mosaic genetic aberrations—i.e., it appears that the relative frequency of cells from a cell clone can first increase and then decrease later in life (*5*, *17*, *18*). In the present analyses, LOY was detected in ≥10% of blood cells from about 15% of elderly males in three cohorts (figs. S3 to S5). The cell clones with LOY were likely detectable in our analyses because they are enriched due to an increased proliferative potential as a consequence of LOY, which is in agreement with chromosome Y containing tumor suppressor genes. Recent analysis of >8200 tumor-normal pairs suggest that two genes (*ZFY* and *UTY*, from the male-specific part of Y) have properties of tumor suppressors (*19*). Interestingly, both genes have homologs on chromosome X and escape X inactivation (*19*, *20*). Moreover, other analyses of various tumor collections show that chromosome Y is lost from numerous types of tumors in frequencies ranging from 15 to 80% of cases (*21*–*24*). Thus, counting both LOY in noncancerous blood clones and in transformed tumor cells, nullisomy Y is among the most common, if not the most common, human mutation. The results presented here suggest that this aneuploidy, affecting 1.6% of the genome, is likely induced by smoking.

In conclusion, we show that LOY is more common in current smokers compared with non-current smokers in three cohorts (Fig. 1 and table S1), that the effect from smoking on LOY is dose dependent, and that this effect appears to be transient, as it disappears after smoking cessation (Fig. 2). Epidemiological observations suggest that smoking could be a greater risk factor for cancer outside the respiratory tract in males compared with females (*2*, *4*, *10*). Moreover, males have a higher incidence and mortality from most sex-unspecific cancers (*3*, *4*). The molecular mechanisms behind these observations are not well understood, but LOY, being a male-specific, smoking-induced risk factor, could provide a missing link and help explain these sex differences.

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SUPPLEMENTARY MATERIALS

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AGING

Lysosomal signaling molecules regulate longevity in *Caenorhabditis elegans*

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Lysosomes are crucial cellular organelles for human health that function in digestion and recycling of extracellular and intracellular macromolecules. We describe a signaling role for lysosomes that affects aging. In the worm *Caenorhabditis elegans*, the lysosomal acid lipase LIPL-4 triggered nuclear translocalization of a lysosomal lipid chaperone LBP-8, which promoted longevity by activating the nuclear hormone receptors NHR-49 and NHR-80. We used high-throughput metabolomic analysis to identify several lipids in which abundance was increased in worms constitutively overexpressing LIPL-4. Among them, oleoylethanolamide directly bound to LBP-8 and NHR-80 proteins, activated transcription of target genes of NHR-49 and NHR-80, and promoted longevity in *C. elegans*. These findings reveal a lysosome-to-nucleus signaling pathway that promotes longevity and suggest a function of lysosomes as signaling organelles in metazoans.

Lysosomes contain acid hydrolytic enzymes, digesting macromolecules taken up by endocytosis and recycling dysfunctional cellular components during autophagy (*1*). Lysosomal deficiency is associated with human diseases. For example, loss of human lysosomal acid lipase, *LIPA*, results in severe systemic metabolic malfunction known as infantile Wolman disease (*2*). Here, we explored how lysosomes might generate signaling molecules that regulate aging by influencing nuclear transcription.

