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AGEING

Staying alive without CRTC-1

Activation of AMP-activated protein kinase (AMPK) or inactivation of the phosphatase calcineurin slows ageing in *Caenorhabditis elegans*, but the mechanism behind this was unknown. Mair *et al.* now reveal that these proteins promote longevity by inhibiting the role of cyclic AMP-regulated transcriptional co-activator-1 (CRTC-1) in transcription.

In mammals, AMPK and calcineurin antagonize CRTCs by modulating their phosphorylation. Thus, the authors proposed that their homologues in *C. elegans* — AAK-2 (AMPK catalytic subunit α-2) and TAX-6, respectively — might regulate longevity through CRTCs. They identified a single *C. elegans* CRTC, CRTC-1, the depletion of which extended lifespan similarly to TAX-6 depletion or AAK-2 activation. Next, as AMPK-mediated phosphorylation of mammalian CRTC2 promotes its interaction with 14-3-3 proteins and sequestration in the cytoplasm, the authors tested whether AAK-2 and TAX-6 regulate CRTC-1 localization. Co-expression of constitutively active AAK-2 with CRTC-1 in *C. elegans* caused the nuclear exclusion of CRTC-1, as did TAX-6 depletion; this was dependent on 14-3-3 proteins. Thus, AAK-2 and TAX-6 control CRTC-1 localization.

> “TAX-6, AAK-2 and CRTC-1 act in the same pathway to promote longevity.”

But do AAK-2 and TAX-6 regulate longevity through CRTC-1? RNA interference (RNAi)-mediated knockdown of TAX-6, or overexpression of AAK-2, had no effect on lifespan in worms expressing a constitutively nuclear CRTC-1 mutant. This suggests that TAX-6, AAK-2 and CRTC-1 act in the same pathway to promote longevity. As the mammalian transcription factor cAMP-responsive element-binding protein (CREB) associates with CRTCs to activate transcription, the authors investigated whether CRH-1, the *C. elegans* homologue of CREB, is a downstream effector of CRTC-1. Indeed, CRH-1 and CRTC-1 do interact, and the direct inactivation of CRH-1 by RNAi increases longevity. Furthermore, CRH-1 mutants did not show extended lifespan following CRTC-1 depletion by RNAi. Thus, the longevity effects of inactivating CRTC-1 occur through the inactivation of CRH-1.

Finally, the authors compared gene expression across the genome of wild-type, AAK-2-overexpressing, TAX-6-null and CRH-1-null *C. elegans*. Worms with an increased lifespan as a result of these mutations had similar transcriptional profiles. Surprisingly, although AMPK and CREB are involved in energy homeostasis in mammals, mutant worms did not show significant changes in the expression of metabolism-related genes. Instead, an increase in the expression of genes involved in endoplasmic reticulum (ER) stress was observed; further studies will reveal whether ER stress has a role in lifespan extension regulated by AMPK–calcineurin–CRTC-1.

So, this study reveals that AMPK and calcineurin promote longevity in *C. elegans* by inactivating CRTC-1 and thus the transcriptional activity of CRH-1. Future studies are likely to identify relevant CRH-1 targets, the downregulation of which is important for longevity.

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ORIGINAL RESEARCH PAPER Mair, W. *et al.* Lifespan extension induced by AMPK and calcineurin is mediated by CRTC-1 and CREB. *Nature* **470**, 404–408 (2011)
FURTHER READING Altarejos, J. Y. & Montminy, M. CREB and the CRTC co-activators: sensors for hormonal and metabolic signals. *Nature Rev. Mol. Cell Biol.* **12**, 141–151 (2011)