General Summary of Division of Molecular Cell Signaling

Scaffold proteins of the mammalian MAP kinase (MAPK) cascades are considered having critical roles in spatio-temporal regulation of MAPK pathways by organizing their signaling components into functional modules. We are particularly interested in the functions of these scaffold proteins, mainly c-Jun NH_2-terminal kinase (JNK)/stress-activated protein kinase-associated protein 1 (JSAP1) and its family member JNK-associated leucine zipper protein (JLP); scaffold proteins that participate in JNK MAPK cascades, both *in vitro* and *in vivo*. Our findings in the past three years are summarized as follows:

A) Role of JSAP1-JNK signaling in cerebellar development

During the development of the cerebellum, massive clonal expansion of granule cell precursors (GCPs) occurs in the outer part of the external granular layer (EGL). We have provided evidence that JSAP1 and active JNK were expressed preferentially in the post-mitotic inner EGL progenitors in the developing cerebellum. Moreover, *Jsap1* deficiency resulted in increasing numbers of proliferating GCPs in mouse embryos. Besides, overexpression of JSAP1 in cultured GCPs led to increased numbers of NeuN-positive cells together with the activation of JNK. Together, these data strongly indicated that JSAP1 promotes the cell-cycle exit and differentiation of GCPs by modulating JNK activity in cerebellar development.

B) Expression of JSAP1 and JNK in mouse brain

We studied JSAP1 and JNK expression in developing and adult mouse brains. Our results obtained by *in situ* hybridization and immunohistochemical analyses strongly suggested that JSAP1-JNK signaling plays important roles in developing and adult mouse brains.

C) Function of JLP in the regulation of cell migration

We investigated the function of JLP by deleting it in cultured cells. Our results strongly suggested that JLP regulates cell migration through an interaction with $G_{\alpha 13}$.

D) Function of JLP in mice

We examined the expression of JLP in various mouse tissues, and found that JLP was strongest in the testis. We also investigated the function of JLP by disrupting the *Jlp* gene in mice, and found that the male homozygotes were subfertile. Taken together, these observations may suggest that JLP plays an important role in testis during development.