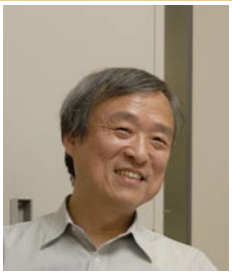
【Grant-in-Aid for Scientific Research(S)】
Integrated Science and Innovative Science (Comprehensive fields)



Title of Project : Functional analyses of axon guidance cue, draxin, and its signaling mechanism

Hideaki Tanaka
(Kumamoto University, Graduate School of Medical Sciences, Professor)

Research Area : Neuroscience, Neurochemistry
Keyword : molecular and cellular neurobiology, development and differentiation

【Purpose and Background of the Research】

Proper brain function depends on the precise establishment of intricate network of billions of neuronal connection. Developing axons from neurons have exquisite motile structures at its tip called, growth cones, which can detect and respond to a variety of attractive and repulsive guidance molecules in its surrounding environment and navigate to its targets in a highly stereotyped and directed manner. Through genetic, biochemical and molecular approaches four conserved families of axon guidance molecules have been identified: netrins, semaphorins, ephrins and slits. Although these molecules have prominent developing effects, considering the immense complexity of nervous system much more await identification. We have found a new axon guidance molecule, which we named draxin (dorsal repulsive axon guidance protein). Since *draxin* gene-deficient mice showed agenesis of all forebrain commissural fibers (corpus callosum, hippocampal commissure and anterior commissure), draxin is considered to be an important guidance cue for brain development. The present study has three major purposes: analyzing the draxin receptors and its signaling mechanism; clarifying draxin functions by using genetically modified mice; and elucidating the molecular basis of the maintenance of the brain.

【Research Methods】

To clarify the role of draxin in brain formation and maintenance mainly we plan to perform the following three research projects in parallel. (1) Elucidation of draxin receptors and signaling, (2) analysis of draxin functions by using transgenic and conditional knockout mice using a variety of Cre mice, (3) evaluation of draxin function after its re-expression in the dentate gyrus granule cell layer of adult transient ischemic brain .

【Expected Research Achievements and Scientific Significance】

In *draxin* knockout mice brain we have found that forebrain commissuers are not formed, indicating that draxin is an important cue for forebrain commissures formation. Despite the absence of sequence homology with other known axon guidance molecules, draxin binds specifically all netrin receptors: DCC, Neogenin, UNC5s, and DSCAM. Netrin is essentially attractive and draxin is repulsive. It would be an interesting and important breakthrough in the field of developmental neurobiology to clarify how the signals though guidance molecules are segregated by the identical set of receptors. Draxin is not only adding one more new guidance cue to the list of axon guidance molecules, but also its signal becomes a new breakthrough in understanding the regulatory mechanisms between axon guidance molecules, and thus elaborate further the basic principles of neural circuit formation.

【Publications Relevant to the Project】

・Ahmed G., Shinmyo Y., Ohta K., Islam S., et al. Draxin Inhibits Axonal Outgrowth through the Netrin Receptor DCC. **J. Neuroscience** (in press).

・Zhang, S., Su, Yuhong, Shinmyo, Y., Islam, S. M., Naser, I. B., Ahmed, G., Tamamaki, N., Tanaka, H. Draxin, a repulsive axon guidance protein, is involved in hippocampal development. **Neurosci. Res.** 66, 53-61 (2010).

・Islam S.M., Shinmyo, Y., Okafuji, T., Su, Y., et al. Draxin, a Repulsive Guidance Protein for Spinal Cord and Forebrain Commissures. **Science** 323, 388-393 (2009).

【Term of Project】 FY2011-2015
【Budget Allocation】 132,700 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.medphas.kumamoto-u.ac.jp/research/bunya/41.html