25th Annual Meeting of the European Charcot Foundation
25 Years of Fundamental Milestones in MS
30 November - 2 December 2017
Grand Hotel Dino Baveno, Italy

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

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Introduction

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).

Results

Short-term cuprizone treatment induces DDIT3 expression selectively in oligodendrocytes

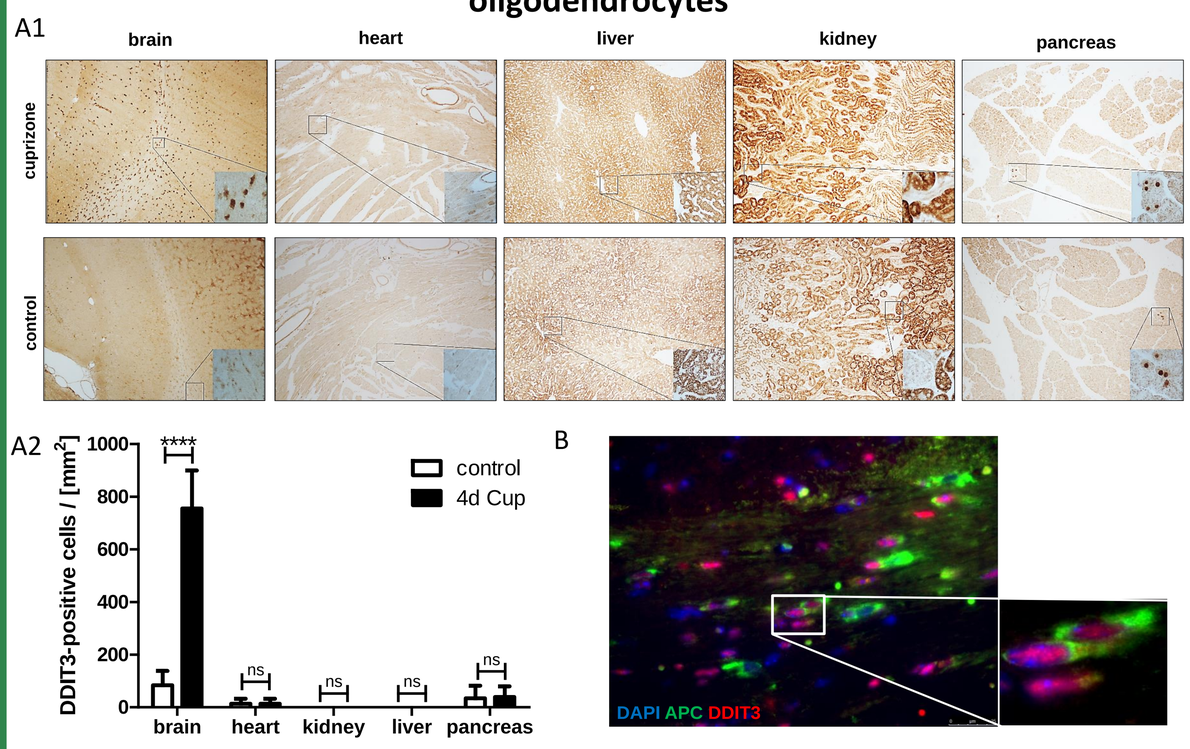
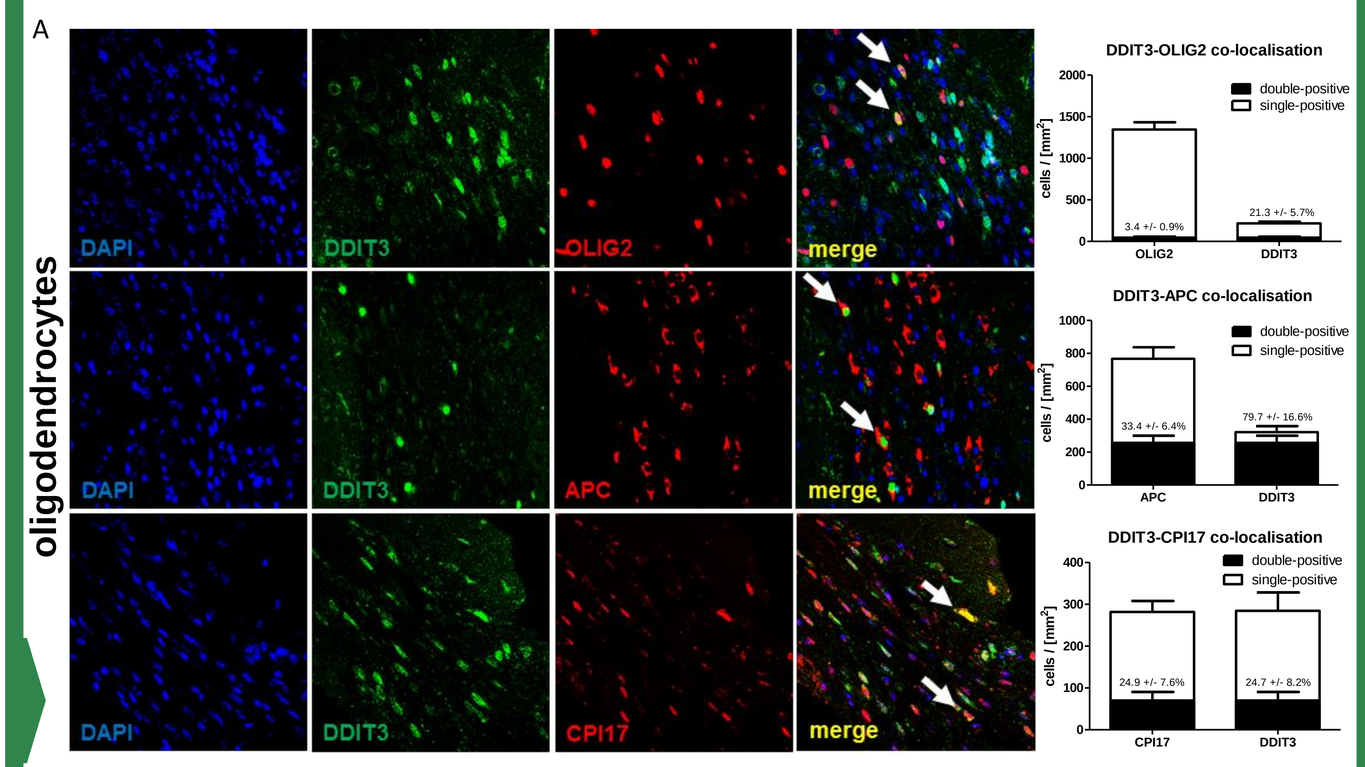
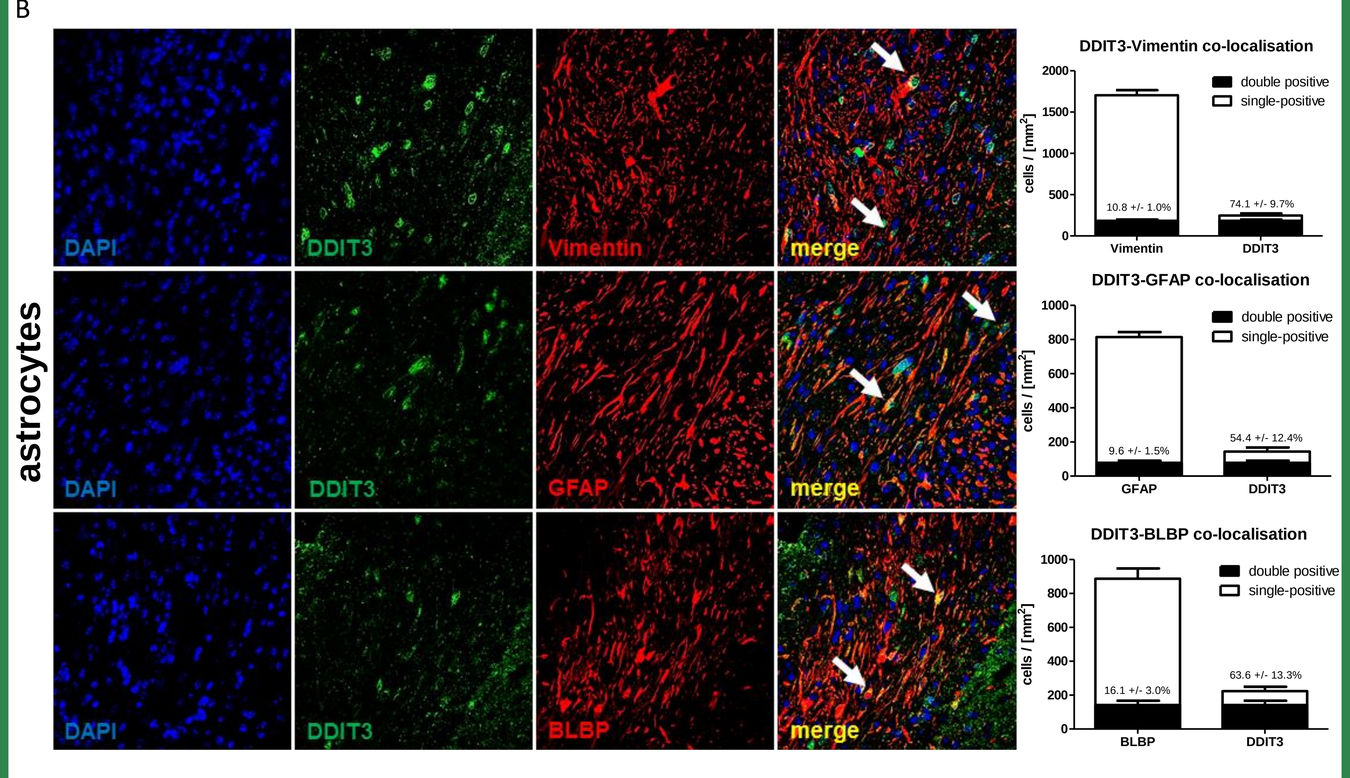
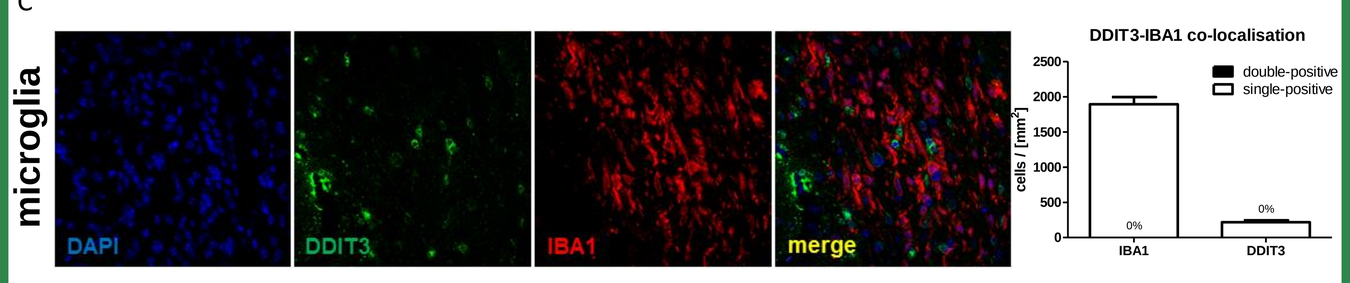


