

論文の内容の要旨

論文題目 : Molecular Genetic Study of Motor Protein KIF21B
(モータータンパク質 KIF21B の分子遺伝学的研究)

氏名 : 森川 桃

Neurons develop highly differentiated neurites. Because the amount of protein synthesis and degradation machinery is small in neurites, proteins that are synthesized in the cell body need to be transported down the neurites to the point where they work and also transported back to the cell body. This intracellular transport is essential for maintaining their survival, proper function, and morphology, and driven by the molecular motor ATPases along the microtubule tracks.

Kinesin superfamily proteins (KIFs) consist one of the major classes of such well-diverged molecular motors. Every KIF possesses a conserved motor domain which contains ATP-binding sequences and microtubule-binding sequences, and hydrolyzes ATP to move directionally along microtubules. KIFs bind to their specific cargoes through their variable tail regions. There are 45 KIF genes in the mouse genome, which are classified into 14 families, according to the result of phylogenetic analyses. Among them, 12 families have a motor domain in the NH₂-terminal region (N-kinesins) and others have in the middle (M-kinesins) or in COOH-terminal region (C-kinesins). This intramolecular position of motor domain is corresponding to the directionality of the KIFs, and N-

kinesins are known to transport their cargoes anterograde which means toward microtubule plus ends or nerve endings. Recent studies on KIFs showed the involvement of various KIFs in neuronal diseases and higher brain function. For example, KIF5 regulates inhibitory neural transmission through transporting GABA_A receptors to the axonal plasma membrane (GABA_AR). Therefore, insufficiency of KIF5 function can cause epilepsy. KIF1A is indispensable for BDNF-mediated hippocampal synaptogenesis and experience-dependent neuroplasticity. KIF17 transports N-methyl-D-aspartate (NMDA) receptor subunit 2B (NR2B) and maintains NR2A/2B balance at synapses which underlies memory processes in vivo. KIF13A controls anxiety through maintaining cell surface expression of serotonin type 1A receptors. These unexpected functions of KIFs were found from the holophrastic analysis of the knockout mice through molecular level to individual level.

Among the N-kinesins, KIF21B belongs to the kinesin-4 family. In addition to the NH₂-terminal motor domain, KIF21B possesses a cluster of negatively charged coiled-coil region in its stalk domain and seven WD-40 repeats in its tail domain. Recently, it has been reported that the SNPs within or close to the *Kif21b* gene as susceptibility locus for multiple sclerosis, Alzheimer's disease, ankylosing spondylitis, and multiple myeloma, suggesting that KIF21B is responsible for neurodegenerative and immune diseases. The motility of KIF21B is reported to be regulated by tripartite-motif containing 3 (TRIM3), a member of E3 ubiquitin ligase, and KIF21B transports and is involved in the surface expression of GABA_AR. However, the precise functional significance and its underlying molecular

mechanism of KIF21B has been still elusive.

In the present study, I succeeded in generating *Kif21b* knockout (*Kif21b*^{-/-}) mice with pure C57BL/6N genetic background, by using RENKA ES cells. The pure genetic background makes an advantage of this model, whose knockout phenotype can be better understood by eliminating the effect of genetic variance due to a mixed background. Here, I introduce the initial investigation of the phenotypic analyses using *Kif21b*^{-/-} mice.