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For Longevity, Perception is Everything

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Abstract

Aging is a risk factor for chronic diseases, and identifying targets for intervention is a goal of the aging field. Burkewitz et al. now describe a mechanism that mediates the specific role for AMPK in longevity, whereby its activity in neurons modulates metabolism and mitochondrial integrity in peripheral tissues.

Because aging is the primary risk factor for the development of many chronic diseases, it is a fundamental public health problem. Therefore, one goal of the aging field is to identify regulatory mechanisms that could become targets of intervention. Animals adjust their metabolic rates and life schedules according to nutrient status. The highly conserved AMP-activated protein kinase, AMPK, which is activated under low nutrient conditions and is required for lifespan extension with dietary restriction (DR), is an attractive target for such interventions. However, AMPK also affects growth, reproduction, and disease development (Mair et al., 2011). Therefore, identifying mechanisms of AMPK activation that slow aging without deleterious effects is important in moving AMPK pathway drugs to a clinical application. Previously, Mair and colleagues showed that inhibition of the cyclic AMP-responsive element (CREB)-regulated transcriptional co-activator (CRTC-1) is required for AMPK-mediated lifespan extension (Mair et al., 2011). In this issue of *Cell,* Burkewitz et al. (2015) now find that CRTC-1 specifically mediates AMPK's role in longevity, but not growth or reproduction, through its activity in neurons, modulating metabolism and mitochondrial integrity in peripheral tissues. Notably, neuronal AMPK/CRTC-1 status is dominant to the pathway's activity in peripheral tissues, which has implications for the development of AMPK-based therapeutics Figure 1.

To identify the mechanisms underlying the specific effect of CRTC-1 on lifespan, the authors first zeroed in on transcriptional targets that correlated solely with AMPK/CRTC-1-dependent longevity. This set was enriched for mitochondrial metabolism genes, and metabolomic analyses demonstrated an increase in TCA cycle intermediates and associated metabolites upon AMPK activation, suggesting a specific coupling of AMPK-mediated metabolic regulation and lifespan extension. Moreover, the authors found that several of these metabolic genes were also regulated by NHR-49, a functional ortholog of the nuclear receptor PPARα, which activates transcription in low energy states, ultimately acting in an antagonistic manner to CRTC-1.

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CRTC-1 is expressed in neurons and intestine, a major site of longevity regulation in *C. elegans* (Libina et al., 2003). Because AMPK is expressed ubiquitously, and many of the factors involved in dietary restriction-mediated longevity, including CRTC-1, are found in peripheral tissues, AMPK and the CRTC-1/CREB complex were previously presumed to directly affect metabolism in tissues in which they are expressed (Mair et al., 2011). However, the authors found that intestinal CRTC-1 had no effect on longevity, while neuronal expression of the constitutively nuclear CRTC-1$^{S76A, S179A}$, which is refractory to AMPK regulation, was sufficient to suppress the longevity effects and metabolic transcription of AMPK activation, and even caused fragmentation of the mitochondrial network in muscle cells. Similarly, neuronal rescue of NHR-49 in an *nhr-49* null mutant induced metabolic changes in neurons, muscle, and intestine. Therefore, the effects of AMPK on peripheral tissues seemed to be modulated by a neuron-derived signal. Indeed, the authors next identified the neuromodulator octopamine as the AMPK/CRTC-1-mediated signal that alters metabolism in peripheral tissues. AMPK/CRTC-1 signaling regulated the expression of octopamine synthesis enzymes, and loss of octopamine abolished the reduced longevity of CRTC-1$^{S76A, S179A}$ animals. Exogenous octopamine treatment even phenocopied the mitochondrial fragmentation seen in muscle tissue upon neuronal CRTC-1 activation. Thus, octopamine, acting as the AMPK neuronal signal, was able to "over-ride" local AMPK signaling in peripheral tissues.

The exact sites of action for some of these players still remain to be identified. Octopamine synthesis enzymes are expressed in the RIC interneurons, a site of CRTC-1 localization, but CRTC-1 and NHR-49 may also act in additional neurons. The specific receptors and receiving cells of the octopamine signal are also unknown, but given that starvation induces CREB activity in SIA neurons to regulate acetylcholine release, it will be interesting to examine whether SIA neurons and/or acetylcholine activity are also involved in the CRTC-1 longevity response. Additionally, the direct transcriptional targets of neuronal NHR-49 and CREB in this context are not known; AMPK's regulation of growth and reproduction does not involve CRTC-1, and CREB's role in growth is largely due to non-neuronal gene expression (Lakhina et al., 2015). Downstream changes in peripheral tissues may be regulated by the activity of the longevity transcription factors DAF-16 or PQM-1 (Tepper et al., 2013), as the DAF-16 Associated Element (DAE) was overrepresented in the promoters of AMPK/CRTC-1's downstream transcriptional targets. The involvement of these transcription factors also suggests that an insulin may act as an intermediate signal upstream of the peripheral tissues. While these are challenging questions, leveraging the distinct neuronal and peripheral tissue transcriptional outputs will help untangle them.

