content is correlated to average axon diameter with smaller-diameter axons corresponding to lower cholesterol and phospholipid content in myelin. When differentiated on synthetic nanofibers in vitro, brain and spinal cord oligodendrocytes maintained differences in myelin lipids but failed to increase myelin cholesterol content in the presence of larger diameter fibers. The production of myelin with distinct lipid profiles in an isolated culture system suggests that brain and spinal cord oligodendrocytes intrinsically produce different myelin profiles without stimulation by neurons or other glia. Regional differences in myelin composition are supported at least in part by the mechanistic target of rapamycin (mTOR) activation, as deletion of mTOR in OPCs leads to diminished differences in regional myelin lipid content. The results of this study further highlight the regional specificity of both myelin and oligodendroglial populations. These data build upon a growing body of literature demonstrating the numerous ways in which glial cells perform regionally distinct functions to support the variety of cellular niches in the central nervous system.