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SPOTLIGHT

Mitochondrial translation, dynamics, and lysosomes combine to extend lifespan

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In this issue, Liu et al. (2019. *J. Cell. Biol.* https://doi.org/10.1083/jcb.201907067) find that the inhibition of mitochondrial ribosomes in combination with impaired mitochondrial fission or fusion increases *C. elegans* lifespan by activating the transcription factor HLH-30, which promotes lysosomal biogenesis.

The mitochondrial network harbors the TCA cycle and oxidative phosphorylation enzymes that promote the conversion of consumed carbon into cellular energy. Mitochondria also serve as signaling hubs that regulate programmed cell death, innate immunity, and longevity. For example, inhibition of mitochondrial ribosomes has been shown to extend the lifespan of worms as well as mice in a manner dependent on the mitochondrial unfolded protein response (UPR^{mt}; 1, 2), which is an adaptive transcriptional response that promotes mitochondrial protein homeostasis (3). Importantly, the functional outputs that extend lifespan downstream of mitochondrial translation inhibition or UPR^{mt} activation remain unclear.

Coincident with UPR^{mt} activation, Liu and colleagues observed dramatic changes in mitochondrial network morphology during mitochondrial ribosome inhibition (1). Mitochondria are dynamic organelles in constant flux that divide via fission and combine via fusion. Thus, the authors sought to understand the impact of mitochondrial dynamics on longevity by inhibiting the fission component *drp-1*, the fusion component *fzo-1*, or both (4, 5). Interestingly, inhibition of both mitochondrial translation and mitochondrial fusion resulted in increased UPR^{mt} activation and an even greater extension of lifespan than translation inhibition alone. Similarly, inhibition of fission along with mitochondrial translation also resulted in a stronger UPR^{mt} and longevity phenotype. However, complete immobilization of the mitochondrial network by impairing both fission and fusion prevented lifespan extension, indicating that mitochondrial dynamics are required for longevity upon mitochondrial ribosome impairment (1).

Surprisingly, despite high UPR^{mt} activation upon complete mitochondrial network immobilization, the transcription factor ATFS-1 that mediates the UPR^{mt}, was not required for lifespan extension, suggesting that an alternative, or additional, signaling pathway contributes to lifespan extension during mitochondrial dysfunction. To obtain clues as to the identity of the protective pathway, Liu and colleagues surveyed a series of *Caenorhabditis elegans* transcription factors known to be required for longevity in diverse paradigms. Of the nine genes examined, only *hlh-30* inhibition prevented the longevity associated with mitochondrial ribosome inhibition combined with impaired fission or fusion. HLH-30 is homologous to the mammalian transcription factor Transcription Factor EB (TFEB) that regulates lysosome biogenesis and autophagy (6). Consistent with increased HLH-30 activation during longevity, HLH-30 was enriched in the nucleus when mitochondrial ribosomes and fusion were impaired. The same conditions also resulted in an *hlh-30*-dependent increase in lysosomes along with multivesicular bodies (MVBs), suggestive of lysosomal biogenesis and increased lysosomal activity. Taken together, these data point toward an essential role for increased lysosomal activity in lifespan extension during mitochondrial dysfunction combined with impaired mitochondrial dynamics (Fig. 1).

The signaling mechanism by which impaired mitochondrial dynamics stimulates HLH-30 when mitochondrial translation is impaired remains to be determined. TFEB activity is known to be regulated by mTOR-dependent phosphorylation, which retains the transcription factor in the cytosol (6). HLH-30 likely functions similarly, as experiments suggest it is also regulated by mTOR (7). The authors' proteomics studies indicate a reduction in oxidative phosphorylation components, which may provide clues to HLH-30 regulation. This could potentially result in reduced cellular energy and activation of AMP kinase, which reduces mTOR activity. Subsequent impairment of mTOR could result in TFEB dephosphorylation, followed by nuclear accumulation and activation of the lysosomal biogenesis

