Deciphering molecular codes control the morphogenesis of the cerebellum

With the support by the National Natural Science Foundation of China and the Beijing Municipal Science and Technology Commission, the research team led by Investigator Wu HaiTao (吴海涛) at the Institute of Basic Medical Sciences, Academy of Military Medical Sciences, uncovered the novel critical molecule named Rack1 (Receptor for activated C kinase 1) plays an essential role for the development of the cerebellum, which was published in *PNAS* (2019, 116(10): 4661—4670).

Cerebellum morphogenesis is critically important in normal brain development. The developmental deficits of the cerebellum can result in motor and higher cognitive dysfunctions. The cellular and molecular assembly of the cerebellar cortex constitute an ideal model for studying neuronal properties and cortical circuitry formation.

Regarding the molecular mechanisms underlying cerebellar development have not yet been fully understood, in this work, Wu's group systematically analyzed and revealed a critical function of Rack1, a WD40-repeat (WDR) domain containing scaffolding protein, in the regulation of cerebellar morphogenesis. They found that during embryonic and early postnatal development, Rack1 oppositely regulates Wnt/β-catenin and Sonic hedgehog (Shh) signaling pathways in distinct developmental stages.

Clinically, dysfunctional Wnt/β-catenin and Shh signaling in cerebellar granule neurons are also associated with medulloblastoma, the most common malignant type of pediatric brain tumor. More importantly, they found that Rack1-mediated stabilization of histone deacetylase 1 (HDAC1)/HDAC2 is essential for the activation of Shh signaling in granule neuron progenitors (GNPs) during cerebellar development. Suppression of HDAC1/HDAC2 activity in the developing cerebellum phenocopies the Rack1 mutant. Given that HDACs have emerged as promising targets in preclinical anti-medulloblastoma drug development, the Rack1-mediated regulation of HDAC1/HDAC2 in GNPs described in this study reveals a potential signaling pathway in medulloblastoma pathogenesis, which requires further exploration.

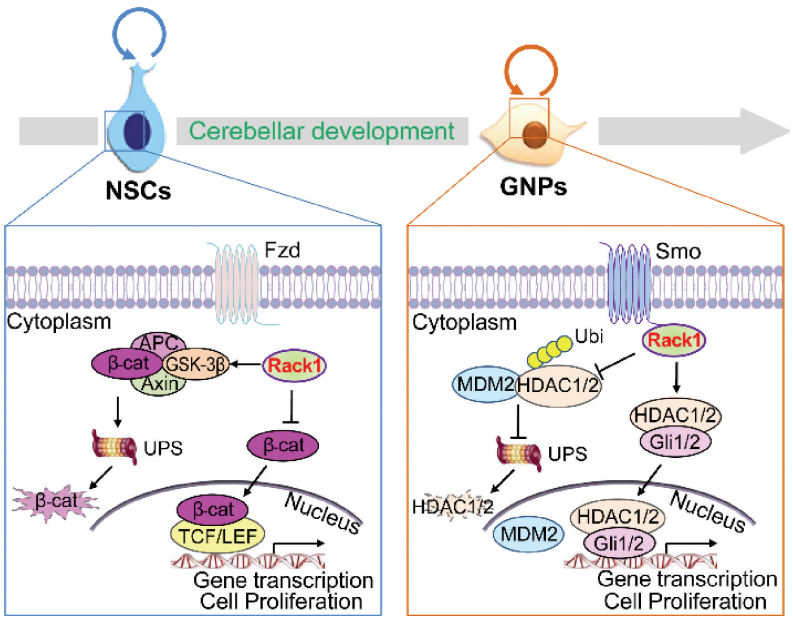

Figure Working model for Rack1 in cerebellar development.

Interestingly, recent human genetic studies have shown the importance of WDR genes in brain disorders, notably in intellectual disabilities associated with microcephaly and abnormal neural development. Rack1 has been previously shown to regulate neurite outgrowth and dendritic transport, suggesting a broader role of Rack1 in the regulation of neural development and brain disorders in addition to controlling cerebellar morphogenesis.