

AGING

REST linked to longevity

Zullo, J.M. et al. *Nature* **574**, 359–364 (2019)

Many outstanding questions still need to be addressed to understand why we age. Most studies into the mechanisms of aging have focused on DNA damage, telomere shortening, loss of proteostasis, and mitochondrial dysfunction, but new theories are under investigation. A new study published in *Nature* combined the use of human data and of two model organisms to identify a conserved mechanism of aging that is mediated by neural activity and regulated by the transcription factor REST.

The investigators first analysed RNA sequencing and microarray data from the brain of aged individuals. They showed that genes related to neural excitation and synaptic function were downregulated in individuals ≥ 85 years of age compared with individuals ≤ 80 years of age, suggesting that extended longevity is associated with reduced neural circuit activity. Switching to the worm, the team showed that Ca²⁺ influx increased in ASH neurons during aging and that drug-mediated suppression of neural

excitation extended *C. elegans* lifespan, suggesting that lifespan is dynamically regulated by the excitatory–inhibitory balance of neural circuits.

The investigators also suggest that the repressor function of REST is upregulated in the brain of individuals with extended longevity, resulting in downregulation of genes that mediate neural excitation. In the mouse, conditional KO of *Rest* increased neural activity in the brain compared with control, whereas in the worm CRISPR/cas9-mediated induction of *spr-4*, which encodes an orthologue of REST, reduced excitation in ASH neurons and extended lifespan.

The team also demonstrated that REST and neural activity converge with insulin–IGF signalling (IIS) to regulate lifespan. RNA interference (RNAi)-mediated knockdown of *daf-16*, which encodes transcription factor DAF-16—the *C. elegans* homolog of FOXO acting downstream of IIS—prevented the extension of lifespan induced by *spr-4* overexpression. The extension of

lifespan induced by RNAi of *daf-2*, which encodes IGF-1 receptor was also inhibited by mutations in *spr-3* and/or *spr-4*. These results suggest that *spr-3* and *spr-4* contribute to the regulation of lifespan via the IIS pathway in worms. The investigators also showed that SPR-3 and SPR-4 contribute to the extreme longevity of *daf-2* mutants by repressing neural excitation, which leads to the activation of DAF-16.

“The activation of *daf-16* by REST orthologues in worms and *FOXO1* by REST in humans might be a mechanism for integration of neural activity with metabolism” explain the investigators in the discussion, before concluding that activation of REST and reduction of excitatory neural activity could be an approach to slowing aging in humans.

Alexandra Le Bras

Published online: 9 December 2019
<https://doi.org/10.1038/s41684-019-0448-x>

Take the PAIN Out of Pain Management

Pharmaceutical grade. FDA-indexed. Simple to order and administer.

NEW Ethiqax XR™ is the first and only **pharmaceutical grade** extended-release buprenorphine, providing 72 hours of analgesia for mice and rats. Coming soon through distributors, Ethiqax XR will be **simple to order**, and its low-viscosity formula is **easy to administer**.

WARNING: Due to serious human safety and abuse concerns, read the entire product insert before using this drug, including the complete Box Warning.

Available Early 2020

Ethiqax XR™
 (buprenorphine extended-release injectable suspension) 1.3 mg/mL
Pure Pain Relief

Find distributors at ethiqaxr.com/BG **833-EthiqaxXR** (833-384-4729)

© 2019 Fidelis Pharmaceuticals, LLC All Rights Reserved December 2019 FID-ETH-024