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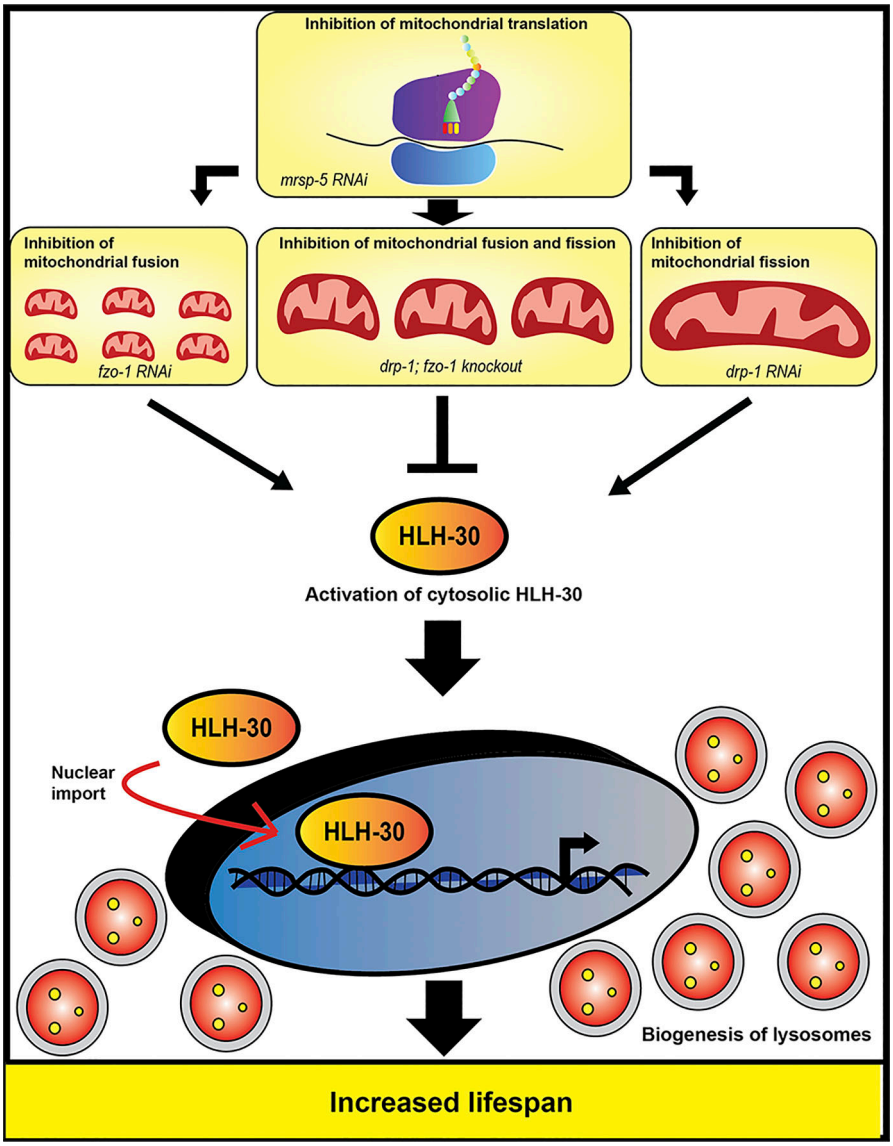

Figure 1. **Mitochondrial dynamics and HLH-30 combine to extend lifespan.** Inhibition of mitochondrial protein synthesis, combined with inhibition of either mitochondrial fusion and fission activates the transcription factor HLH-30 (TFEB in mammals) resulting in lysosomal biogenesis and lifespan extension in *C. elegans*. However, inhibition of both mitochondrial fission and fusion prevents the lifespan extension conferred by mitochondrial protein synthesis inhibition. *mrps-5* is a mitochondrial ribosome component, *fzo-1* is a fusion component, and *drp-1* is a fission component.

program (6). However, the authors' metabolomics calculations indicate that cellular energy status was not significantly reduced. Thus, the relationship between mitochondrial dynamics, translation, and TFEB activation remains to be determined.

hlh-30 has been previously implicated in lifespan extension caused by impaired ubiquinone synthesis that perturbs mitochondrial function (7); however, the interaction between lysosomal activity and mitochondria that extends lifespan remains unclear. The authors favor a model in which increased lysosomal activity allows for increased autophagy capacity, potentially to rid the cell of severely damaged mitochondria. Interestingly, simultaneous inhibition of fission and fusion still stimulates HLH-30 activation, but lifespan extension does not ensue. The authors propose that complete inhibition of mitochondrial dynamics may prevent damaged organelles from entering the autophagy pathway, suggesting that dysfunctional mitochondrial accumulation limits lifespan. Alternatively, complete inhibition of mitochondrial dynamics may also impair the generation of functional mitochondria.

In conclusion, the authors describe a mechanism by which inhibition of mitochondrial translation concurrent with loss of either mitochondrial fusion or fission causes activation of the transcription factor HLH-30. This response triggers biogenesis of lysosomes, leading to increased lifespan, potentially by accelerating clearance of damaged cellular components. However, lysosomes have been found to contribute to lifespan in multiple contexts, including the maintenance of iron homeostasis, leaving future studies to determine the role of lysosomal activity in longevity (8).

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