Compact Myelin Detachment after metabolic Oligodendrocyte injury

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Introduction: Multiple sclerosis (MS) is characterized by demyelination and oligodendrocyte degeneration. The pathology of white matter injury induces neurodegeneration and in consequence accumulation of irreversible clinical disability. Mechanisms leading to oligodendrocyte and myelin degeneration are poorly understood, however centrifugal (early oligodendrocyte cell body pathology) and centripetal (early myelin sheath pathology) mechanisms have been described. Here we investigate structural consequences of Cuprizone-induced centrifugal oligodendrocyte degeneration.

Methods: Tissues of Cuprizone-treated mice were, in addition to immunohistochemistry, ultrastructurally analyzed by transmission electron microscopy (TEM) and serial block-face scanning electron microscopy (3D-EM). Electrophysiological studies were performed to correlate axon structural integrity with callosal axon conduction.

Results: After two days of Cuprizone intoxication, oligodendrocytes express the stress sensor 'activating transcription factor 3'. At week one, numbers of mature oligodendrocytes were decreased, whereas immunohistochemical staining intensity for various myelin proteins remained stable. In line with this finding, TEM studies verified absence of demyelination at this early time point. At the beginning of active demyelination (i.e., at week three) 3D-EM showed a detachment of the myelin sheath from the axolemma as the predominant early myelin pathology (called **co**mpact **my**elin **d**etachment; CoMyD). High magnification analyses eventually showed rupture of the axolemma at sites of myelin pathology, which was paralleled by severe axonal injury. Myelin detachment was predominantly asymmetric. Quantitative analyses showed that CoMyD mainly occurs in medium fiber axons (median: 0.55 µm, interquartile range: 0.44-0.67 µm). Functional analyses revealed a severe impairment of action potential propagation at this early time point.

Conclusion: Our studies show a centrifugal progression of oligodendrocyte pathology during Cuprizone-induced metabolic injury. After initial oligodendrocyte cell body pathology, we propose that retraction of oligodendrocytes' processes leads to retraction forces, resulting in CoMyD eventually paralleled by axonal injury. Future studies have to show whether CoMyD as well occurs in MS, and which factors regulate this process.