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Developmental Characterization of the Choroid Plexus in Sialidosis (Neu1 Deficient) Mice

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Developmental Characterization of the Choroid Plexus in Sialidosis (Neu1 Deficient) Mice

Abstract

The lysosomal sialidase Neuraminidase-1 (Neu1) initiates the hydrolysis of sialoglycoconjugates by cleaving their terminal sialic acid residues. Neu1 creates a complex with the carboxypeptidase protective protein/cathepsin A (PPCA), which is necessary for its catalytic activation and its transport to the lysosomal compartment. In humans, a primary deficiency of this enzyme leads to a pediatric, catastrophic, neurodegenerative lysosomal storage disorder called sialidosis. Mice deficient in Neu1 exemplify the early-onset severe form of sialidosis. Our laboratory has recently discovered that loss of Neu1 exacerbates the process of lysosomal exocytosis (LyEXO) in various cell types by influencing the sialic acid content of lysosomal associated membrane protein-1 (LAMP-1). LyEXO is a calcium-regulated physiological process which results in the fusion of lysosomes with the plasma membrane and consequent remodeling of the PM and release of lysosomal luminal content into the extracellular space. Defective processing of the sialic acid residues of LAMP-1 in absence of Neu1, prolongs its half-life and leaves lysosomes disposed to dock at the PM and take part in LyEXO. So far, Neu1 deficient mice are the only disease model currently available that shows excessive LyEXO.

This dissertation focused on a brain structure, which has an intrinsic exocytic/endocytic capacity: the choroid plexus (CP). The CP is responsible for producing and secreting the cerebrospinal fluid (CSF) and functions as the barrier interface between the blood and the CSF. The specific aim of this research was to investigate the consequences of Neu1 deficiency on the structural and functional characteristics of the CP as assessed by a comprehensive analysis of several CP markers during development and adulthood.

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