A major focus of our lab is the study of the mechanisms that control maintenance and remodeling of the nervous system. Previous work in our lab showed that the genes Numb and Numblike have essential roles in the proper development of neural stem cells during cortical neurogenesis in mouse embryo. We developed a novel system, the inducible nestin-creERtm transgenic mice, to study the postnatal functions of these proteins. Upon tamoxifen induction in newborns, CreERtm-mediated recombination efficiently removed Numb and Numblike expression from most differentiating neuroprogenitors and ependymal cells in the neurogenic niche. We found that Numb and Numblike have cell-intrinsic function in neuroprogenitors as well as an essential role in maintaining adhesion junctions. Further, these results strongly indicate that Numb and Numblike have multiple functions. Besides their role in regulating neuroprogenitors, they are also required for the integrity of the neuroepithelium likely through E-Cadherin. In addition, we found that the postnatal subventricular zone (SVZ) neurogenic niche is capable of responding and repairing local damages. This project not only addresses basic issue in neural development but also has considerable implications in regenerative medicine.

We are also interested in the maintenance and remodeling of neuronal morphology, more specifically, dendritic morphology. Dendrite arborization patterns are critical determinants of neural circuit formation and influence the type of synaptic or sensory inputs a neuron is able to receive. Moreover, dendrite defects are associated with a variety of known human mental disorders such as Autism. At present, relatively little is known about the molecular mechanisms that control dendrite development. To use Drosophila genetics to identify core programs that control dendrite development, we developed a simple assay system. We use the fly transgenic technique to express green fluorescent protein (GFP) in the dendritic arborization (da) neurons, a group of sensory neurons with a stereotyped dendritic branching pattern. This allows us to visualize the development of the dendrites of da neurons in the living fly embryos and to use them as an assay system for a genetic dissection of dendrite
Our genetic screen revealed specific mechanisms that function to ensure maintenance of dendritic arbors. We found the tumor suppressor Warts (Wts), one of the two NDR family kinase in Drosophila (the other being Trc), as well as the Polycomb group of genes are required for the maintenance of the class IV da dendrites. Loss-of-function mutants of any of those genes cause a progressive defect in the maintenance of dendritic tiling, resulting in large gaps in the receptive field. How are establishment and maintenance of dendritic fields coordinated? In Drosophila class IV neurons, the Ste-20-related tumor suppressor kinase Hippo (Hpo) can directly phosphorylate and regulate both Trc, which functions in the establishment of dendritic tiling, and Wts, which functions in the maintenance of dendritic tiling. How Hpo regulates the transition from establishment to maintenance of dendritic fields remains to be determined.

Drosophila class IV neurons undergo dramatic remodeling during metamorphosis. Early in pupal stage, those neurons prune all their dendrites. Later they grow a completely new dendrite for adult function. While the dendrites are being remodeled, the axons stay largely intact. We have begun to identify the molecular mechanisms that control this large scale dendrite specific remodeling.

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