The Role of Neuronal Primary Cilia in Alzheimer's Disease

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Alzheimer's disease (AD) is the leading cause of dementia, accounting for 60-80% of cases in the United States. Failed interventions, aimed at the symptoms of the disease, have created a drive to better understand how the disease progresses. This study investigates the role of the primary cilia—an antenna-like organelle that integrates cellular signaling and neuronal homeostasis—in AD. Primary cilia are critically understudied in AD, comprising less than 0.18% of publications. My analysis revealed that primary cilia were the second most affected organelle undergoing differential gene expression in AD subjects compared to non-AD subjects. Notably, gene ontology analysis revealed that the most affected biological process related to those genes was cilium assembly, suggesting that primary cilia function is reduced during AD pathology. To determine how primary cilia are affected during disease progression in AD, I utilized a preclinical mouse model for AD (5xFAD mice). To visualize primary cilia, I performed immunohistochemical analysis with the neuronal primary cilia specific adenylate cyclase 3 (AC3) and DAPI (nuclei). Consistent with the downregulation of cilia genes in AD subjects, there was a significant decrease in both the length and number of primary cilia relative to their respective control group as the disease progressed in 5xFAD mice. These findings reinforce the importance of primary cilia alterations in AD and establish the primary cilia as a locus of injury and a potential therapeutic target for future AD drug development.