論　文　内　容　の　要　旨
Synopsis of Thesis

氏　　名 Ｎａｍｅ	張　彧　(ZHANG YU)
論文題名 Title	Rab6-mediated polarized transport of synaptic vesicle precursors is essential for the establishment of neuronal polarity and brain formation (低分子量GTPase Rab6によるシナプス小胞前駆体の極性輸送は脳の発生において神経細胞の極性形成を制御する)

論文内容の要旨

〔目　的(Purpose)〕

Neurons are highly polarized cells that are composed of a single axon and multiple dendrites. Axon-dendrite polarity is essential for proper tissue formation and brain functions. Intracellular protein transport plays an important role in the establishment of neuronal polarity. However, the regulatory mechanism of polarized transport remains unclear. Rab6 is an evolutionarily conserved Rab GTPase that is mainly localized on the trans-Golgi and trans-Golgi network (TGN) regulating divergent steps in the intracellular transport of proteins and lipids. Rab6-mediated polarized apical transport in radial glial cells (RGCs) was critical for the prevention of RGC delamination. However, its function in mature neurons has not been identified.

〔方法ならびに成績(Methods/Results)〕

We generated central nervous system (CNS)-specific Rab6 DKO mice and observed severe hypoplasia of DKO brains, similar to the one in the recent report mentioned above. In addition to the abnormalities in RGCs, the neocortex of Rab6 DKO mice showed an extremely thin intermediate zone (IZ) caused by impaired axonal extension of newborn neurons. By using primary cultured neurons, we found the loss of neuronal polarity and the accumulation of synaptic vesicle precursors (SVPs) adjacent to the Golgi apparatus in Rab6 DKO neurons. Furthermore, we found the dysfunctional and abnormal enlarged lysosomes in the soma of Rab6 DKO neurons.

〔総　括(Conclusion)〕

Our results reveal that Rab6-mediated polarized transport of SVPs is crucial for neuronal polarization and subsequent brain formation.

論文審査の結果の要旨及び担当者

（申請者氏名）　張瑀（Zhang Yu）

	（職）	氏　名	
論文審査担当者	主　査　大阪大学教授	原田彰宏	原田彰宏
	副　査　大阪大学教授	島田昌一	島田昌一
	副　査　大阪大学教授	佐藤真	佐藤真

論文審査の結果の要旨

In this research, the authors utilized CNS-specific Rab6a/b double knock-out (Rab6 DKO) mice to explore the consequences of Rab6 deficiency on the brain. One of the most striking findings from the Rab6 DKO mice was the severe dysplasia observed in both the cerebral cortex and the cerebellum. The cortical structure in these mice was significantly thinner, and the overall size of the cerebellum was markedly reduced compared to wild-type controls. These structural abnormalities are indicative of disrupted brain development, underscoring the critical role of Rab6 in ensuring proper formation and maturation of brain structures. Further examination of the Rab6 DKO mice revealed impaired axonal extension, particularly in the neocortex. Axons, which are responsible for transmitting electrical signals between neurons, showed significantly stunted growth, leading to a hypoplastic intermediate zone (IZ). The intermediate zone is a crucial region in the brain that consists of axonal projections from neurons, and its proper development is vital for establishing the intricate network of neuronal connections necessary for brain function. The study also focused on cultured neurons derived from Rab6 KO mice. Rab6 DKO neurons displayed a loss of axon–dendrite polarity, a fundamental characteristic of neuronal differentiation and function. Normally, neurons develop a single long axon and multiple shorter dendrites, establishing the polarity required for directional signal transmission. However, in the absence of Rab6, this polarity was disrupted, leading to abnormal neuronal architecture. The loss of polarity was associated with the abnormal accumulation of synaptic vesicle precursors (SVPs) adjacent to the Golgi apparatus. Another significant finding was the expansion of lysosomes within the soma of neurons lacking Rab6. Lysosomes are cellular organelles involved in the degradation and recycling of cellular waste. The enlargement and accumulation of lysosomes in Rab6-deficient neurons indicate a disruption in normal lysosomal function, which could have broader implications for neuronal health and viability. The researchers identified a critical interaction between Rab6 and KIF1A, a motor protein involved in anterograde transport along microtubules. Rab6 was found to recruit KIF1A during the transport of SVPs, facilitating their polarized distribution within neurons. This interaction is essential for the proper delivery of SVPs to the axonal growth cone, supporting axonal extension and neuronal polarity. Overall, the results of this study demonstrate that Rab6-mediated polarized transport of SVPs is vital for neuronal polarization and subsequent brain formation. The severe brain dysplasia and functional impairments observed in Rab6 DKO mice underscore the essential role of Rab6 in neurodevelopment. These findings provide significant insights into the molecular mechanisms underlying neuronal polarity and brain development, highlighting the importance of intracellular transport processes. This research is worth being granted a doctoral degree(medicine).