Role of Sirt1 during Oligodendrocyte Progenitor Proliferation in Cerebellar White Matter after Hypoxia

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Preterm infants are at a high risk of developing diffuse white matter injury (DWMI) after chronic hypoxia. DWMI is a leading cause of permanent neurodevelopmental disabilities and has been linked with a loss of oligodendrocytes (OLs) in white matter. Mature OLs are generated from proliferating oligodendrocyte progenitor cells (OPCs), which may have the capacity to restore the injured regions. Previous research has demonstrated that hypoxia causes OPC regeneration by activating the cyclin-dependent kinase 2 (Cdk2) pathway in cortical white matter and the cyclin-dependent kinase 4 (Cdk4) pathway in the subventricular zone. Sirt1, a NAD-dependent class III histone deacetylase, is known to modulate these types of cell cycle regulatory pathways and may thus be involved in cell development and determination. Additionally, since the cerebellum is responsible for cognitive function as well as motor coordination and learning, it may play a critical role in the behavioral abnormalities of preterm children. Thus, the objective of the present investigation was to determine Sirt1 expression in OPCs of cerebellar white matter after hypoxia, using tissue samples from a clinically relevant mouse model. Immunocytochemistry experiments suggested that hypoxia enhances cell proliferation. Additionally, Sirt1 is upregulated in OPCs after hypoxia. Western blot analysis revealed that the Cdk4/Cyclin D/p107 signaling pathway is activated after hypoxia. The results suggest that cerebellar white matter exhibits a regenerative response to chronic neonatal hypoxia, which may be modulated by upregulation of Sirt1 in oligodendrocyte progenitor cells.

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