Figure 1: DDIT3 positive cells were quantified after 4 days of cuprizone intoxication in tissues with high protein-synthesis (i. e. brain, heart, liver, kidney, pancreas). **A1-2:** Quantification of DDIT3+ cells in different organs **B:**Immunofluorescence double staining shows co-localization of the oligodendrocyte marker protein APC and DDIT3 after short-term cuprizone exposure

Oligodendrocytes and astrocytes express DDIT3 after 5 weeks of cuprizone intoxication







Ddit3$^{-/-}$ mice are less vulnerable to cuprizone-induced demyelination

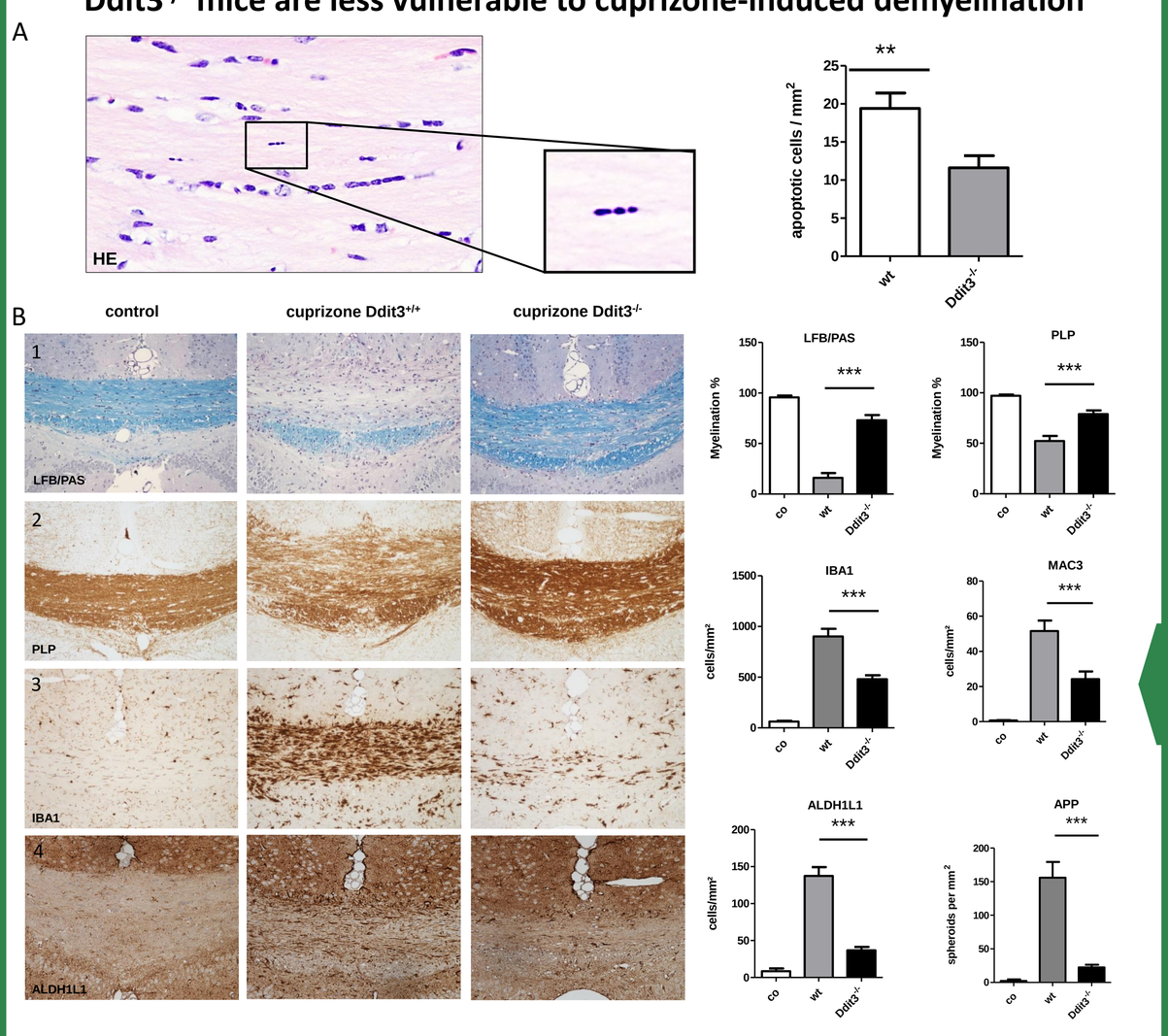


Figure 3: A: HE-staining shows less apoptotic cells in Ddit3$^{-/-}$ animals. **B:** Stainings and quantification of medial corpus callosum at the level of rostral hippocampus. Note less severe demyelination (**1-2**), less microgliosis (**3**) and less astrocytosis (**4**). Graphs (right side) show also less activation of microglia (MAC3) and less axonal damage (APP)

Figure 2: Immunofluorescence double stainings of DDIT3 and different gliacell markers after 5 weeks of cuprizone intoxication **A:** Co-localisation of DDIT3 with the oligodendrocyte specific proteins OLIG2 (upper row), APC (middle row) and CPI 17 (lower row). **B:** Co-localisation of DDIT3 with the astrocyte specific proteins Vimentin (upper row), GFAP (middle row) and BLBP (lower row. **C**: Co-localisation of DDIT3 with the microgliacell specific marker IBA1

Discussion

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. It is our aim to point out the importance of developing therapeutic strategies to protect oligodendrocytes and eventually axons especially in progressive MS.

Literature

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We would like to thank S. Wübbel, A. Baltruschat, S. Tost and B. Aschauer for their excellent technical assistance.

The authors state no conflict of interest.