PERTURBATION OF CHOLESTEROL BIOSYNTHESIS DISRUPTS ASTROCYTE-MICROGLIA CROSSTALK: ROLE IN NEURODEVELOPMENTAL DISORDERS

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The brain is the most cholesterol rich organ in the body, containing ~25% of the body's total cholesterol content. Due to the blood-brain barrier, cholesterol in the brain is primarily synthesized de novo by astrocytes and transported to neurons. Genetic disorders of cholesterol biosynthetic enzymes result in reduced CNS cholesterol levels and sterol precursor accumulation. Smith-Lemli-Opitz syndrome (SLOS), caused by mutations in 7-dehydrocholesterol reductase (DHCR7), results in broad neurodevelopmental malformations and neurological deficits. While much work has focused on the neuronal deficits present, the impact of DHCR7 disruption on astrocyte formation and function remains unknown. As the predominant cell type in the brain, astrocytes are critical regulators of many neurological processes, including neuroinflammatory response and cholesterol synthesis/transport. Using a hypomorphic Dhcr7 mouse model, immunohistochemistry indicates regional deficits in astrocyte development. Through analysis of primary astrocytes, we demonstrate that Dhcr7 disruption contributes to broad cellular dysfunction. Dhcr7 astrocytes display hallmark signs of reactivity, including increased expression of glial fibrillary acidic protein (GFAP) and cellular hypertrophy, while transcript analyses demonstrate extensive immune activation, including type A1 reactivity resulting from exposure to reactive microglia. Functionally, Dhcr7 astrocytes exhibit hyper-responsiveness to glutamate stimulation and correlative changes in calcium flux. Our data are the first to define the impact of Dhcr7 on astrocyte biology and suggest astrocyte deficits resulting from astrocyte-microglia crosstalk may contribute to the neurological phenotypes observed in disorders of cholesterol biosynthesis. This work also further elucidates the complex role lipid metabolism plays within the astrocyte-immune axis and lipid impacts on neurological disease.