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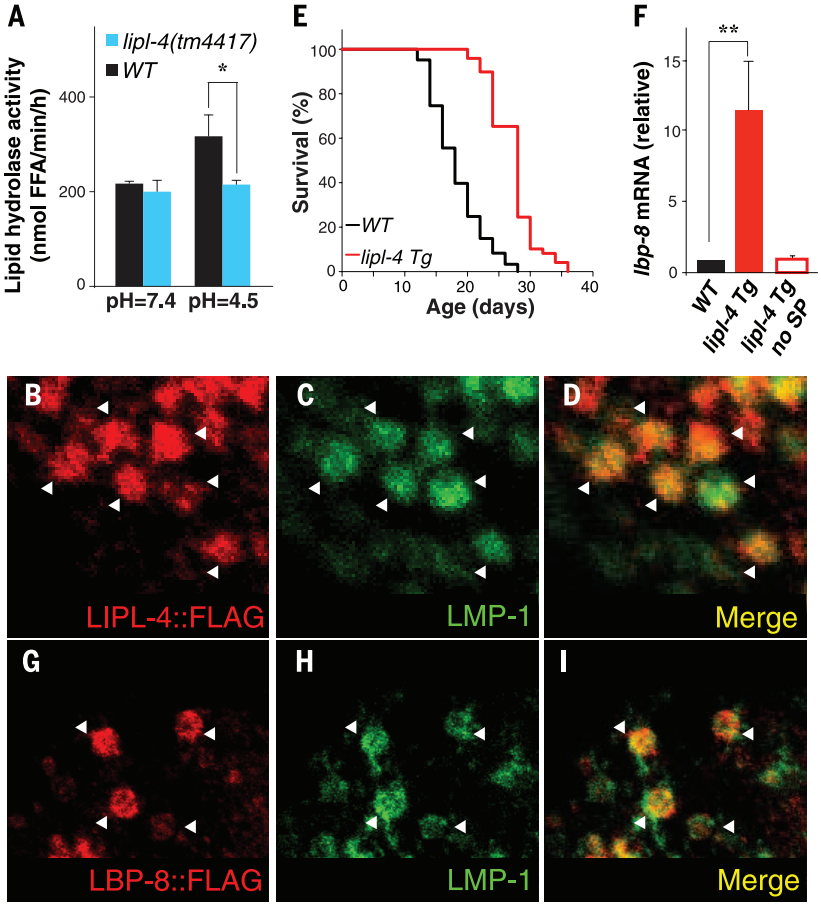
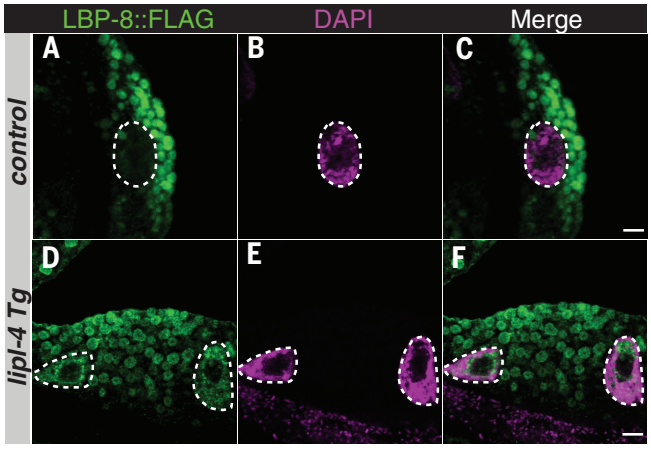
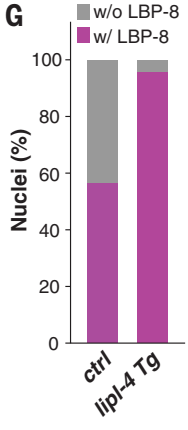
We analyzed a *Caenorhabditis elegans* longevity-promoting lipase, LIPL-4, which has sequence and functional similarities with human *LIPA* (fig. S1). Lipid hydrolase activity was decreased in *lipl-4(tm4417)* loss-of-function mutants at pH 4.5 but not at pH 7.4 (Fig. 1A). FLAG-tagged LIPL-4 protein was localized to intestinal lysosomes (Fig. 1, B to D, and fig. S2). Increased *lipl-4* expression is associated with longevity (*3*). A transgenic strain (*lipl-4 Tg*) that constitutively expressed *lipl-4* in the intestine had 55% mean life-span increase compared with wild-type (WT) animals (Fig. 1E and table S1) and delayed age-related decline of physical activity (fig. S3A). Constitutive expression of LIPL-4 without the signal peptide (*lipl-4 Tg no SP*), which was not targeted to the lysosome, caused little extension of life span (fig. S4 and table S1), which suggests that the lysosomal activity of LIPL-4 is essential for its longevity effect.

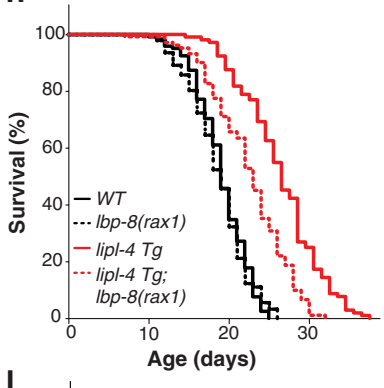
To elucidate whether lipid signals are affected by the LIPL-4 lipase, we examined fatty acid–binding proteins (FABPs) that are intracellular lipid chaperones shuttling lipid molecules between cellular

