Abstract of Dissertation

論文の内容の要旨

論文題目:

Characterization of the function and localization of KIF16B in neuron

（キネシンスーパーファミリーモーター蛋白、KIF16B　の機能と局在機構の研究）

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Kinesin superfamily proteins (KIFs) are microtubule (MT) and ATP-dependent motor proteins, most members of which transport cargos to the + end of MTs. The intra-neuronal localisation of organelles, such as mitochondria, synaptic vesicle precursors and RNA-protein complexes, is regulated by KIFs. KIF16B was originally identified as a motor protein that transports Rab5-positive early endosomes and Rab14-positive vesicles in non-neuronal cells. KIF16B has a conserved motor domain, several coiled-coil domains, and a PX domain.

The early endosome is a member of organelle that serves as a hub for receptor sorting and trafficking, signal transduction and protein degradation. The sorting mechanisms of organelle are significant problem in neuronal cell biology.

An organelle's subcellular localisation is closely related to its functions. Early endosomes require localisation to somatodendritic regions to enable their functions in neuronal morphogenesis, polarised sorting and signal transduction to occur. However, it is not known how the somatodendritic localisation of early endosomes is determined. At the same time the mechanism of directional transport toward axon vs dendrites is fundamental for neuronal morphogenesis and functioning. Although several mechanisms such as motor domain's preferential binding to the axonal microtubules and regulation of directional transport by cargo association and dissociation have been proposed, the whole mechanism for directional transport remains still elusive.

Here, we show that Kinesin superfamily protein 16B (KIF16B) is essential for correct localisation of endosomes in neurons and PX domain of KIF16B is critical for binding to early endosomes. Loss of KIF16B function induced aggregated endosomes, while, interestingly, in neurons expressing a stalkless KIF16B, endosomes were mistransported to axons. The binding between the motor domain of KIF16B and microtubules was inhibited by the stalk domain, which mediates a self-adjusting regulation mechanism that directs the protein to its correct destination.

Thus, “the stalk inhibition” mechanism of KIF16B determines the somatodendritic localisation of endosomes in neurons. This study will provide a new concept of auto-regulation mechanism both for regulation of sorting of early endosomes and directional transport in neurons.