Integrated stress response (ISR) regulates oligodendrocyte death and axonal damage in the cuprizone model

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The primary functions of oligodendrocytes are to produce the myelin sheath and to provide nutritional support to axons. Oligodendrocyte death with concomitant demyelination and axonal degeneration are hallmarks of multiple sclerosis (MS). What kills the oligodendrocytes and to what extent this is linked to axonal degeneration, is not well understood.
Oligodendrocytes are unique with respect to their high lipid and membrane biosynthesis. This makes the endoplasmic reticulum (ER) vulnerable against any kind of homeostasis dysregulation. If stress exceeds a certain level, cells induce the expression of specific ER-stress-genes, like the pro-apoptotic transcription factor DNA damage inducible transcript 3 (DDIT3). Oligodendrocytes are highly susceptible to this cellular response that is well known as integrated stress response (ISR).
In this study, we applied a genome wide array analysis that revealed ISR induction and apoptosis in mature oligodendrocytes early after initiation of metabolic oligodendrocyte injury induced by cuprizone intoxication. While other tissues with massive protein-synthesis (i.e., pancreas, liver, kidney, heart) showed no DDIT3-induction, within the brain Ddit3 selectively was expressed in oligodendrocytes. Furthermore, we investigated the vulnerability of other glia cells during five weeks of cuprizone exposure. Immunofluorescence-double-stainings showed 60% co-localization of the DDIT3-positive cells with astrocyte markers (GFAP, Vimentin, BLBP) and 21% with the oligodendrocyte-marker OLIG2. DDIT3 was not expressed in IBA1-positive microglia-cells. Besides the amelioration of toxin-induced oligodendrocyte apoptosis, demyelination, microgliosis, astrocytosis and acute axonal damage were less intense in *Ddit3*-null mutants.
In summary, we demonstrate that the activation of an ISR, specifically the induction of DDIT3, mediates metabolic oligodendrocyte degeneration and concomitant axonal damage. Furthermore, activation of an ISR is tightly regulated with early activation in oligodendrocytes and concomitant activation in astrocytes in established lesions. The knowledge followed by these studies will provide a foundation for developing therapeutic strategies that protect oligodendrocytes and eventually axons in progressive MS.