Poster Number: 6

MetroHealth Medical Center
RESEARCH DAY 2023
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Poster Title: **The Role of Astrocytes in the Neural Glymphatic System: A Literature Review on the Evolving Theory of Cerebrospinal Fluid Dynamics**

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Category: **Molecular & Cellular Biology**

Introduction: The traditional view of CSF production and flow postulates that after its production from the choroid plexus of the ventricles, CSF flows through the subarachnoid space surrounding the brain and spinal cord before exiting into the venous sinuses via arachnoid villi. However, seminal translational studies in the past decade have uncovered alternate routes of CSF production and efflux, calling for an expansion of this classical model. The goal of this review is to summarize the changing landscape of scientific theory surrounding the production, flow, and absorption of cerebrospinal fluid, with particular emphasis on astrocytic function. We hope that this review will advance the conception and funding of basic, translational, and clinical research endeavors investigating neuroglia as therapeutic targets.

Discussion: In recent years, scientists have uncovered a novel function of astrocytes in regulating the perivascular microenvironment. Perivascular "glymphatic" pathways allow fluid movement through the interstitial matrix, facilitated by the expansion and contraction of astrocytic endfeet, specialized extensions that wrap around vasculature and neurons, forming a network that guides the flow of interstitial fluid as it cleanses the brain parenchyma. An abundance of literature suggests that the clustering of aquaporin-4 channels within the astrocytic endfeet is responsible for the generation of interstitial fluid that flows through the glymphatic pathway. Ultrastructural analysis of the mouse brain with electron microscopy suggests that astrocytic endfeet cover >60% of the capillary vasculature. Immunohistochemical studies of the rat brain connect the structural density of aquaporin-4 channels in astrocytic endfeet to the functional properties of these glial cells in creating a low-resistance, convective current of interstitial fluid that flows through the perivascular regions of the brain parenchyma - also known as Virchow-Robin spaces. It is worth noting that aquaporin-4 is also present in the basolateral membrane of ventricular ependyma. In 2018, a meta-analysis performed by Mestre et al. demonstrated that knockout of the aquaporin-4 gene in several different mouse models reduces tracer flux through the interstitium and CSF, thus corroborating the function of aquaporin-4 in regulating fluid dynamics within the CNS. In 2017, Simon et al. performed analysis on human transcriptome data to determine the expression profile of genes encoding the dystrophin associated complex (DAC) which provides structural support for the localization of aquaporin-4 in the astroglial perivascular membrane. This study found differential DAC gene expression that correlated to cognitive changes in dementia patients. The evolution in scientific thought provoked by these recent discoveries on CSF dynamics has yet to be fully realized in the clinical realm. The critical role of glial function in maintaining fluid homeostasis within the CNS exposes astrocytes as potential therapeutic targets for neurological conditions characterized by dysregulated CSF composition or flow.

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