Novel mouse mutants revealing oligodendrocyte dysfunction as a primary cause of axonal loss and inflammatory demyelination

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Oligodendrocytes myelinate axons for rapid impulse conduction and contribute to normal axonal functions in the central nervous system. In multiple sclerosis, demyelination is caused by autoimmune attacks, but the role of oligodendroglial cells in disease progression and axon degeneration is unclear. Several genes that are expressed exclusively in mature oligodendrocytes, such as *Plp1* or *Cnp1*, are not essential for myelination, but for maintaining axonal integrity (Lappe-Siefke et al. Nat. Genet., 2003). Recent evidence suggest that oligodendrocytes harbor peroxisomes whose function is particular important for maintaining white matter tracts. By selectively inactivating the import factor PEX5 in myelinating glia, we generated mutant mice that developed normally, but within several months exhibited ataxia, tremor, and premature death. Absence of functional peroxisomes from oligodendrocytes caused widespread axonal degeneration and progressive subcortical demyelination, but did not interfere with glial survival. Surprisingly, peroxisomal dysfunctions caused a strong proinflammatory milieu and the infiltration of B and activated CD8(+) T cells into brain lesions (Kassmann et al., Nat Genet., 2007). Taken together, oligodendrocytes themselves provide a neuroprotective function against axonal degeneration and neuroinflammation, which is relevant for human demyelinating diseases.