Neuronal regulation of peripheral tissue responses has been observed in varied contexts; for example, dietary restriction activates the transcription factor SKN-1 in ASI neurons, which signals peripheral tissues to increase metabolic activity and whole-body respiration (Bishop and Guarente, 2007), and heat stress activates the AFD thermosensory neurons to elicit serotonin release, which turns on HSF-1-mediated transcription in distant germline tissues (Tatum et al., 2015). Sensory cues can regulate longevity of the whole organism, as loss of ciliated sensory neurons, odorant receptors, and the TRPV1 receptor extend lifespan in worms and mice (Apfeld and Kenyon 1999; Riera et al., 2014). CRTC1 activity in mammalian neurons also affects organismal metabolism (Riera et al., 2014), and

upregulation of AMPK in *Drosophila* neurons increases autophagy in the brain as well as intestine (Ulgherait et al., 2014), underscoring the conservation of the signaling logic. The present findings extend this theme of regulation of whole organism and peripheral tissue status by neuronal signaling, but in this case, the activity of neuronal AMPK appears to have the ability to ignore its own signaling elsewhere. At least in worms, it seems that *perception* of nutrient status is more important than the actual status in peripheral tissues themselves. While it is not clear how often these might become uncoupled, this remarkable finding suggests that current therapies aimed primarily at regulating AMPK signaling in peripheral tissues may be altered by neuronal signaling; or, seen in a more promising light, that sensing of AMPK status may be sufficient to induce beneficial metabolic effects. Therefore, future therapeutic investigations should include the consideration of effects on brain AMPK and CRTC1 signaling, in addition to more direct effects in peripheral tissues themselves.

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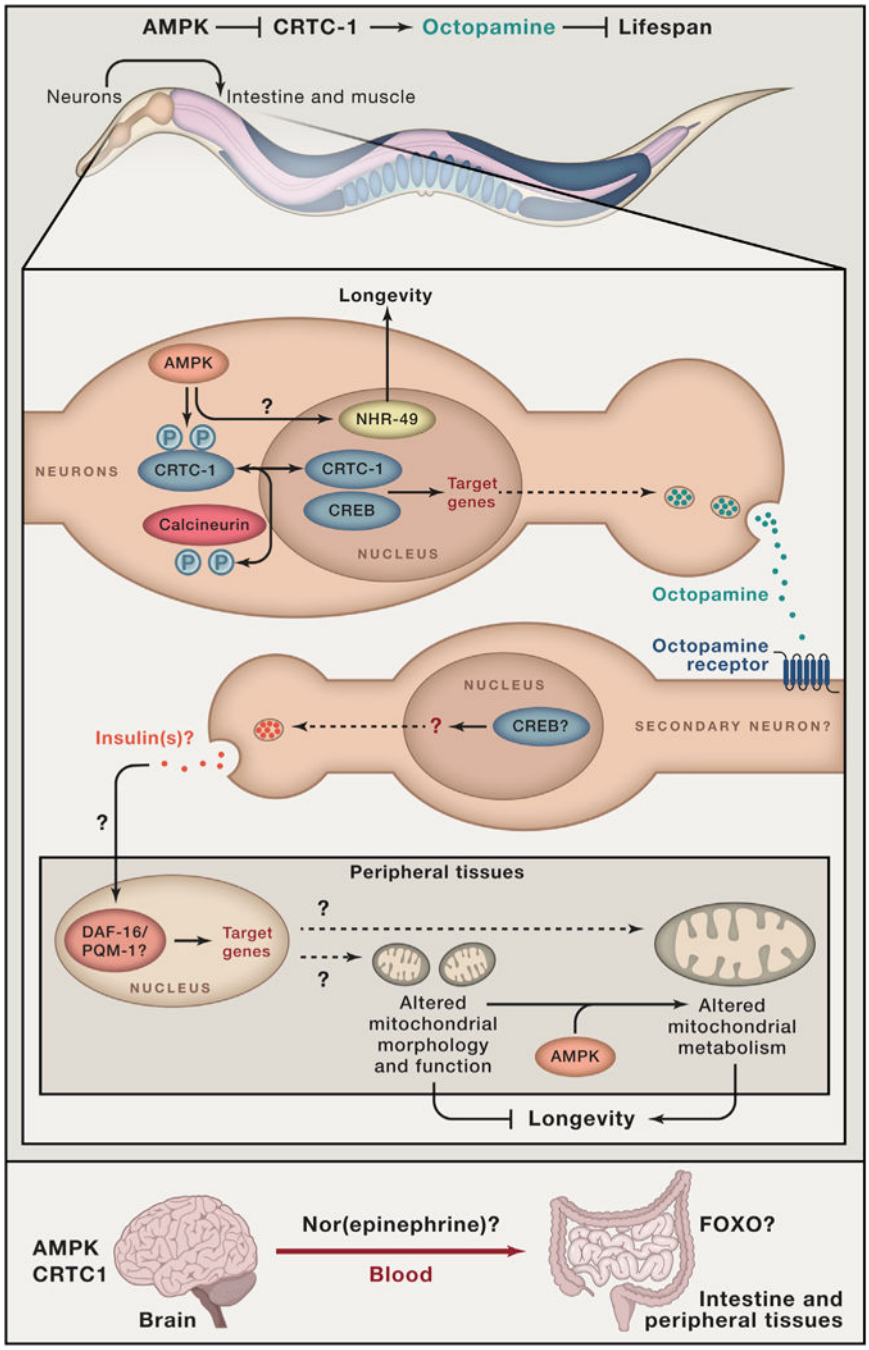

Figure 1. Nutrient Status Sensing in Neurons by AMPK May Relay a Signal between Neurons to Peripheral Tissues

(Top) Upon reduced AMPK activity in neurons, CRTC-1 induces octopamine secretion, which alters metabolic gene expression and causes mitochondrial fragmentation in peripheral tissues, potentially due to the transcriptional activity of DAF-16/PQM-1 within these tissues. Octopamine is most likely sensed by intermediate neurons, which may signal to peripheral cells via secreted cues such as insulins. (Bottom) AMPK/CRTC1 in the human

brain may communicate via (nor)epinephrine to the intestine and peripheral tissues to regulate the pro-longevity factors, such as FOXO.