
Vesicular Dysfunction in Oligodendrocytes Causes Inflammatory Demyelination in the Central Nervous System

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Introduction: Myelin is an insulation surrounding axons permitting rapid conduction of electrical signals. Demyelination is evident in neurological disorders such as Multiple Sclerosis and Alzheimer's Disease, impacting motor, sensory, and cognitive functions. Optic neuritis, an inflammatory demyelination in the optic nerves, remains a major optic neuropathy causing visual loss. Oligodendrocytes are cells forming myelin in the central nervous system. However, the molecular machinery underlying the maintenance of myelin in adults remains elusive. We hypothesize that SNARE-dependent vesicular fusion is necessary for sustaining myelin integrity and hence, removing a critical SNARE protein will lead to demyelination with neuroinflammation.

Methods: To investigate the role of vesicular trafficking in oligodendrocytes, we generated oligodendrocyte-specific conditional knockout of SNAP-23, a SNARE protein expressed in oligodendrocytes, in young adult mice to analyze the behavioural, structural, and functional impairments associated with demyelination.

Results: 5-to-10 weeks after induction of SNAP-23 conditional knockout (SNAP-23 icKO), mice developed tremors, hindlimb weakness, and limp tail. Accelerating rotarod test indicated impaired motor performance and learning in SNAP-23 icKO mice. Further, SNAP-23 conditional knockout mice demonstrated demyelination across the central nervous system with axonal conduction deficits. Compound action potential conductance in the optic nerves was significantly reduced in SNAP-23 icKO. In vivo, SNAP-23 icKO had a delayed flash visual evoked potential response, suggesting impaired visual processing. Neuroinflammation with infiltration of peripheral immune T cells, mainly CD8+ cytotoxic T cells, into the central nervous system was also observed. Mechanistically, SNAP-23 removal in oligodendrocytes caused abnormal axon-myelin structures and impaired myelin protein trafficking underlying autoimmunity and demyelination.

Conclusion: SNAP-23-dependent vesicular trafficking is necessary for oligodendrocytes to maintain healthy myelin in adults. Impaired vesicular fusion in oligodendrocytes causes inflammation and demyelination in the optic nerves, ultimately affecting visual information conduction. Understanding a novel mechanism of demyelination induced by oligodendrocytes will provide potential therapeutic targets for neurological disorders with myelin abnormalities and restore vision in optic neuritis.