

## OUTLOOK

# Neuronal regulation of longevity by staying cool

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**Aging is fundamental to life and reflects functional declines in different tissues at the organismal level. As a systematic process, aging can be influenced by the interplay between genetic and environmental factors, and the nervous system plays a crucial role in this regulation. Environmental inputs can be sensed by the nervous system, which consequently triggers signaling outputs toward peripheral tissues to regulate gene expression systematically. Thus, understanding the underlying molecular mechanisms behind environmentally triggered neuron-periphery cross-talk is crucial for the promotion of an organism's health and longevity.**

Pioneering studies in worms and flies revealed that the sensory nervous system is vital for the regulation of life span (Alcedo and Kenyon 2004; Libert et al. 2007). Recently, the progressive accumulation of evidence has highlighted the role of sensory neurons in perceiving environmental stimuli, such as nutrient availability, olfactory/gustatory cues, or oxygen levels, and in turn modulating protein and mitochondrial homeostasis, metabolic activities, and/or stress responses in the peripheral tissues (Weir and Mair 2016). Neuroendocrine signals mediate these communications between sensory neurons and peripheral tissues and act through specific downstream cellular and molecular mechanisms to regulate longevity (Weir and Mair 2016). Similar brain-peripheral cross-talk in modulating the aging process has also been shown in mammals (Satoh and Imai 2014). Enhanced neuronal activities in certain areas of the hypothalamus and pituitary gland can affect the secretion of specific hormones. In turn, these hormones can then directly or indirectly promote youthful physiology and behaviors at the organismal level, resulting in the stabilization of muscle functions, cognitive health, and respiration efficiency (Satoh and Imai 2014).

Among a variety of environmental inputs, temperature has been recognized recently for its active roles in regulating an organism's life span. People noticed that cold-

blooded animals, such as worms, flies, and fish, live longer at cool temperatures and, conversely, a shorter time at warm temperatures. Even for warm-blooded mammals, decreasing core body temperature by 0.3°C–0.5°C in mice can extend life span by 12%–20% (Conti et al. 2006). It has long been mistakenly thought that these phenomena are simply due to different rates of biochemical reactions at different temperatures, since temperature is a fundamental factor for kinetic energy. However, collective evidence proves that this simple assumption is incorrect, as it turns out that temperature affects life span not solely because of a thermodynamic process but through a genetically regulated process. Through genetic screening in *Caenorhabditis elegans*, Lee and Kenyon (2009) identified the neuronal ion channel encoded by *tax-2* and *tax-4* that is involved in life span shortening in a warm environment, which acts through the DAF-12 nuclear hormone receptor (NHR) signaling pathway. On the other hand, Xiao et al. (2013) discovered that cold temperature activates the TRPA1 ion channel in neurons, which subsequently signals to the transcription factor DAF-16/FOXO to prolong life span. It is interesting that specific neuronal signaling mechanisms mediate this systemic regulation in response to temperature cues.

These exciting findings on the temperature regulation of aging raise a new question: What are the neural circuits that prompt neuroendocrine signaling to regulate life span? Delineating such a specific neural circuit would advance our current understanding of the temperature control of longevity and open possibilities for targeted neuronal manipulation to improve fitness under environmental fluctuation. In this issue of *Genes & Development*, Zhang et al. (2018) take advantage of the powerful genetics in *C. elegans* and pinpoint the specific neurons and neuroendocrine factors that transduce temperature cues to signal the periphery and regulate an organism's life span (Fig. 1).

In the present work, through rigorous neuronal screening, Zhang et al. (2018) identified the IL-1 sensory neurons

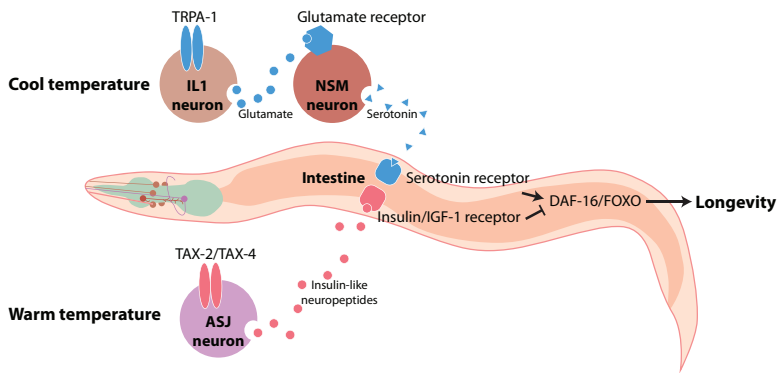
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Lin et al.



