logical techniques, he distinguished persisters from resistant mutants, showed that their levels could be enhanced by stress, and anticipated that they would be in a "dormant nondividing phase" and present among other bacterial pathogens (*2*). The recent exciting progress on mechanisms of TA function establishes these toxins as key inducers of the persister state. Future research should elucidate the many functions of TAs and how they work collectively during persistent bacterial infections. For example, it is unclear whether different stresses activate different TA subsets, and what the profiles of toxin activation are in individual bacterial cells. Some toxins have been shown to be sequence-specific ribonucleases, but whether this specificity has physiological implications is uncertain. It could be that bacteria perceive signals that trigger their exit from quiescence, but the mechanisms involved are unknown.

If persisters lead to recurrent infections requiring multiple courses of antibiotics, then they are likely to contribute appreciably to the current worldwide crisis of antibiotic resistance. Yet, surprisingly little is known about the relative usage of antibiotics for persistent infections and the degree to which persisters influence the emergence of resistance. In the long term, TAs and associated signaling molecules may provide targets for drugs that can either prevent persisters from being formed, or—perhaps more feasibly—coax them out of the nonreplicating state so that they resume susceptibility to antibiotics. This might finally enable complete eradication of an otherwise recurrent or persistent infection, so that, as Bigger put it, "the success of penicillin therapy will become more commensurate with its potentialities" (*2*). ■

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CELL BIOLOGY

Lysosomal lipid lengthens life span

A fatty acid moves from the lysosome to the nucleus, altering gene expression and extending longevity in the worm

By **Shuo Han** *and* **Anne Brunet**

Lysosomes were discovered more than 60 years ago as highly acidic cellular organelles containing many enzymes responsible for breaking down macromolecules (*1*). Since then, their roles have expanded. Lysosomes function in autophagy, the process that breaks down cellular components to allow cell survival and homeostasis in the face of starvation (*1*). These organelles also have emerged as a signaling hub for the enzyme mechanistic target of rapamycin (mTOR), a protein kinase involved in cellular and organismal growth responses to nutrient availability (*2*). We also now recognize links between aberrant lysosomal function and several diseases, including lysosomal storage diseases (e.g., Tay-Sachs disease) and neurodegenerative disorders (e.g., Parkinson's disease), and also with aging (*1*). On page 83 of this issue, Folick *et al.* (*3*) indicate how lysosomes play a role in the latter—by deploying a lipid molecule to the nucleus, whose impact on gene expression extends life span in an animal model (the nematode *Caenorhabditis elegans*). The study not only uncovers a lysosome-to-nucleus signaling pathway but also highlights the potential of lipids in mediating long-range physiological effects.

Lysosomes contain about 60 enzymes, including many well-conserved lipases involved in fatty acid breakdown. Defects in lysosomal acid lipase A (LIPA) lead to several human lysosomal storage diseases, including Wolman disease, a disorder characterized by metabolic defects and death in childhood (*4*). In *C. elegans*, the LIPA homolog LIPL-4 is highly expressed in specific conditions that are linked to life-span extension (*5*, *6*). However, the mechanism by which this enzyme modulates aging has remained elusive.

Using a combination of genetics, metabolomics, biochemistry, and immunocytochemistry, Folick *et al.* explored the molecular mechanisms by which lysosomal LIPL-4 activation regulates aging in *C. elegans*. They show that worms overexpressing LIPL-4 live substantially longer than normal worms and produce increased amounts of several bioactive lipids, notably the fatty acid oleoylethanolamide (OEA). OEA is likely generated by the breakdown of more complex lipids in the lysosome by LIPL-4. LIPL-4–overexpressing worms also exhibit an increased amount of a fatty acid binding protein called lipid-binding protein-8 [(LBP-8); the human homolog is fatty acid binding protein (FABP)]. Elegantly coupling fluorescence imaging with mutations that alter protein targeting to the lysosome, Folick *et al.* demonstrate that LIPL-4 must reside within the lysosome to extend life span. By contrast, LBP-8 translocates from the lysosome into the nucleus to ensure increased longevity. As LBP-8 can directly bind to OEA, these results suggest that LBP-8 is a lipid chaperone assisting OEA entry into the nucleus (see the figure).

