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A TALE OF TWO REGIONS: mTOR REGULATION OF OLIGODENDROCYTE FUNCTION IN THE BRAIN AND SPINAL CORD

by

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ABSTRACT

Myelin is an insulating sheath that wraps axons and allows for fast conductance of electrical impulses. It also provides metabolic and trophic support for neurons, and loss of myelin can lead to neurodegeneration. Myelin deficits during development can cause diseases such as Leukodystrophies, and adult demyelination is the primary pathology of diseases such as Multiple Sclerosis. Oligodendrocytes are the cells that produce myelin in the central nervous system.

Mechanistic target of rapamycin (mTOR) signaling is essential for normal oligodendrocyte function; ablation of mTOR signaling, particularly through mTORC1, results in oligodendrocyte differentiation deficits and hypomyelination. Interestingly, oligodendroglial-specific loss of mTOR results in different phenotypes in the brain and spinal cord during developmental myelination. Oligodendroglia from the two CNS regions also have distinct functional characteristics. Recent single-cell sequencing reports have described heterogeneity among oligodendrocytes, but have not identified distinctions between brain and spinal cord oligodendroglia.

By analyzing a specific stage of oligodendroglia during myelin initiation, we demonstrate that brain and spinal cord precursors are transcriptionally distinct; spinal cord oligodendroglia exhibit higher cholesterol biosynthesis than brain oligodendroglia. Moreover, cell autonomous loss of mTOR results in appearance of a distinct dysregulated population of oligodendrocytes with cholesterol biosynthesis deficits. Oligodendroglial loss of mTOR results in an overall reduction in cholesterol in the cells in both spinal cord and brain with deficits persisting into adulthood. Although mTOR loss has a greater impact on developmental myelination in the spinal cord, loss of mTOR in brain oligodendroglia ultimately results in oligodendrocyte death, spontaneous demyelination, and impaired axonal function, demonstrating that mTOR is required for myelin maintenance in the adult brain. Taken together, the studies in this thesis reveal that differential cholesterol metabolism is a molecular basis for the functional differences in brain and spinal cord oligodendrocytes, and further demonstrate that mTOR promotes oligodendrocyte function and myelin maintenance in part by regulating cholesterol biosynthesis.