**Figure 1.** Neuron–peripheral signaling pathways mediate the temperature regulation of life span. Cool temperatures activate the ion channel TRPA-1 in IL1 neurons, which release glutamate to modulate serotonin signals from NSM neurons. Circulating serotonin is then sensed by its receptors in the intestine and activates the FOXO transcription factor DAF-16 to prolong life span. On the other hand, warm temperatures activate the ion channel TAX-2/TAX-4 in ASJ neurons, which subsequently secrete insulin-like peptides to inhibit intestinal DAF-16/FOXO activity, leading to life span reduction.

as the originators of the cool-induced longevity phenotype initiated through the activation of the TRPA-1 ion channel. Furthermore, the investigators found that, upon stimulation, the IL-1 neurons signal and activate the NSM neuronal pair through the neurotransmitter glutamate. As an intermediate in the signal propagation, the NSM neurons then use a second neurotransmitter, serotonin, to inform the intestine to respond to the low environmental temperature. Cell-autonomously in the intestine, the classical FOXO transcription factor DAF-16 mediates the life span-extending effect. Zhang et al. (2018) thus reveal a novel neural circuit in the longevity regulation responding to cool temperature and demonstrate at the molecular level a cool-induced neuroendocrine axis signaling from the brain to the gut.

As a juxtaposition to this cool-induced longevity phenotype, the investigators have also investigated how warmth can elicit the opposing phenotype: a shortened life span. Zhang et al. (2018) began by confirming the previously described role of the TAX-2/TAX-4 heteromeric ion channel as warm-responsive (Lee and Kenyon 2009) and then identified ASJ neurons as the site for this channel in its role in mediating warmth-induced life span reduction. Following the discovery of the importance of the ASJ neurons, the investigators further showed that the activation of these neurons shortens life span at high temperatures via the release of insulin-like neuropeptides. These neuropeptides signal the intestine through their downstream receptor (DAF-2) and transcription factor (DAF-16).

Together, the investigators have defined the previously unknown molecular mechanisms through which two well-known phenotypes (temperature-dependent life span extension and shortening) are generated. Furthermore, using genetic screening methods, the investigators have demonstrated two distinct and antagonistic neuron–gut neuroendocrine communication mechanisms. Discovery of these new neuron–periphery regulatory pathways highlights the significance of temperature sensing in the active control of longevity and paves the road for further investigation of similar thermo-control longevity mechanisms in other systems. This body of work further delineates the importance of environmentally induced neuro-sensation and the communication of this signal to

the effector tissues in the maintenance of physiological homeostasis. Any individual animal lacking this ability to adapt to environmental stimuli runs the risk of being at a biological disadvantage when compared with its compatriots. With this pathway so beautifully highlighted in the relatively simple organism *C. elegans*, it now falls on the field to determine whether similar neuroendocrine pathways exist in more complex models and underlie their physiological adaptation to environmental stimuli.

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### References

- Alcedo J, Kenyon C. 2004. Regulation of *C. elegans* longevity by specific gustatory and olfactory neurons. *Neuron* **41**: 45–55.
- Conti B, Sanchez-Alavez M, Winsky-Sommerer R, Morale MC, Lucero J, Brownell S, Fabre V, Huitron-Resendiz S, Henriksen S, Zorrilla EP, et al. 2006. Transgenic mice with a reduced core body temperature have an increased life span. *Science* **314**: 825–828.
- Lee SJ, Kenyon C. 2009. Regulation of the longevity response to temperature by thermosensory neurons in *Caenorhabditis elegans*. *Curr Biol* **19**: 715–722.
- Libert S, Zwiener J, Chu X, Vanvoorhies W, Roman G, Pletcher SD. 2007. Regulation of *Drosophila* life span by olfaction and food-derived odors. *Science* **315**: 1133–1137.
- Satoh A, Imai S. 2014. Systemic regulation of mammalian ageing and longevity by brain sirtuins. *Nat Commun* **5**: 4211.
- Weir HJ, Mair WB. 2016. SnapShot: neuronal regulation of aging. *Cell* **166**: 784–784 e781.
- Xiao R, Zhang B, Dong Y, Gong J, Xu T, Liu J, Xu XZ. 2013. A genetic program promotes *C. elegans* longevity at cold temperatures via a thermosensitive TRP channel. *Cell* **152**: 806–817.
- Zhang B, Gong J, Zhang W, Xiao R, Liu J, Xu XZ. 2018. Brain–gut communications via distinct neuroendocrine signals bidirectionally regulate longevity in *C. elegans*. *Genes Dev* (this issue). doi: 10.1101/gad.309625.117.



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