Nature Reviews Molecular Cell Biology | AOP, published online 13 November 2013; doi:10.1038/nrm3703

Thinkstock

AGEING

A little bit of stress does you good

Although mitochondrial stress is usually associated with ageing it can promote longevity at low levels, probably by initiating compensatory stress signalling. Perrimon and colleagues shed light on this in *Drosophila melanogaster*, revealing that partially disrupting the function of muscle mitochondria activates components of the mitochondrial unfolded protein response (UPR^{mt}) and ImpL2 (an orthologue of human insulin-like growth factor-binding protein 7 (IGFBP7)), and that this prolongs lifespan.

The authors investigated whether knockdown of *ND75* (a component of the electron transport chain) in muscles would benefit flies. As permanent knockdown prevented larvae from developing into adults, they devised a system in which *ND75* knockdown, and thus mitochondrial stress, was temporarily induced in muscles at 29 °C (called TDN flies based on the system used to knock down *ND75*). Larvae incubated at 29 °C for 120 hours developed into adults with reduced size and lifespan. By contrast, larvae grown at 29 °C for only 24 hours, and thus subject to less mitochondrial stress, grew into adults with an increased lifespan and climbing ability (locomotion is normally impaired with age). Hence, mild mitochondrial stress benefits flies.

What might cause these stress-induced advantages? The authors discovered that the gene encoding heat shock protein Hsp60C — an orthologue of a gene in *Caenorhabditis elegans*, the protein product of which has been implicated in the UPR^{mt} — was required, as knocking out this gene in TDN flies was lethal. Moreover, transgenic flies overexpressing Hsp60C or its paralogue Hsp60 in muscles had an increased lifespan; muscle mitochondrial integrity and locomotory ability were also increased in flies overexpressing Hsp60.

As the authors observed that TDN flies have higher levels of reactive oxygen species (ROS), and that antioxidants prevented the benefits of mild mitochondrial stress, they investigated whether redox signalling upregulates the UPR^{mt} in TDN flies. Indeed, the redox-sensitive JUN N-terminal kinase (JNK) signalling pathway was upregulated in parallel with UPR^{mt} markers, and overexpression of the JNK-activated transcription factor Jun (also known as Jra) induced several UPR^{mt} markers. The disruption of Jun reduced the longevity of TDN flies. Thus, a ROS–JNK signalling–UPR^{mt} pathway contributes to the increased lifespan afforded to flies by mild mitochondrial stress.

Incubation of larvae at 29 °C for 120 hours resulted in flies that not only had smaller muscles, but also had shorter wings and were smaller overall. How might this growth-inhibitory phenotype spread from muscles to other parts of the fly? The authors found that ImpL2, which inhibits insulin signalling, was expressed in thorax muscles in TDN flies; this correlated with the induction of markers for insulin repression. These markers were also induced non-autonomously in the abdomen and head. Importantly, disruption of ImpL2 function in the muscles of TDN flies reduced their longevity, whereas its temporary expression increased it. Thus, ImpL2 seems to systemically inhibit insulin signalling to promote longevity.

Overexpression of ImpL2 did not induce the UPR^{mt}, but the authors found that ImpL2 overexpression increased the number of lysosomes in muscle from TDN flies. As mitophagy (a form of autophagy that degrades damaged mitochondria in conjunction with lysosomes) was active in, and important for the increased lifespan of, TDN flies, ImpL2 may also promote longevity by facilitating mitophagy.

In short, this study shows that ROS signalling, the UPR^{mt} and the systemic repression of insulin signalling together preserve mitochondrial function in the face of mild stress, preventing the adverse effects of ageing on muscle function and prolonging lifespan.

Katharine H. Wrighton

> “ROS signalling, the UPR^{mt} and the systemic repression of insulin signalling together preserve mitochondrial function in the face of mild stress”

ORIGINAL RESEARCH PAPER Owusu-Ansah, E., Song, W. & Perrimon, N. Muscle mitohormesis promotes longevity via systemic repression of insulin signaling. *Cell* **155**, 699–712 (2013)