The *m*-AAA protease, involved in hereditary spastic paraplegia and spinocerebellar ataxia, is essential for oligodendrocyte survival and myelin maintenance

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The *m*-AAA protease in the mitochondrial inner membrane degrades misfolded polypeptides and processes specific substrates, thereby regulating mitochondrial function. Mutations in subunits of the *m*-AAA protease, paraplegin and AFG3L2, cause hereditary spastic paraplegia and spinocerebellar ataxia, respectively. Whether deficiencies of the *m*-AAA protease in glia contribute to neurodegeneration is poorly understood. Interestingly, post-myelination oligodendrocytes can survive despite mitochondrial respiratory defects by switching their metabolism to glycolysis, and can support axons metabolically by supplying lactate as energy source. We generated oligodendrocyte-specific knock-outs of *Afg3l2* alone or the entire *m*-AAA protease in the postnatal brain, after myelination is completed. While deletion of *Afg3l2* in oligodendrocytes was asymptomatic for several months, deletion of the *m*-AAA protease led to early and progressive weight loss and frank motor impairment. Targeted oligodendrocytes showed fragmented mitochondrial network, and died within a few weeks by apoptosis. Consistently, we found progressive axonal demyelination, axonal degeneration and secondary inflammation in both brain and spinal cord. Our study demonstrates different requirements of the *m*-AAA protease in glia versus neurons, unravels a crucial role of the *m*-AAA protease in protection against apoptosis, which is independent from respiratory function, and further elucidates the role of mitochondrial dysfunction in glia.