【Grant-in-Aid for Specially Promoted Research】
Biological Sciences

Title of Project：Integrative Biological Research on Function and Regulation of Kinesin superfamily Molecular Motors

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Research Area：Biology

Keyword：Kinesin superfamily molecular motors(KIFs), intracellular transport, microtubules

【Purpose and Background of the Research】

The intracellular transport is fundamental for cell morphogenesis and functions by transporting various cargos such as membrane organelles, protein complexes and mRNAs not only in highly polarized cells such as neurons but also in all kinds of cells. We discovered kinesin superfamily proteins, KIFs in mice brain and identified all 45 kif genes, in mammals such as human and mice. We have characterized the functions of KIFs mainly in neurons showing that various cargoes are transported properly by distinct motors to proper direction and at distinct velocity. We revealed also that KIFs typically use adaptor/scaffold proteins for recognizing and binding cargos. Our molecular genetics also uncovered important functions of KIFs at the whole body level and elucidated the mechanism of unknown physiological processes such as brain wiring, activity dependent neuronal survival, left/right determination of our body, suppression of tumorigenesis, and control of enteric nervous system development. The defects of these KIFs cause diseases such as neuropathy, brain malformation, brain tumor, laterality defect and megacolon.

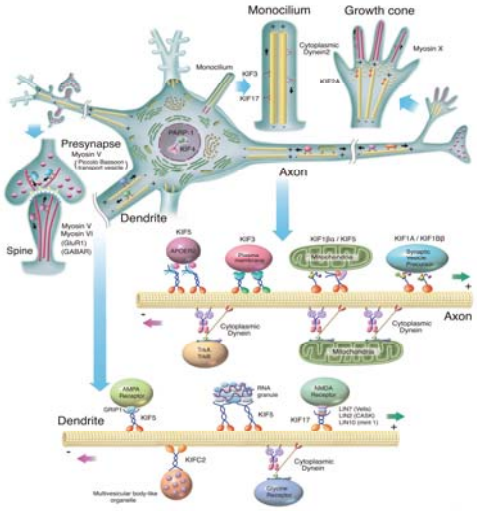
However, there are numbers of KIFs whose functions are still unknown at the cellular as well as whole body levels. The mechanisms of regulation of KIFs for controlling motor activity and cargo recognition and binding are also largely unsolved. As for the neuroscience the relationships between neuronal activity and control of expression and function of KIFs need to be solved. Furthermore, the elucidation of the dynamics of motors, adaptors, and cargos and the interaction of motors and rail microtubules at very high temporal and spetial resolution in living cells are final goals for solving the mechanisms of intracellular transport. This project aims to solve these important questions.

【Research Methods】

We will utilize various methods including molecular cell biology, molecular imaging, molecular genetics, electrophysiology, and structural biology such as cryo-electron microscopy and X-ray crystallography.

【Expected Research Achievements and Scientific Significance】

The intracellular transport is very fundamental mechanism for cellular functions and survival. This project will answer important questions remained unsolved. Further, molecular genetics will reveal unexpected new functions of KIFs for various fundamental physiological processes. Thus this project will contribute significantly not only for molecular cell biology and neuroscience, but also clinical medicine by uncovering pathogenesis of neurological and other diseases.



【Publications Relevant to the Project】

1. Zhou R., S. Niwa, N. Homma, Y. Takei, and **N. Hirokawa**. KIF26A is an unconventional kinesin and regulates GDNF-Ret signaling in enteric neuronal development. ***Cell*** 139 (4): 802-813, 2009.
2. **Hirokawa, N.**, S. Niwa and Y. Tanaka. Molecular motors in neurons: Transport mechanisms and roles in brain function, development and disease. ***Neuron*** 18; 610-638, 2010

【Term of Project】 FY2011-2015

【Budget Allocation】 500,000 Thousand Yen

【 Homepage Address and Other Contact Information】

http://cb.m.u-tokyo.ac.jp