Oligodendrocytes as modifiers of disease progression in a mouse model of inherited Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis is a fatal adult–onset neurodegenerative disease characterized by abnormal accumulation of aggregates containing SOD1, FUS and TDP-43 proteins in affected motor neurons and glial cells. To further characterize aggregates, we used immunohistochemical analysis to search for SOD1 containing inclusions in SOD1-G93A and Lox-SOD1-G37R mouse models. We detected aggregates of different size and shape in motor neurons and extracellular space in ventral gray matter and ventrolateral white matter of lumbar spinal cords. Surprisingly, we detected no SOD1 inclusions in the majority of matured oligodendrocytes, yet we found evidence for the presence of aggregates in the non-compact regions of their myelin sheath. The role of oligodendrocytes in ALS pathogenesis is becoming increasingly recognized. Selective excision of mutant SOD1 from OPCs (Oligodendrocyte Precursor cells or NG2+ glia cells) significantly delayed disease onset and prolonged survival in mice. To further investigate the role of oligodendroglial lineage cells, we generated two novel mouse models whereby mutant SOD1 was selectively excised using Cnp-Cre and Sox10-Cre driver lines. Selective removal of mutant SOD1 from oligodendroglia lineage cells and a subset of motor neurons by Cnp-Cre resulted in near complete rescue while in oligodendroglial lineage cells and a subset of myelinating Schwann cells with the use of Sox10-Cre prolonged survival and significantly reduced microglial activation in spinal cord gray matter at the onset of the disease. To provide a mechanistic insight on how mutant SOD1 in oligodendrocytes might lead to motor neuron loss, we hypothesized that SOD1 aggregates might clog myelinic channels resulting in the loss of metabolic support to adjacent axons. To test our assumption, we generated mouse models that express mutant SOD1 (Sod1+/-) and have altered compact to non-compact myelin ratio (Mbp+/- or Cnp+/-), rendering a difference in the strength of oligodendroglial support. However, we observed a tendency towards a worsening in disease phenotype and neuropathological hallmarks in both double mutants (Sod1+/-/ Cnp+/- and Sod1+/-/ Mbp+/-) when compared to Sod1+/- single mutants.