【Grant-in-Aid for Scientific Research (S)】

Biological Sciences (Biological Sciences)

Title of Project : Integrated studies of regulation of neuronal function and development by kinesin superfamily motors, KIFs

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Research Project Number : 16H06372 Researcher Number : 20010085
Research Area : Molecular Cell Biology, Neuroscience, Developmental Biology
Keyword : Kinesin Motors, Microtubules, Neuroscience, Development

【Purpose and Background of the Research】

The intracellular transport is fundamental for cells by transporting various kinds of cargoes in cells in general. Kinesin superfamily proteins, KIFs are major players in this mechanism. Our molecular genetics also uncovered the mechanisms of important physiological processes such as higher brain function (**Neuron** 2010, 2011,2012), brain wiring(**Cell** 2003), left/right determination of our body, suppression of tumorigenesis, and control of nervous system development. The defects of these KIFs cause diseases such as neuropathy, brain malformation, brain tumor, laterality defect and megacolon (**JCB** 1998; **Cell** 1998; **Cell** 2001; **Cell** 2003; **Cell** 2009), epilepsy (**Neuron** 2012b**),** anxiety neurosis (**Cell Rep** 2013), hydrocephalus and female infertility (**Dev Cell** 2012), and Diabetes (**Dev Cell** 2014). Some KIFs have new functions such as KIF4 (**Cell** 2006) and KIF26A (**Cell** 2009) as signaling molecules and KIF2A (**Cell** 2003) and KIF19A as microtubule depolymerizers (**Dev Cell** 2012). However, there are numbers of KIFs whose functions are still unknown and the mechanisms of regulation of KIFs especially by phosphorylation for controlling motor activity and cargo binding are also largely unsolved. As for the neuroscience KIFs' involvement for higher brain function/neuronal activity/neuronal plasticity need to be solved and KIFs also could control fundamental mechanisms for development. Thus, there are numbers of problems which need to be solved and studies of them will contribute significantly not only for molecular cell biology /neuroscience/ developmental biology, but also for medical science.

【Research Methods】

Multidisciplinary approaches such as molecular cell biology, molecular genetics, biophysics and structural biology will be used.

【Expected Research Achievements and Scientific Significance】

In out project we will study following objects.
I) Analysis of the mechanism of regulation of KIFs: A) The mechanism of regulation of motility and transport of cargoes by phosphorylation of KIFs. We have developed a new quantitative method to analyze phosphorylation of KIFs and responsible kinases (**Cell Rep** 2015; **Neuron** 2015). We will focus on major KIF motors. B) The mechanism of depolymerization of microtubules by KIF2A and KIF19A.
II) The mechanism of regulation of neuronal plasticity, memory/learning, and neuronal functions by KIFs: A) a) Function of KIF21B for learning and memory and the mechanism of disorder caused by deletion of KIF21B. b) Role of KIF3 for neuronal plasticity and the mechanism of psychiatric disorder caused by defect of KIF3. c) Role of KIFs for development and neuronal plasticity of visual cortex at the critical period. d) Role of KIF17 on retrieval phase of learning and memory. B) a) Function of KIF1A for pain sensation and the mechanism of its defect caused by deletion of KIF1A. b) Function of KIF26 for pain sensation and the mechanism of hyper sensitivity for pain by deletion of KIF26.
III) The mechanism of regulation of development by KIFs: A) Function of KIF2A during brain development and the mechanism of malformation of cortical development and epilepsy caused by defect of KIF2A. B) New role of KIF3 for formation of morphogen gradient during development. These studies contribute significantly for molecular cell biology, neuroscience, developmental biology and medical science.

【Publications Relevant to the Project】

Hirokawa, N., et. al., Molecular motors in neurons: Transport mechanisms and roles in brain function, development, and disease. **Neuron** 68: 610-638, 2010.
Ichinose, S., et. al., Mechanism of activity-dependent cargo loading via the phosphorylation of KIF3A by PKA and CaMKIIa. **Neuron** 87: 1022–1035, 2015

【Term of Project】 FY2016-2018

【Budget Allocation】 142,900 Thousand Yen

【Homepage Address and Other Contact Information】 http://cb.m.u-tokyo.ac.jp