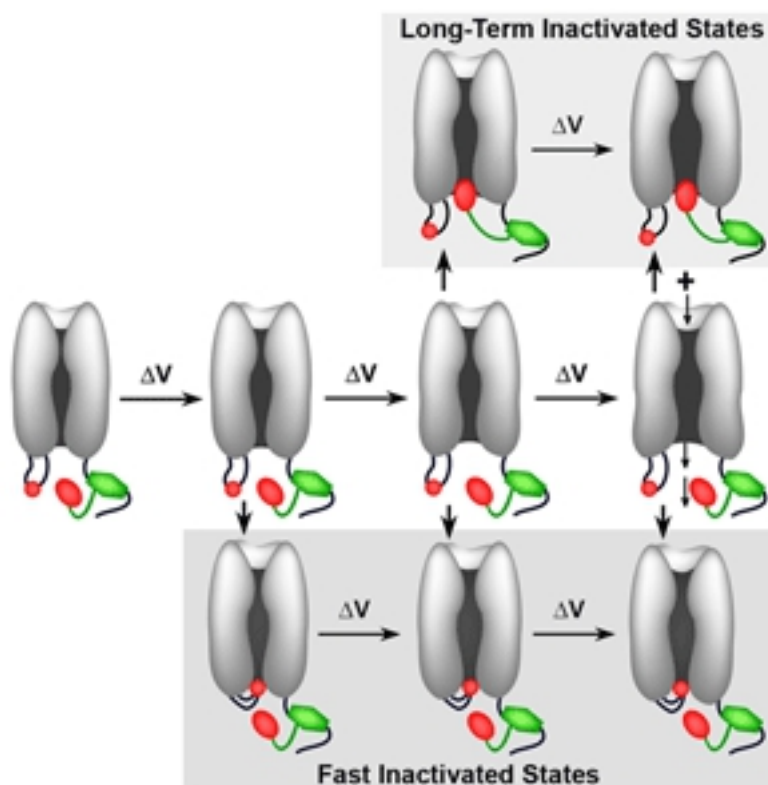


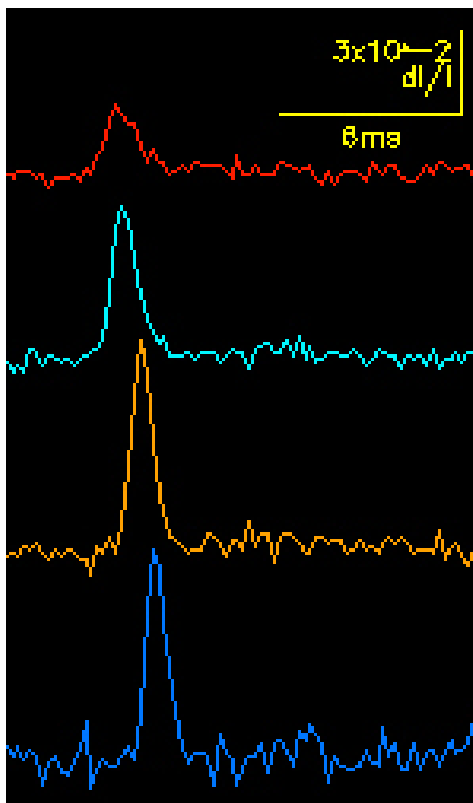
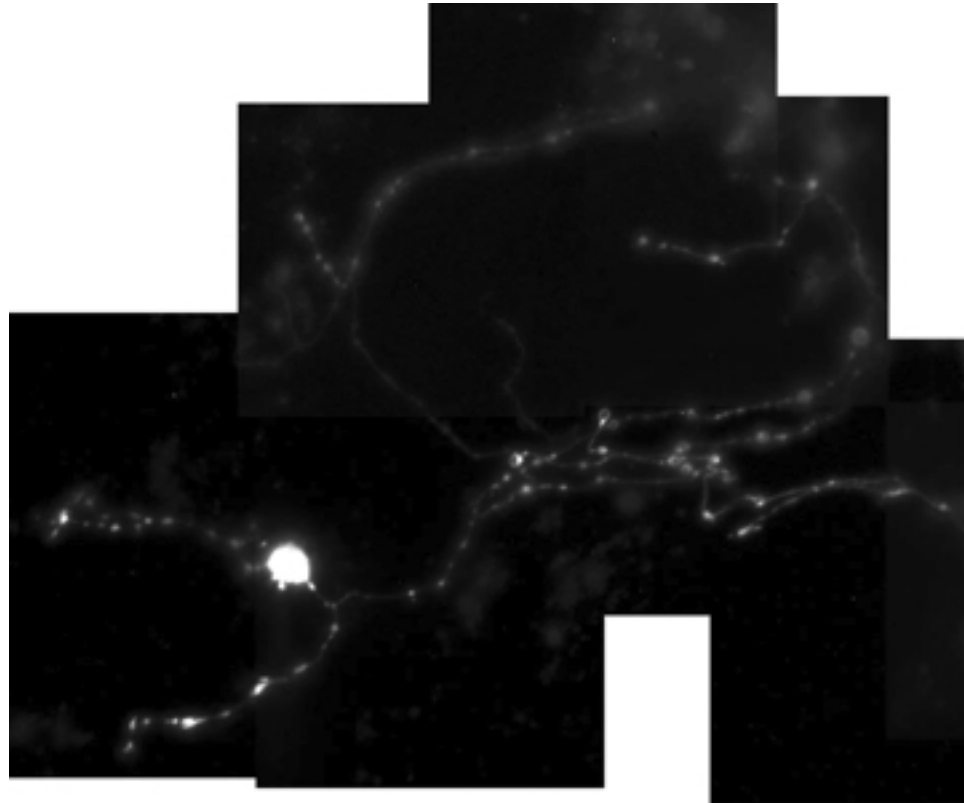
- FGF Homologous Factors: Regulators of Sodium Channels and Neuronal Function

