

# A Day at the BEACH for Synapse Formation

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The number of synaptic connections in the human brain is estimated to be greater than the number of stars in the Milky Way. Disruptions in this galaxy of neuronal connections lead to diverse neurological disorders including autism, epilepsy, and schizophrenia, and understanding the basic building blocks of the brain thus has profound implications for combating these conditions. The brain contains two types of synapses, chemical and electrical, but the mechanisms underlying the formation of the latter are poorly understood. To gain insight into the formation of electrical synapses, postdoctoral fellow Dr. Adam Miller and colleagues in the laboratory of Dr. Cecilia Moens (Basic Sciences Division) undertook a zebrafish genetic screen. The authors found that the gene *neurobeachin* (*nbea*) is required for the formation of both chemical and electrical synapses and is necessary in the "information receiving" postsynaptic neuron for these processes. These results may also have implications for understanding neurological disorders as mutations in human *Nbea* are associated with autism.

To identify genes necessary for electrical synapse formation, the authors focused on the Mauthner neural circuit (M), which is involved in the startle response and contains a relatively simple circuitry of chemical and electrical synapses. M makes both electrical and chemical synapses with unique targets in the hindbrain and spinal cord. Mutations in the zebrafish genome were induced using a chemical mutagen and electrical synapse formation was assessed in mutant embryos 3 days post-fertilization (dpf) by staining for a marker called Cx36. The authors identified a mutation termed *disconnect4* (*dis4*) that resulted in markedly decreased Cx36 staining in M, as well as in other prominent electrical synapses in the brain, suggesting a general role for the *dis4*-encoded protein in electrical synapse formation.

To map the *dis4* mutation, the authors made use of a high-throughput RNA sequencing (RNA-seq) approach that they previously developed (Miller et al., 2013). This analysis led to the identification of a nonsense mutation in *nbea* that would presumably lead to degradation of its mRNA. Indeed, *dis4* mutant embryos displayed reduced expression of *Nbea*. Independent mutant alleles in *Nbea* generated via TALEN enzymes resulted in identical synapse defects as seen in *dis4* mutants, confirming that *dis4* is an allele of *nbea* and that *Nbea* is required for electrical synapse formation.

Nbea is a large protein and is a member of the BEACH (Beige and Chediak-Higashi) protein family, which has been implicated in cellular cargo transport. Nbea has also been previously shown to be required for efficient chemical synaptic transmission. The authors found that *nbea* mutants had defects in electrical synapse function. Moreover, the mutants could perform normal escape behaviors in response to startling stimuli, but at a reduced frequency compared to wild-type animals.

Synapses require two neurons, one presynaptic or "information sending", the other postsynaptic or information receiving. Further analysis revealed that Nbea is required in the postsynaptic neuron at both electrical and chemical synapses. The authors also analyzed the effect of removing *nbea* on the structural formation of the M dendrites, which are the specialized neuronal postsynaptic compartment. Neurons are extremely polarized cells, generally containing many branchlike dendrites and a single. In the *nbea* mutants, there is greatly reduced dendritic branching and a loss of fine dendritic processes (see figure), indicating that Nbea is needed in M for the maintenance of dendritic complexity.

The results presented in this study reveal a widespread and unexpected role for Nbea in synapse formation. "Because of the very different biochemical properties of electrical and chemical synapses it was surprising that Nbea controlled the formation of both types. And this points to the critical open question, what is the molecular function of Nbea in synapse formation? Currently we don't know the details, however based on its localization and inferring from the function of related proteins, Nbea likely acts in the cellular "postal" system (endomembrane compartments) to control the trafficking of synaptic components within the postsynaptic neuron," said Dr. Miller

[Miller AC, Voelker LH, Shah AN, Moens CB](#). 2014. Neurobeachin Is Required Postsynaptically for Electrical and Chemical Synapse Formation. *Curr Biol* 25(1):16-28.

See also: [Miller AC, Obholzer ND, Shah AN, Megason SG, Moens CB](#). 2013. RNA-seq-based mapping and candidate identification of mutations from forward genetic screens. *Genome Res* 23(4):679-686.

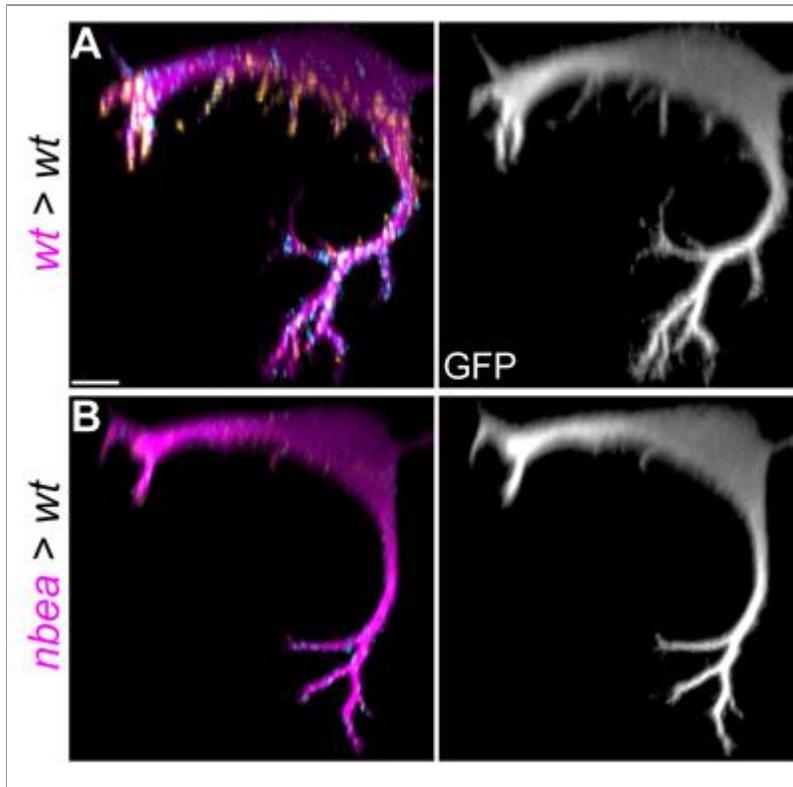


Image provided by Dr. Adam Miller

(A) In completely wild-type embryos, there is high dendritic complexity as indicated by the orange and cyan projections. (B) In wild-type embryos with a *nbea* mutation in the Mauthner circuit, dendritic complexity is lost.