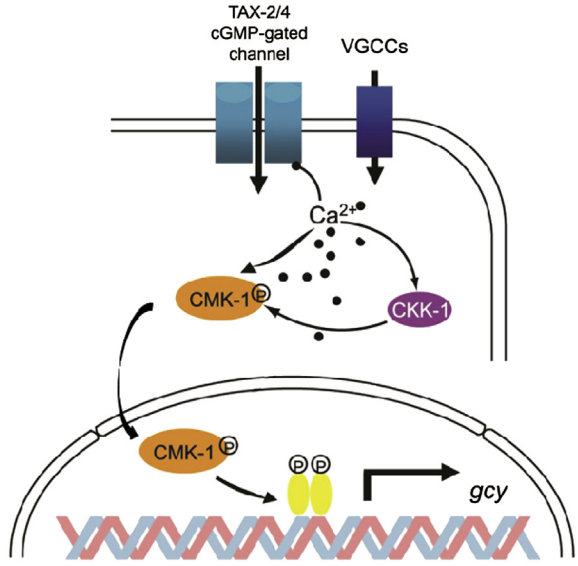
BOX 1



Signaling to the Nucleus in* C. elegans *Neurons

The CaM Kinase-dependent nuclear signaling pathway in nematodes is inherently interesting and serves as motivation for this review of signaling in mammalian neurons. On December 3, 2014, two research articles [59,60] were published in *Neuron* on the subject of *C. elegans*' ability to alter thermotaxis based on past experience. These studies built on years of work showing that CaM Kinase cascade signals to CREB and other transcription factors in the nematode [61,62]. Both studies characterized experience-dependent response properties and homeostasis in thermosensory neurons, within a full behavioral context.

In the worm's head, all the elements of the CaM Kinase cascade operate in individual cells that mediate specific behaviors. AFD neurons are known to mediate thermotaxis toward a preferred temperature, while the FLP neurons modulate thermotaxis away from noxious thermosensory stimuli. CMK-1 was identified through a forward genetic screen, where a gain of function mutant demonstrated abnormally low thermal avoidance. Remarkably, these studies demonstrate that activity-dependent translocation of a CaM kinase is directly responsible not only for transcriptional regulation, but also for a clear behavioral response to the external environment.

Schild et al. and Yu et al. demonstrated, in two separate neuron types and to two different physiological ends, that this CaMK signaling is functionally important in experience-dependent thermotaxis and heat avoidance. In AFD neurons, a threshold for temperature-evoked activity is set based on the animal's cultivation temperature. Nematodes adapted their thermotaxis behavior, tolerating warmer temperatures if they had been incubated at higher temperatures. CMK-1 regulates this physiological set point via modulation of guanylyl cyclase gene (*gcy*) expression levels [60]. In FLP nociceptors, cytoplasmic CMK-1 promotes thermal avoidance in the face of noxious temperatures. In contrast, nuclear CMK-1 produces analgesia and a decrease in thermal avoidance [59]. Interestingly, the mechanism of Ca^{2+} signaling is conserved between these two scenarios. CMK-1 translocates to the nucleus in a CKK-1 dependent manner, regulating gene transcription that controls behavioral output (portrayed in the schematic figure above, adapted from Ref. [60]).

Information transfer between a surface membrane and the nucleus is clearly a key to neuronal adaptation, and these studies are an elegant example of one such mechanism of nuclear communication. This CaMK cascade is particularly notable for its direct regulation of a behavioral output, a discovery for which we thank the relative simplicity of the nematode nervous system.