

**Stony Brook University
The Graduate School**

Doctoral Defense Announcement

Abstract

Dissection of Neurofibromatosis type 1-regulated pathways and its role in distinct phases of memory

By

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Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder characterized by benign tumors of the peripheral nervous system called neurofibromas, café au lait spots, and extreme freckling. In addition, at least 40% of afflicted children have learning difficulties. The NF1 protein contains a highly conserved GTPase-activating protein (GAP) domain that inhibits Ras activity, and the C-terminal region regulates G protein-dependent activation of adenylyl cyclase (AC). Behavioral analysis has indicated that learning and memory is also disrupted in *Drosophila* and mouse NF1 models, however, the learning defect in flies is attributed to altered activation of the cAMP pathway, whereas the mouse learning deficit results from increased Ras activity. Because of the enormous difference in the time scale involved in training paradigms for mice (water maze) and flies (odor-foot shock association), we suspected that different components of memory were being affected. In this study I first show that NF1 regulates two separate signaling pathways that lead to adenylyl cyclase (AC) stimulation. Interestingly, different regions of the NF1 protein are required for mediating each of these pathways. The GAP-related domain, together with the Ras protein, is required for mediating growth factor stimulating AC, while the C-terminal region is essential for conferring neurotransmitter signaling for AC stimulation. Here, I also show for the first time that not only short-term memory but also long-term memory was defective in *Drosophila Nf1* mutants. The underlying signaling mechanisms for these two behavioral phenotypes of the NF1 mutants are also examined. I found that the GAP-related domain with its GAP activity and binding with Ras was necessary and sufficient for long-term memory, while the C-terminal domain of NF1 that is required for G protein-dependent activation of AC was critical for learning. Thus, this study shows that two functional domains of the same protein participate independently in two distinct signaling pathways, as well as the formation of two memory components.

Date: July 19th, 2007

Time: 3:00pm

Place: Gerry Conference Room, Marks Building, CSHL

Program: Genetics

Dissertation Advisor: Yi Zhong