The Distinct Roles of Autophagy in Oligodendrocytes and Neurons During Perinatal Brain Injury

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Perinatal HI brain injury is not limited to grey matter lesions but also markedly affects the developing white matter. In both human newborns and preclinical rodent models, white matter abnormalities are associated with adverse neurodevelopmental outcomes. The oligodendrocyte lineage is particularly vulnerable during this period of rapid proliferation, differentiation, and maturation. Hypoxia-ischemia (HI)-induced white matter injury may result from both oligodendrocyte precursor cell (OPC) death and impaired oligodendrocyte (OL) maturation, ultimately compromising myelination.

In previous studies, we showed that HI triggers deregulated, excessive autophagy in developing neurons, leading to autophagy-dependent cell death (autosis), and we demonstrated that inhibition of neuronal autophagy provided neuroprotection. However, autophagy may play different roles across brain cell types in HI, such as in the oligodendrocyte lineage, where autophagy is essential for OPC survival, differentiation, OL maturation, and myelin homeostasis.

To investigate the role of autophagy in OPCs/OLs after HI, we used a co-culture model of primary developing neurons and oligodendrocytes exposed to a stimulation mimicking HI conditions (combining excitotoxicity and hypoxia). HI induced either OPC loss (~10%) or significant changes in OPC morphological and biochemical properties (increased process extension and branching at 24 h after injury, followed by reduced MBP expression one week later), indicating impaired OL maturation and myelination. Interestingly, HI induced an early, transient impairment of autophagic flux in OPCs. ATG7 downregulation, and thus autophagy inhibition, further reduced OPC survival, whereas ATG7 overexpression promoted survival and preserved OL maturation after HI.

Together, these findings reveal divergent, cell-type-specific effects of HI on autophagy. HI induces excessive neuronal autophagy, which contributes to neuronal death, whereas it impairs autophagy in OPC/OLs, contributing to OPC/OL death and deregulated maturation.