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Molecular Genetic Analysis of Synaptic Plasticity

The capacity of the brain to modify connections in response to levels of activity is termed plasticity. Plasticity is a prominent feature of brain development, and in the adult underlies learning and memory and adaptive reorganization of sensory maps. To understand the cellular mechanisms that underlie activity-dependent plasticity in the developing and adult brain, we are identifying and characterizing the participating genes and the function of the proteins they encode. This work began with the cloning of a large number of activity-regulate genes that we termed candidate plasticity genes (CPGs). Although only a small subset of these genes have been pursued to date, it is clear that the pool is highly enriched for genes that are relevant to neuronal and synaptic function.

One CPG characterized in depth, CPG2, has emerged as a key component of a specialized postsynaptic endocytic mechanism devoted to internalization of synaptic proteins, including glutamate receptors. Another, CPG15, plays a dual role in the brain: as a survival factor that rescues cells from apoptosis, and as a growth and differentiation factor that affects process outgrowth and synaptic maturation.

In collaboration with Dr. So's group in the Dept. of Mechanical Engineering at MIT we have fabricated a custom designed multi-photon microscope for chronic *in vivo* imaging of neuronal morphology in the intact rodent cerebral cortex. Using this system we have imaged and reconstructed the dendritic trees of neurons in visual cortex of *thy1*-EGFP transgenic mice. These mice express EGFP in a random subset of neurons sparsely distributed within the superficial cortical layers that are optically accessible through surgically implanted cranial windows. Chronic imaging of the same neurons over a period of months, revealed an unexpected degree of remodeling in adult neurons. Establishing the baseline dynamics of dendritic remodeling now allows us to examine the brains of mice deficient in specific CPGs and ask how they compare with normal brains.

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