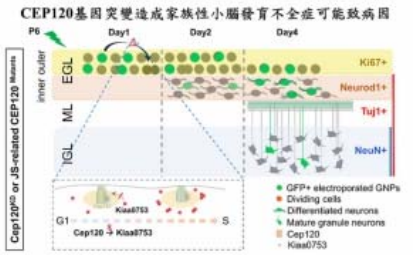
[Research] 2021/10/29

Unraveling the Mysterious Role of Centriolar Protein CEP120 in Joubert Syndrome, a Congenital Cerebellar Disorder



Abstract:

Dr. Tang K. Tang, a distinguished research fellow in the Institute of Biomedical Sciences of Academia Sinica, leads a research group, working on the roles of centriolar proteins in neuron progenitors during cerebellar development and investigating how the defects in this process impacts the pathogenesis of Joubert syndrome. This work was published in Genes & Development, a prestigious journal renowned in the field of genes and developmental biology.

Main content:

The cerebellum executes sensory-motor coordination, postural balance, and fine movements. These amazing behaviors rely on the proper development of granule neuron progenitors (GNP), the major neural stem cells whose proliferation depends on the primary cilium-mediated Shh signaling in the developing cerebellum. Defects in ciliogenesis result in the malformation of the cerebellar vermis, such as Joubert syndrome, which is characterized as a hereditary autosomal-recessive ciliopathy. The main clinical features of Joubert syndrome are “Molar tooth sign” shown in MRI imaging (a signature of cerebellum-brain stem malformation), hypotonia, and developmental retardation. However, the underlining molecular mechanism remains largely unknown.

Currently, at least 35 genes have been identified as the cause of Joubert syndrome (JS); interestingly, most of these JS-associated proteins are involved in the formation of the basal body, a modified mother centriole found at the base of a cilium, which serves as a nucleation site for the assembly of primary cilium. Dr. Tang’s lab has been dedicated to the field of centriole biogenesis for decades and discovered the role of the centriolar protein CEP120 in the regulation of centriole length (J Cell Biol, 2013) and the formation of distal appendages for proper ciliogenesis by recruiting TALPID3 and C2CD3 on centriole (Sci. Rep. 2019). Interestingly, the mutations on CEP120 were reported to be one of the major causes of Joubert syndrome. In the present study, Dr. Tang and his lab members found that reducing Cep120 expression, triggered by in vivo cerebellar electroporation of short hairpin RNA (shRNA) against Cep120 in murine cerebellum, not only led to decreased ciliogenesis in GNPs, but also resulted in the appearance of ectopic neurons in the developing cerebellum. This finding is consistent with previous pathological reports in Joubert syndrome. Remarkably, Dr. Tang’s lab found that Cep120 recruits another Joubert syndrome-related protein, Kiaa0753, onto the centrioles by which this interaction is crucial for timely differentiation of GNPs. Substantially, three Joubert syndrome-associated CEP120 mutants (A549V, L712F, L726P) impeded the recruitment of Kiaa0753 onto

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the centrioles, resulting in a delay of neuronal differentiation and the accumulation of ectopic progenitor cells in the developing cerebellum. This is the first report that describes the molecular interactions of two JS-associated proteins, CEP120 and KIAA0753, in the pathogenesis of Joubert syndrome, thereby providing a crucial clue for how defects in centriole assembly may lead to congenital cerebellar diseases.

The research team is led by Dr. Tang K. Tang (Institute of Biomedical Sciences, Academia Sinica), and the research work is completed by Dr. Chia-Hsiang Chang, Dr. Ting-Yu Chen, Dr. I-Ling Lu, Mr. Rong-Bin Li, Mr. Jhih-Jie Tsai, Ms. Pin-Yeh Lin. The study is funded by Academia Sinica and Ministry of Science and Technology.

The paper can be read online at:
http://genesdev.cshlp.org/content/early/2021/10/26/gad.348636.121.abstract?sid=bd72d13c-ed63-4c71-8f65-40029bb3ef8c

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