What happens once OEA is shuttled into the nucleus? Folick *et al.* found that OEA physically binds to and activates conserved nuclear hormone receptors, thereby activating the transcription of target genes. Fatty acid ligands have been reported to control the transcriptional activity of subfamilies of nuclear receptors (*7*), and OEA can bind to the nuclear receptor peroxisome proliferator–activated receptor-α (PPARα) in mice (*8*). The authors report that two particular nuclear receptors—nuclear hormone receptor-49 (NHR-49) and NHR-80, the *C. elegans* homologs of mammalian PPARα and hepatic nuclear factor 4, respectively—are both required for LIPL-4–induced longevity, and that OEA can directly bind to NHR-80. This observation is consistent with previous reports that NHR-49 and NHR-80 play critical roles in life-span regulation in *C. elegans* (*9*, *10*).

> ***"...dietary modulation of fatty acids...has the potential to delay aging."***

What about dietary supplementation of OEA? Folick *et al.* found that feeding worms OEA during their adult life is sufficient to

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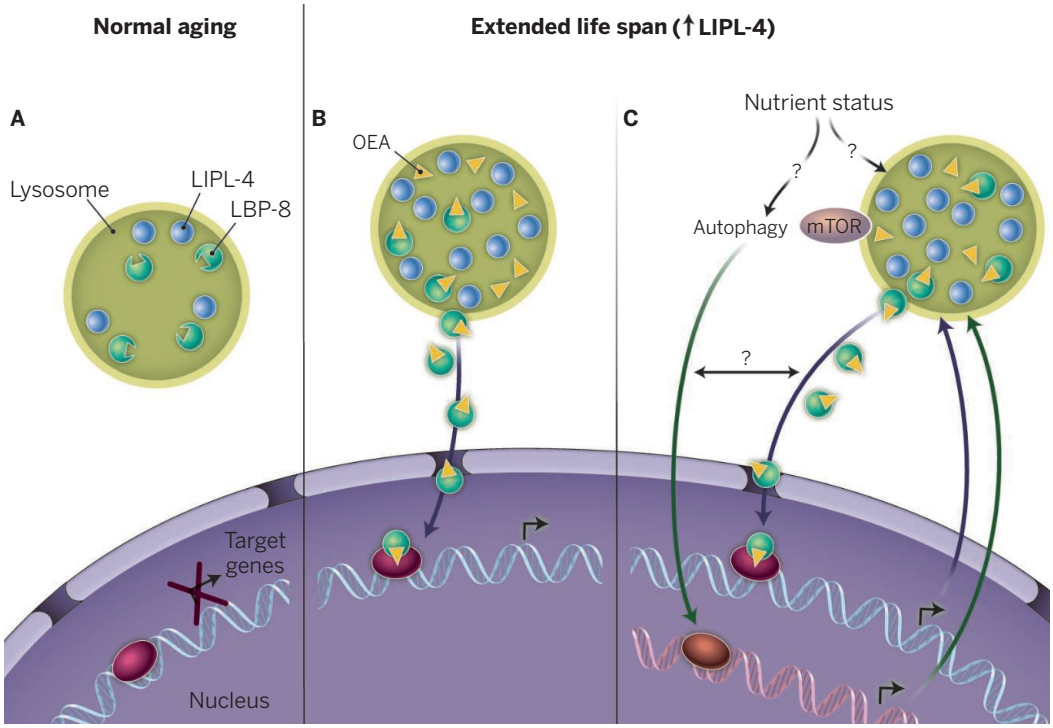

