A neuron’s essential function is to relay information in the form of the action potential, a rapid change in the neuronal membrane voltage. Ion channels generate and maintain action potentials by harnessing the ionic gradients across neuronal membranes. Neurons express a wide array of ion channels whose regulation and subcellular localization have important consequences for neuronal function. In the past year, we described 2 modes of ion channel regulation mediated by fibroblast growth factor homologous factors (FHFs) in neurons.¹,²

FHFs (FGF11-FGF14) are members of the fibroblast growth factor (FGF) family but function differently than canonical FGFs.³ FHFs, in contrast to canonical FGFs, interact with voltage-gated sodium channels (VGSCs) and modify VGSC behavior.⁴ Previous studies hinted that the ways in which particular FHFs affected specific VGSCs vary depending on cell type and the particular FHF-VGSC pair queried, but individual roles for distinct FHFs within the same neuron had not been examined.⁵

With that background, we queried the function of 2 FHFs, FGF13 and FGF14, in the same hippocampal pyramidal neuron. Since VGSCs are highly concentrated in the neuronal axon initial segment (AIS) relative to the neuronal soma and dendrites, we first examined the consequences of FGF13 or FGF14 knockdown by shRNA to VGSCs in the AIS.¹ We observed FGF14 knockdown led to a loss of VGSCs in the AIS. Furthermore, we found fewer VGSCs at the neuronal membrane, as indicated by surface biotinylation and voltage clamp experiments. In contrast, FGF13 knockdown increased membrane localized VGSCs in the somatodendritic compartment. These contrasting results fit well with the differing subcellular localizations of FGF14 and FGF13. While FGF14 is mostly concentrated in the AIS, FGF13 is much more widespread and is found abundantly in the somatodendritic compartment.

The differential roles we observed for FGF13 and FGF14 provided insight into the “selective endocytosis” model for VGSC localization in neurons.⁶ In this model, VGSCs are trafficked to both axonal and somatodendritic compartments and are then selectively internalized from the somatodendritic compartment, leading to the characteristic pattern of VGSC localization in the AIS. Thus, our results show FGF14 is an important mediator of VGSC trafficking to the membrane whereas FGF13 regulates the selective endocytosis of VGSCs in the somatodendritic compartment. Additionally, we used structure-guided mutations to show that both FGF13 interaction with VGSCs and FGF14 interaction with VGSCs are necessary for their respective effects on VGSCs. Thus, although FGF13 and FGF14 are nearly identical in their core region sequence (~80%), and bind VGSCs at identical interfaces, they participate in different complementary pathways.
The differences in FGF13 and FGF14 functions are further exemplified in our second study, in which we observed that, in addition to its effects on VGSCs, FGF14 knockdown led to a loss of voltage-gated potassium channel KCNQ2 at the AIS.\(^2\) Knockdown of FGF13, on the other hand, had no effect on KCNQ2 localization. While VGSCs initiate the action potential, neuronal KCNQ channels control resting membrane potential and are important in relieving the voltage-dependent inactivation of VGSCs. Accordingly, knockdown of FGF14 led to a depolarization of the resting membrane potential, changes in membrane properties, and excitability, all of which were consistent with a loss of both VGSCs and KCNQ2-containing channels. Moreover, FGF14 (but not FGF13) regulated KCNQ2-containing channels in a heterologous expression system devoid of VGSCs, therefore showing that the effect was VGSC-independent. Bringing the 2 roles of FGF14 described in our papers together (VGSC regulation and KCNQ2-containing channel regulation), we found that FGF14 is capable of binding both KCNQ2 and VGSCs in immunoprecipitation experiments, and can thus serve as a “bridge” between these 2 types of ion channels.

Taken together, our studies show “division of labor” in ion channel regulation wherein different members of the same regulatory protein family exert different effects on the same ion channel targets. Our studies also show that ion channel regulatory proteins can “multitask,” as a single regulator can affect different types of ion channels. The exact molecular determinants for the functional differences among specific FHFs are exciting topics for future studies. Although our studies provided an unexpected perspective on FHF functions, multitasking by ion channel regulators is not unprecedented, as shown by calmodulin (CaM) and the VGSC auxiliary subunit Nav\(\beta1\). CaM regulates many ion channels including voltage-gated calcium, sodium and potassium channels.\(^7\) And Nav\(\beta1\), once thought to be strictly a sodium channel subunit, is promiscuous, as recently uncovered by reports showing that Nav\(\beta1\) also interacts with and regulates voltage-gated potassium channels.\(^8\) We expect that for both homeostasis and neuronal plasticity, coordinated regulation of a neuron’s variety of ion channels will be the norm rather than the exception.

**Disclosure of potential conflicts of interest**

No potential conflicts of interest were disclosed.

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**Figure 1.** Model of FGF13 and FGF14 function in hippocampal pyramidal neurons. FGF13 mediates somatodendritic endocytosis of VGSCs while FGF14 ensures proper localization of VGSC and KCNQ channels at the axon initial segment. For simplicity, the well-defined network of interactions known to tether VGSC and KCNQ channels to the underlying cytoskeleton is not depicted.
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