Deciphering the Complex Role of Human Microcephaly Proteins in Centriole Duplication and Ciliogenesis

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Abstract

Centrioles are highly conserved microtubule (MT)-based organelles that form the core of the animal centrosome and serve as templates for the formation of cilia and flagella. The mother centriole has sub-distal (SDA) and distal appendages (DA), which are essential for microtubule anchoring, membrane attachment, and cilia formation. The cilium is a microtubule-based structure, known as axoneme, that protrudes from the basal body (mother centriole) present in most animal cells. The primary cilium acts as a sensory organelle that transfers signaling from the extracellular environment to the cell interior. Centrosome abnormalities have been proposed to contribute to aneuploidy, cancer, and primary microcephaly. Ciliary defect has been attributed to a number of human diseases known as ciliopathies, including retinal degeneration, polycystic kidney disease, Bardet-Biedl syndrome, and neural tube defects. During the past years, my lab has identified several key proteins (CPAP, STIL, CEP135, RTTN, CEP120, and Myosin-Va) that participate at the different stages of centriole duplication and ciliogenesis in humans. Primary microcephaly (MCPH) is an autosomal recessive congenital disorder in humans characterized by smaller brain size with mild to severe mental retardation. Interestingly, most known MCPH proteins are localized to the centrioles/centrosomes for at least part of the cell cycle, implying the centrosomal roles of MCPH proteins in regulating neurogenesis in developing brain, yet with an unclear mechanism. Recently, mutations in CPAP, STIL, CEP135, and RTTN genes have been reported to cause MCPH, while, mutations in the CEP120 gene lead to severe human genetic diseases, including Jeune asphyxiating thoracic dystrophy (JATD), Joubert syndrome (JS), and complex ciliopathy phenotypes. Currently, we do not yet fully understand the molecular basis of how a mature centriole is built-up and how the deregulation of the process of centriole duplication cause MCPH and ciliopathy. We are interested in the mechanisms underlying centriole/centrosome duplication and cilia formation, and their related diseases (primary microcephaly and ciliopathy). In my lab, we are using a multidisciplinary approach including structural, cellular, and molecular approaches, accompanied with the CRISPR/Cas9-mediated gene knockout-in animal model and hiPSC-derived cerebral organoid to understand how the cellular organelles (centrioles or cilia) are established and how mutations in centriole biogenesis/ciliogenesis genes cause primary microcephlay and ciliopathies in humans.

Keywords – Centriole, Centrosome, Cilium, Primary Microcephaly, Ciliopathy

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