Segmental demyelination of internodes triggers mitochondrial redistribution

Julia Nedelcu, Felix Schweiger, Felix Fischbach, Markus Kipp

Oligodendrocytes, myelin sheaths and axons form a closely linked functional network, known as the axon-myelin unit. Neuronal cell bodies, which replenish the axon with mitochondria through anterograde transport, are directly implicated in the pathophysiology of progressive MS. While we know that the spatial distribution of intra-axonal mitochondria is severely disturbed in MS, underlying mechanisms are poorly understood. Specifically, to what extent loss of the myelin sheath (i.e., demyelination) per se regulates mitochondrial distribution is currently unknown. In this study, we first examined whether oligodendrocytes die simultaneously or sequentially, and then investigated mitochondrial distribution by means of 3D-electronmicroscopy.

Immunoflourescence double stains were performed to visualize stressed oligodendrocytes. Serial block-face scanning electron microscopy (3D-EM) was performed to reconstruct the axon-myelin unit. Quantitative measurements were performed to define changes of different mitochondrial parameters.

During initial cuprizone-induced metabolic stress (i.e. at week 1), almost all mature oligodendrocytes express the stress marker protein ATF3 (activating transcription factor 3). 3D-EM at the stage of early demyelination (i.e. at week 3) frequently showed a complete demyelination of single internodes. Such demyelinated internodes were flanked at both sites by normally myelinated axonal segments. This allowed us to study to what extent focal loss of the myelin sheath affects the distribution of axonal mitochondria in one and the same axon. Individual mitochondrial volumes and mitochondrial densities were significantly increased in areas of preserved internodes compared to demyelinated axonal segments.

We showed that metabolic stress results in an “out of phase” degeneration of oligodendrocytes, indicating a graded – and probably regulated - oligodendrocyte vulnerability. During initial demyelination, mitochondria accumulate at internodes with a preserved myelin sheath. We, therefore, conclude that loss of the myelin sheath critically contributes to mitochondrial pathology in MS.