Pleiotropic activities of the (atypical ?) kinesin KIF21B during cortical development

Par

Juliette Godin

(Invitée par Julien Courchet)

Institut de Génétique et Biologie Moléculaire et Cellulaire
Strasbourg, France

http://www.igbmc.fr/

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Salle des Pas Perdus
Faculté de Médecine Lyon Est
1er étage
8, Avenue Rockefeller
69008 LYON
Abstract:

Cortical development progresses through concurrent steps, including neural proliferation, migration and differentiation, that rely on dynamic cell shape remodeling which largely depends on the tight regulation of the microtubules (MT) cytoskeleton. Mutations in tubulin, MT associated proteins or motors have been linked to several neurodevelopmental disorders including malformation of cortical development (MCDs), affecting 2.5% of the world population. Here we identified KIF21B gene as a major locus of human neurodevelopmental disorder. We identified 4 de novo variants in KIF21B gene in patients with intellectual disabilities associated with several brain malformations, including microcephaly, corpus callosum agenesis or facial dimorphism. In support of the pathogenic potential of the discovered alleles, expression of KIF21B variant in mice using in utero electroporation or in zebrafish embryos recapitulated key neurodevelopmental phenotypes, namely migration and microcephaly. In addition, longitudinal neuroanatomical analysis of Kif21b KO model showed strong morphological defects starting prenatally and worsening with time. Finally, we demonstrated that Kif21b regulates migration of projection neurons through the tight control of locomotion and neural shape. Although its motility is dispensable, the regulatory function cytoskeleton dynamics is essential for neuronal migration. Altogether, our data represent an important step to delineate the mechanisms involving KIF21B-mediated MT dynamics and trafficking in the context of brain development.

Selected publications:


