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DISSERTATION

"A novel mouse model revealing the multifaceted spectrum of Tuberous Sclerosis Complex; from compromised myelin acquisition, to seizures and autistic-like behaviors"

by

Angelina Evangelou
Cell Biology, Neuroscience and Physiology Program

BSc. 2014, University of Athens, Greece

Thesis Advisor:

Teresa L. Wood, Ph.D.
Department of Pharmacology, Physiology & Neuroscience

Tuesday, December 14th, 2021
11.00 A.M.
Limited attendance in MSB-H609

Join Zoom presentation
https://rutgers.zoom.us/j/4155444251?pwd=aGVRYTEyR3pxS09qQnZybk5tYlNrdz09

Meeting ID: 415 544 4251
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ABSTRACT

Myelin acts as an insulating material to promote rapid saltatory conduction, whereas it also provides metabolic support to the axons. Thus, loss of myelin, in the case of demyelinating diseases, leads to defective propagation of electrical signals and ultimately axonal deterioration. A considerable focus of past and current research is to uncover mechanisms to stimulate new myelination by oligodendrocytes, the myelin producing cells in the central nervous system (CNS).

The mechanistic target of rapamycin (mTOR) has an important role in oligodendrocyte development and CNS myelination. Our prior studies demonstrated that deleting mTOR from the oligodendrocyte lineage in mice leads to hypomyelination in the spinal cord. In contrast, other groups reported that disrupting tuberous sclerosis complex (TSC), a negative upstream regulator of mTOR complex 1 (mTORC1), resulted in hypomyelination instead of the predicted hypermyelination. However, deletion of *Tsc1* or *Tsc2,* the genes encoding the two TSC complex proteins, in these prior reports was introduced during specification or early oligodendrocyte differentiation and led to decreased numbers of mature oligodendrocytes. Thus, the function of TSC in myelination independent of oligodendrocyte differentiation has not been evaluated.

To assess how myelin production is altered when mTORC1 signaling is up-regulated exclusively in mature oligodendrocytes, we induced *Tsc1* deletion in proteolipid protein (PLP) expressing, premyelinating oligodendrocytes during early mouse postnatal development. Our data reveal that although myelin is produced in normal levels developmentally, oligodendrocyte loss of *Tsc1* leads to compromised myelin acquisition, a process whereby myelin thickness increases with age. Deletion of *Tsc1* from adult oligodendrocytes after developmental myelination was complete led to similar deficits in myelin acquisition, accompanied by behavioral deficits and decreased axonal conduction velocity.

Unexpectedly, early postnatal deletion of *Tsc1* in PLP-expressing cells induced epileptogenesis and autistic-like behaviors. Lineage tracing analysis revealed recombination in Bergmann glial cells of the cerebellum in addition to oligodendrocytes, supporting the conclusion that the seizure phenotype was due to dysregulation of cerebellar circuits. As TSC is a human disorder where the majority of patients suffer from seizures, autism-like behaviors and white matter abnormalities, this mouse model is a novel tool for studying the human TSC disease.