A pathway to longevity. (**A**) During normal aging, the lipase LIPL-4 and lipid-binding protein LBP-8 reside in the lysosome. (**B**) In long-lived worms, there is an increase in LIPL-4 and the fatty acid OEA in the lysosome. OEA translocates into the nucleus by binding to the chaperone LBP-8. OEA binds to the nuclear receptor NHR-80 to affect the expression of genes that regulate longevity. (**C**) Nutrient status could also affect LIPL-4 activity. A positive feedback loop likely exists between nuclear transcription factors and the lysosome. The mTOR and autophagy pathways could modulate this lysosome-to-nucleus pathway for longevity.

activate these nuclear hormone receptors and promote longevity. OEA may therefore represent a key ligand that activates these nuclear receptors to modulate aging, although it remains to be determined whether OEA affects aging entirely by acting through these transcription factors or whether it has other effects on the organism. The ensemble of target genes downstream of these nuclear receptors that promote longevity also remains to be identified.

The findings of Folick *et al.* are exciting because they are the first to establish a lysosome-to-nucleus signal that functions in aging regulation and to show that dietary modulation of fatty acids such as OEA has the potential to delay aging. Because genes in this pathway are conserved, the findings also provide insights on the regulation of human nuclear receptors by lysosomal signaling. Given that OEA affects feeding behavior and body weight in mice by acting through PPARα (*8*), dietary OEA may also have an impact on aging in mammals. The availability of bioactive lipids such as OEA could depend on the internal nutritional state of the organism. Environmental interventions such as fasting or overfeeding could alter the availability and composition of the lipid pool, consequently changing the binding status of nuclear receptors, altering downstream transcription programs, and affecting aging.

Signaling between the lysosome and the nucleus is likely to be a two-way street. Indeed, recent reports in mammalian cells have established that lysosomal autophagy can be regulated by lipid-sensing transcription factors in the nucleus during the feeding and fasting cycles, namely the transcription factors farnesoid X receptor (FXR) (*11*), cyclic adenosine monophosphate responsive element binding protein (CREB) (*11*), and PPARα (*12*). Thus, while lysosomes release diffusible lipid messengers that affect transcription, lipid-sensing transcription factors could provide feedback regulation of the lysosome, maintaining metabolic homeostasis based on nutrient status.

Lysosomes are involved in controlling the activity of mTOR and the execution of autophagy (an intracellular mechanism that breaks down cellular components) in response to nutrient availability (*13*). LIPL-4 itself is important for inducing autophagy in *C. elegans* (*6*). Therefore, a key remaining question concerns the connection between this lysosome-to-nucleus signaling and the TOR-autophagy pathway. Could TOR and autophagy play a role in the longevity of LIPL-4–overexpressing animals? Conversely, does an increase in OEA extend life span because of inhibition of the TOR pathway? More generally, it will be important to determine whether this lysosome-to-nucleus signaling pathway is important for longevity conditions that have been shown to require LIPL-4, such as the lack of an intact germ line (*5*, *6*).

In a broader context, these findings raise the question of the site of action of this lysosome-to-nucleus signaling pathway and whether it is entirely cell-autonomous. Both LIPL-4 and LBP-8 are expressed in the gut of the worm, and presumably this is also the site of action of OEA. However, an interesting possibility could be that OEA, as a cell-permeable lipid, is secreted outside the gut to activate nuclear receptors in other tissues. In this way, an inter-tissue lipid signaling network may exist during the aging process and might be involved in systemic lifespan regulation (*14*).

In addition to OEA, other lipids or metabolites could act as diffusible signals between different organelles to orchestrate coordinated cellular responses. Unbiased metabolomic profiling is a promising discovery tool to decipher the mechanisms underlying many human metabolic diseases. This approach would also help to identify the elusive ligands for many nuclear receptors (*15*). Ultimately, modulations of bioactive lipids could be a therapeutic strategy for a wide range of human metabolic disorders and age-related diseases. ■

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