

NEWS AND VIEWS

Systematic temperature signaling regulates behavior plasticity

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The perception and response of environmental temperatures are vital for the survival, fitness and reproduction of all animal species. As a critical variable that affects the rate and nature of all biological and chemical reactions of the body, temperature has dramatic effect on animal physiology and behaviors. Homeotherms such as mammals maintain a relatively constant core body temperature despite of ambient temperature; changes of body temperature of transgenic mice greatly affect their energy efficiency and life span (Clos et al, 1993). However, Poikilotherms such as *C. elegans* and *D. Melanogaster* vary their body temperature with environmental temperature; they have the ability to memorize their cultivation temperature as the comfortable temperature, and migrate to the temperature with the smallest deviation from the comfortable temperature when placed on a thermal gradient, a behavior called thermotaxis. They also have the ability to shift their comfortable temperature and migrate to a new cultivation temperature a few hours after shifting to the new cultivation temperature.

The mechanism underlying thermotaxis behavior has been widely studied. A neural model for thermotaxis has been provided by previous studies with *C. elegans*, a common and useful model organism for the study of molecular and cellular mechanisms of sensory signaling because of their relatively simple structure. It is proposed in that model that a neural circuit, composed of primary thermosensory neuron AFD, a secondary thermosensory neuron AWC, and interneurons, is responsible for the detection, processing and memorization of temperature, and generation of thermotaxis behavior. In a recent edition of *Nature Neuroscience* (Sugi et al, 2011), a collaborative effort led by Mori group in the Department of Molecular Engineering of Kyoto University in Japan revealed a mechanism of systematic temperature signaling. They proposed that non-neuronal cells as well as neuronal cells respond to environmental temperature through a heat-shock transcription factor HSF-1 and a newly identified gene expression dynamics, and systemic temperature signaling

induces modulation of the thermotactic neural circuit in *C. elegans*.

A genome-wide profiling highlights HSF-1 as a protein closely related to thermotactic behavior. By comparison of the transcriptional profile of worms conditioned to migrate to the previous cultivation temperature of 23°C with that of worms conditioned to migrate to the new cultivation temperature of 17°C, they detected 79 candidate genes, including genes that are likely to involve in thermotactic behavior. HSF-1, which is well known for its responsiveness to transient heat-shock (Conti et al, 2006), stands out as the regulator of several *hsp* genes that have substantial changes in expression. It was also confirmed *in vivo* that a cultivation temperature shift between approximately 15°C and 25°C activates *C. elegans* HSF-1 by examining transgenic strains with GFP expression under the promoters of HSF-1 binding elements. A reduction-of-function mutant was made and addressed the necessity of HSF-1 for thermotactic behavior: mutants cultivated at 23°C did not migrate to the cultivation temperature, and in a temperature shift assay from 17°C to 23°C, they also failed to migrate to the higher temperature, even with longer cultivation time; the mutants have normal thermotactic behavior, excluding the possibility of temperature sensitive debility. On the other hand, worms expressing an HSF-1 dominant negative form (HSF-1DN) under the promoter of *hsp-16.2*, which is regulated by HSF-1, were established and confirmed that HSF-1 actually acts after a temperature shift from 17°C to 23°C. The most amazing experiments Mori's group has done are those exploring where HSF-1 functions to regulate thermotactic behavior. HSF-1 is detected throughout the body, although with higher expression in body wall muscles and intestine. *Hsf-1* cDNA was expressed with different promoters in *hsf-1* mutants. Expression of *hsf-1* in all neurons of the thermotactic circuits restored the thermotactic migration of *hsf-1* mutants, and expression in several neurons of the circuits weakly restored the behavior. Notably, expression of *hsf-1* cDNA in body wall muscles or in

intestines almost fully restored the behavior. The results suggested non-neuronal expression of HSF-1 is enough to restore the thermotactic behavior, and HSF-1 acts throughout the body.

They next investigated how HSF-1 mediated signaling regulates the thermotactic neuronal circuit. Temperature is sensed by bilateral AFD and AWC neurons, primary and secondary thermosensory neurons respectively; temperature signal is then transmitted to AIY and AIZ interneurons, and finally transduced and integrated in the RIA interneuron (Mori and Ohshima, 1995). By calcium imaging experiments and genetic epistasis analysis, they also found that HSF-1 signaling is involved in modulation of the responsiveness of AFD and AWC neurons as well as AIY interneurons, and they found that HSF-1 signaling is important for the cultivation temperature dependent response of the AFD neurons, not the AWC neurons.

In the last, they addressed how HSF-1 signaling regulates the thermosensory neurons. They found that *dhs-4* and *cyp-37B1*, two of the genes acting downstream of HSF-1, are also important genes in the estrogen signaling pathway, which leads to the hypothesis that HSF-1 signaling regulates thermosensory neurons at least partially through the estrogen signaling pathway. To confirm the hypothesis, they exogenously applied 17 beta-estradiol, a main form of estrogen, to wild-type worms and *hsf-1* mutant worms, and found that an application of estradiol caused thermophilic movement in a dose-dependent manner for wild-type worms, and could partially restore the behavioral defects of the mutant

worms. Genetic epistasis analysis and calcium imaging also confirmed that HSF-1 signaling acts at least partially through the estrogen signaling to regulate the thermosensory neurons.

In summary, the paper demonstrated that non-neuronal cells also participate in the temperature-triggered behavior response in *C. elegans*, despite of the principle view in the field of sensory neuron science that thermal perception is detected and processed by thermosensory neurons in the nervous system. Since HSP-1 protein and the downstream signaling heat shock factors are highly reserved proteins through evolution, the strategy of systemic temperature signaling might be retained in other organisms, and thus it is an attractive topic for further exploration.

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