Effect of neuronal primary cilia on axonal tract development


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Abstract:

Appropriate axonal growth and connectivity are essential for functional wiring of the brain. Joubert Syndrome Related disorders (JSRD), a group of ciliopathies in which mutations disrupt primary cilia function, are characterized by axonal tract malformations. However, little is known about how cilia-driven signaling regulates axonal growth and connectivity. We demonstrate that the deletion of JSRD genes, Arl13b and Inpp5e, in projection neurons leads to de-fasciculated and mis-oriented axons in superior cerebellar peduncle (SCP), corticospinal tract (CST), and corpus callosum (CC) axonal tracts. Arl13b deletion disrupts the function of its downstream effector Inpp5e and deregulates ciliary-PI3K/AKT signaling necessary for axonal development. Chemogenetic activation of ciliary-GPCR signaling and cilia-specific optogenetic modulation of downstream second messenger cascades (PI3K, AKT, AC3) commonly regulated by ciliary signaling receptors induce rapid changes in axonal dynamics. Further, Arl13b deletion leads to changes in transcriptional landscape associated with dysregulated PI3K/AKT signaling activity. These data suggest that ciliary signaling cascades act to modulate patterns of axonal tracts and connectivity in the developing brain and that impaired primary cilia signaling underlies axonal tract defects in JSRD.