Proteolipid protein is required for transport of sirtuin 2 into CNS myelin.


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Mice lacking the expression of proteolipid protein (PLP)/DM20 in oligodendrocytes provide a genuine model for spastic paraplegia (SPG-2). Their axons are well myelinated but exhibit impaired axonal transport and progressive degeneration, which is difficult to attribute to the absence of a single myelin protein. We hypothesized that secondary molecular changes in PLP(null) myelin contribute to the loss of PLP/DM20-dependent neuroprotection and provide more insight into glia-axonal interactions in this disease model. By gel-based proteome analysis, we identified >160 proteins in purified myelin membranes, which allowed us to systematically monitor the CNS myelin proteome of adult PLP(null) mice, before the onset of disease. We identified three proteins of the septin family to be reduced in abundance, but the nicotinamide adenine dinucleotide (NAD+)-dependent deacetylase sirtuin 2 (SIRT2) was virtually absent. SIRT2 is expressed throughout the oligodendrocyte lineage, and immunoelectron microscopy revealed its association with myelin. Loss of SIRT2 in PLP(null) was posttranscriptional, suggesting that PLP/DM20 is required for its transport into the myelin compartment. Because normal SIRT2 activity is controlled by the NAD+/NADH ratio, its function may be coupled to the axo-glial metabolism and the long-term support of axons by oligodendrocytes.