FORMIN PROTEIN DAAM2 MODIFIES NEURAL CIRCUIT AND NEUROVASCULAR UNIT IN THE CNS

Juyeon Jo[1], Kyoungin Kim[2], Junsung Woo[3], Hyun Kyoung Lee[2]

[1] Baylor College of Medicine, Department of Pediatrics, Neurology & Developmental Neuroscience

[2] Baylor College of Medicine, Pediatrics/NRI, Neurology

[3] Baylor College of Medicine, Center for Cell and Gene Therapy,

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Background: Astrocytes are the most diverse and abundant glial cells in the CNS, and play dynamic roles in synaptogenesis, neurotransmission, neural circuit formation, and blood-brain-barrier formation. Consequently, dysregulation of astrocytes is closely associated with numerous neurological disorders and malignancies. Extraordinarily complex morphology of astrocytes is essential for their diverse functions during development as well as in pathological condition. Despite its' importance, yet the molecular and cellular mechanisms that link astrocyte morphology to neural circuit and neurovascular development remain largely undiscovered. Formin proteins are key regulators of the cytoskeleton and cellular morphology; however, their role in astrocytes morphogenesis and associated physiological functions is unknown. Formin protein Daam2 is highly expressed in astrocytes while its' function in astrocyte morphology and function remains enigmatic.

Materials/Methods: For loss- and gain-of-functional studies during development and in disease model, whole-body and astrocyte-specific conditional knockout mice for Daam2, and viral manipulation are used. To decipher morphological alterations in astrocytes, sparse single cell labeling method is used and images are analyzed by IMARIS. Astrocytic calcium imaging and electrophysiological recording of neuronal activity were performed to investigate physiological alterations by Daam2 loss. To reveal function of Daam2 in pathological condition, photothrombotic stroke is induced and integrity of neurovascular unit is analyzed by examination of BBB leakage and cellular markers.

Results: We found that loss of Daam2 in astrocytes results in increased morphological complexity in cortex, which elicits inhibition effects on astrocytic calcium dynamics. Loss of Daam2 in astrocytes also modifies synaptogenesis and resulted in increased excitatory synaptic activity but no changes in inhibitory synaptic activity in cortex. Photothrombotic stroke injury revealed that loss of Daam2 results in cerebrovascular impairment and aggravates BBB leakage by injury, leading to delayed tissue repair.

Conclusions: Together, our results reveal new mechanisms regulating astrocyte morphology and further show that changes in astrocyte morphology can differentially influence excitatory and inhibitory circuit function. Importantly, we found function of Daam2 in neurovascular unit, providing further insight into the therapeutic potential of Daam2 in pathological condition.

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