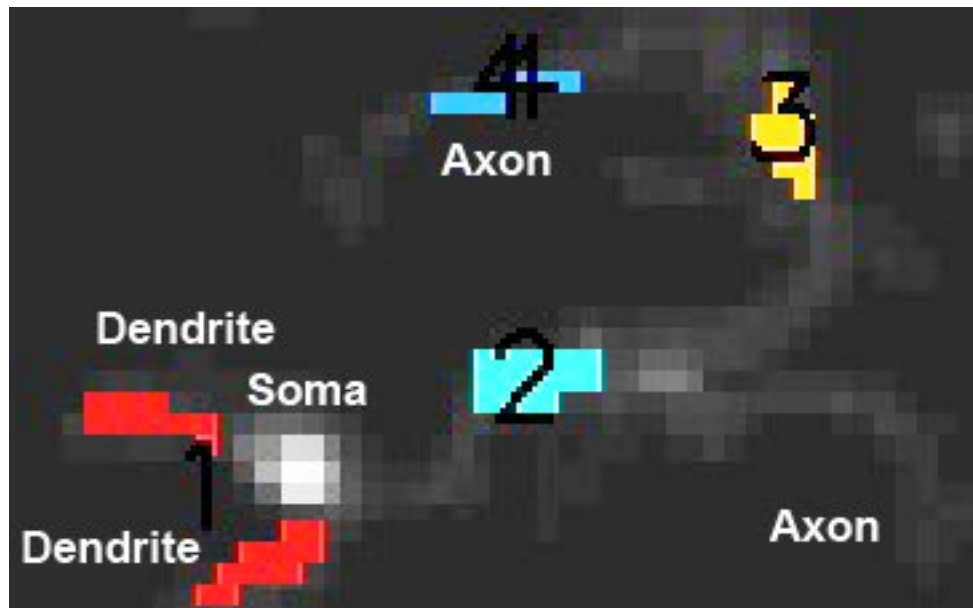
We have discovered and are studying proteins called fibroblast growth factor homologous factors (FHF). FHF gene mutations engineered in mice or occurring naturally in humans are associated with a range of neurological disorders. FHF were discovered by virtue of their sequence homology to fibroblast growth factors (FGFs). While FGFs exert pleiotropic biological effects through interactions with their cell surface FGF receptors, we have demonstrated that FHF are intracellular and bind to specific neuronal protein targets. A principal set of targets are the alpha subunits for voltage-gated sodium channels. Using FHF knockout mice, we have shown that FHF are required for neurons to fire robustly, and this is accomplished by FHF modulation of sodium channel fast inactivation. We have also shown that some FHF induce a rapid onset long-term inactivation of sodium channels, which is mediated by an inactivation particle in the effector N-terminus of these FHF isoforms (Fig. 1). Long-term inactivation prevents sustained repetitive firing of neurons. Ongoing studies are defining the physical mechanisms of FHF actions and functional significance of neuron-type-specific and neuron-compartment-specific distribution of FHF protein isoforms. These studies entail the use of fast-responsive voltage sensitive dyes to visualize action potentials along axons and dendrites. An example on this technique applied to cultured cerebellar granule cells is shown in Figure 2.



- Fig. 1. A long-term inactivation schematic of voltage-dependent sodium channel transitions. The core domain of FHF (green) is shown tethered to the channel cytoplasmic tail.

The channel's intrinsic inactivation particle in the short cytoplasmic loop (small red oval) and the larger long-term inactivation particle at N-terminus of tethered A-type FHF (larger red oval) competes for access to inactivate the channel at more depolarized voltage-driven transitions near the open state, making long-term inactivation use-dependent. (from Dover et al., J. Physiol. 588:3695; 2010)





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Fig. 2. Visualization of action potential conduction with voltage-sensitive dye. A cultured granule cell was filled with fast-responsive voltage-sensitive dye by break-in with patch pipette, and viewed at either high spatial resolution (upper left panel) or high sensitivity (lower left panel). Voltage changes throughout cellular processes were subsequently monitored by fluorescence imaging during cell stimulation by current injection. The traces shown (upper right panel) correspond to color-highlighted dendrite and axonal regions (lower left panel). The fluorescence changes were color encoded to generate a movie (lower right panel), with each frame representing 0.2 msec. The action potential emerges from somatic region and propagates through all axonal branches.

- **Islet Brain-2, A Synaptic Protein Linked to Autism Spectrum Disorder**

- Deletion of the human SHANK3 gene near the terminus of chromosome 22q is associated with Phelan McDermid syndrome and autism spectrum disorders. Nearly all such deletions also span the tightly linked IB2 gene. IB2 is a neuronal protein with poorly understood function, interacting with other proteins suggesting a role in scaffolding p38 MAPK signaling. More recently, we have shown that IB2 protein is broadly distributed in the brain and is highly enriched within postsynaptic densities. Experimental disruption of the IB2 gene in mice reduces AMPA and enhances NMDA receptor-mediated glutamatergic transmission in cerebellum, changes the morphology of Purkinje cell dendritic arbors, and induces motor and cognitive deficits suggesting an autism phenotype. These findings support a role for human IB2 mutation as a contributing genetic factor in Chr22qter-associated cognitive disorders.