Form 1-5-2

Japan-US Brain Research Cooperative Program
The Dispatch of Joint Researcher Report in 2008 fiscal year

[field: 1]

1. Affiliation/ Title/ Name: Yutaro Obara, PhD. Assistant professor.
   Department of Cellular Signaling, Graduate School of Pharmaceutical Sciences, Tohoku University.

2. The Project Title: Clarification of the mechanism of ERK5 activation by NGF and its physiological roles in neuronal cells

3. U.S. Investigator's Name, Title, and Affiliation:
   Philip Stork, MD. Senior Scientist.
   Vollum Institute, Oregon Health Sciences University

4. The Term of Research: From Y. 2008 M. 8 D. 1 To Y. 2008 M. 8 D. 31 (1 Months)

5. The Abstract, the Result and the Significance of Research (300 Words):

ERK5, a member of MAPK family is a kinase regulated by growth factors and neurotrophic factors. We have investigated the physiological roles of ERK5 in neuronal cells. First, when PC12 cells, a model of neuronal cells, were stimulated with NGF or dbcAMP, both drugs induced sustained ERK1/2 activation while only NGF induced ERK5 activation. Next, we examined an involvement of ERK5 in differentiation of neurons. The differentiation of PC12 cells by NGF was clearly blocked by ERK5-selective inhibitor. In addition, by overexpression of kinase-dead ERK5 mutant or dominant-negative MEK5 mutant, the NGF-induced differentiation was significantly inhibited although differentiation by dbcAMP was not affected at all. Therefore, it was suggested that NGF induced differentiation of PC12 cells by activating ERK5. On the hand, we examined the mechanism of ERK5 activation by NGF, focusing on small G proteins, Ras and Rap1. By using adenoviruse encoding dominant-negative Ras mutant (RasN17), activation of ERK1/2 by NGF or EGF was largely inhibited while ERK5 activation by both drugs were not blocked. In addition, by overexpression of constitutively active Ras mutant (RasV12), ERK1/2 activation was induced whereas ERK5 was not activated at all. Furthermore, by overexpression of Rap1GAP which inactivates Rap1, ERK5 activation by NGF or EGF was not blocked. Also, ERK5 activation was not blocked by siRNA knock-down of C3G, a Rap1-activating GEF. Taking these result together, neither small G proteins, Ras nor Rap1 is involved in ERK5 activation by NGF. The manuscript containing these results has been submitted to scientific journal, *J Biol Chem*, and now in revision.

6. The Others (Other Comments):

As staying in US for relatively long time, visiting scientists may be glad if the expense for health insurance is also provided. *In case of the program "invitation fellowship for research in Japan" managed by Japan society for the promotion of science (JSPS), expense for the insurance is provided to visiting foreign scientists.