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Unraveling the Interplay between B-Raf and mTOR Signaling in Oligodendrocytes and CNS Myelination

By

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Tuesday, March 3rd 2026
12:00 PM (Noon)
Cancer Center, G-1196

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ABSTRACT

Oligodendrocytes are a glial cell-type in the central nervous system (CNS) responsible for synthesizing a specialized lipid-rich membrane known as myelin. Myelin is a vital component of the CNS that facilitates saltatory conduction essential for rapid propagation of electrical impulses between neurons, provides metabolic support to axons and helps preserve long-term neuronal integrity. Consequently, disruption of myelin through genetic abnormalities or neuroinflammation can lead to wide range of neurological impairments including deficits in cognitive, motor and sensory function. Among the multiple extracellular and intracellular signaling pathways implicated in oligodendrocyte biology, Ras/Raf/ERK (MAPK) and PI3K/AKT/mTOR pathways have emerged as crucial regulators of oligodendrocyte maturation, myelin formation and maintenance. Recent studies have shown that both these pathways autonomously regulate CNS myelination. However, the mechanisms by which Ras/Raf/ERK and PI3K/Akt/mTOR pathways integrate in oligodendrocytes to support myelinogenesis and preserve myelin integrity remain unexplored.

Using oligodendrocyte-lineage specific cre-drivers we generated mice with single deletions of B-Raf or mTOR as well as B-Raf;mTOR double knockout (dKO) animals and assessed the impact on myelin lipid and protein levels, myelin ultrastructure and motor behavior. While individual loss of B-Raf or mTOR produced modest myelination defects, combined deletion resulted in profound hypomyelination across the white matter tracts in the spinal cord which was associated with a concomitant reduction in myelin-related proteins and lipid synthesis enzymes during early and late adulthood. Consistent with these pathological changes, dKO mice exhibited severe deficits in motor function and motor skill beginning in early adulthood. Reductions in myelin protein levels in dKO mice were also evident in the cerebellum and cortex.

To gain mechanistic insight into how B-Raf and mTOR signaling regulate oligodendrocyte development and function, we performed phospho- and total proteomic profiling of primary oligodendrocytes treated with pharmacological inhibitors of B-Raf and/or mTOR. Total proteome analyses revealed widespread downregulation of proteins involved in myelin structure, lipid biosynthesis and metabolism in cells treated with both B-Raf and mTOR inhibitors. Interestingly with simultaneous pharmacological inhibition of B-Raf and mTOR in OPCs we also identified activation of Wnt/planar cell polarity signaling, accompanied by remodeling of actin-cytoskeletal machinery and upregulation of keratin-associated protein expression. These changes may reflect a compensatory or stress-associated response to impaired myelin related protein and lipid biosynthesis following combined loss of B-Raf and mTOR signaling.

Although the proteomic analyses were performed utilizing an acute in vitro pharmacological paradigm, whereas the observed in vivo hypomyelination phenotype resulted from genetic deletions, the convergence of the molecular and pathological findings support a shared underlying disruption of myelinogenic programs. Collectively, these findings suggest that a coordinated interplay of B-Raf and mTOR signaling is essential to maintain oligodendrocytes in a myelin producing state characterized by active and efficient protein and lipid synthesis. Loss of this signaling integration drives a functional reprogramming of oligodendrocytes that culminates in hypomyelination and motor-skill impairment in vivo.

Commented [TW1]: with combined pathway inhibitors?