Fig. 1. Lysosomal lipid chaperone is increased in long-lived worms. (**A**) The amount of free fatty acids (FFAs) liberated from [^{3}H]triolein is significantly decreased in the *lipl-4(tm4417)* loss-of-function mutant compared with wild-type (WT) at pH = 4.5 but not at pH = 7.4. *$P < 0.05$, Student's *t* test. (**B** to **D**) Adult worms (*raxEx20[ges-1p::lipl-4::3xFLAG]*) were stained with antibodies against FLAG and LMP-1. LIPL-4 colocalizes with LMP-1, an established protein marker of lysosomes (*18*). Scale bar, 10 μm. (**E**) Mean life span is increased 55% in *lipl-4 Tg* worms (*raxIs3[ges-1p::lipl-4::sl2gfp]*) compared with WT. $P < 0.0001$, log-rank test. (**F**) *lbp-8* mRNA amounts were increased in *lipl4 Tg* compared with WT but not in the transgenic strain overexpressing *lipl-4* that lacks the signal peptide for lysosomal expression (*lipl-4 Tg no SP*). Error bars represent standard deviation (SD). **$P < 0.001$, Student's *t* test. (**G** to **I**) Adult worms (*raxEx31[lbp-8p::lbp-8::3xFLAG]*) were stained with antibodies against FLAG and LMP-1. LBP-8 colocalizes with LMP-1 in intestinal lysosomes. Scale bar, 10 μm.









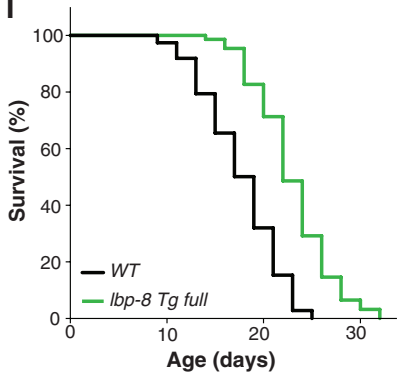
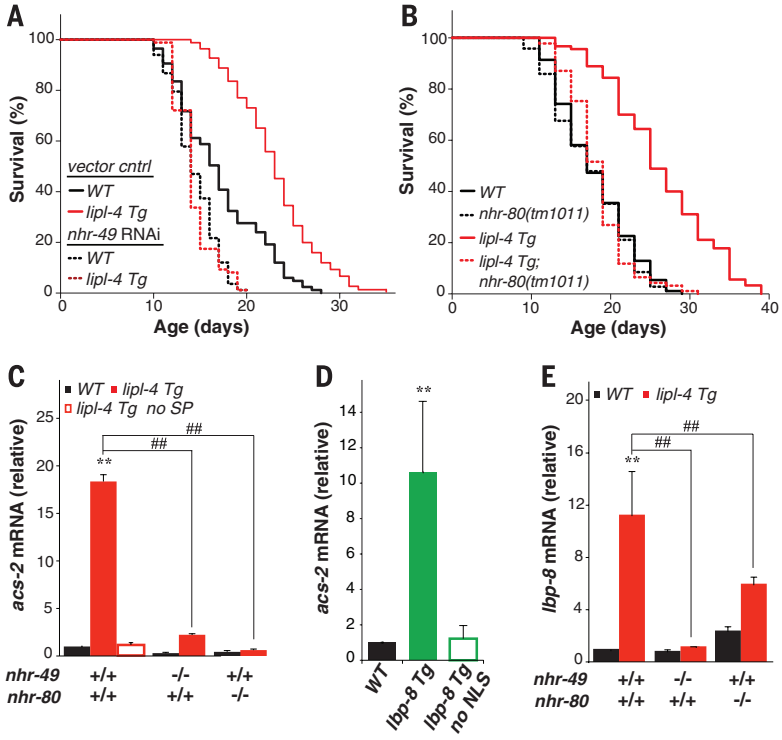


Fig. 2. Lysosomal lipid chaperone promotes longevity. (**A** to **F**) Adult worms expressing LBP-8::3xFLAG were stained with FLAG-specific antibody and 4′,6-diamidino-2-phenylindole (DAPI). More LBP-8 nuclear staining in *lipl-4 Tg* versus control worms. Scale bar, 10 μm. (**G**) Quantification of the percentage of nuclei positive for LBP-8::3xFLAG staining. $n = 100$. (**H**) The *lbp-8(rax1)* loss-of-function mutation reduces mean life-span extension in *lipl-4 Tg* by 46% ($P < 0.0001$) but has no effect on the life span of WT ($P > 0.05$). Log-rank test. (**I**) Mean life span is increased 30% in *lbp-8 Tg* (*raxIs4[lbp-8p::lbp-8::sl2gfp]*) compared with WT. $P < 0.0001$, log-rank test.



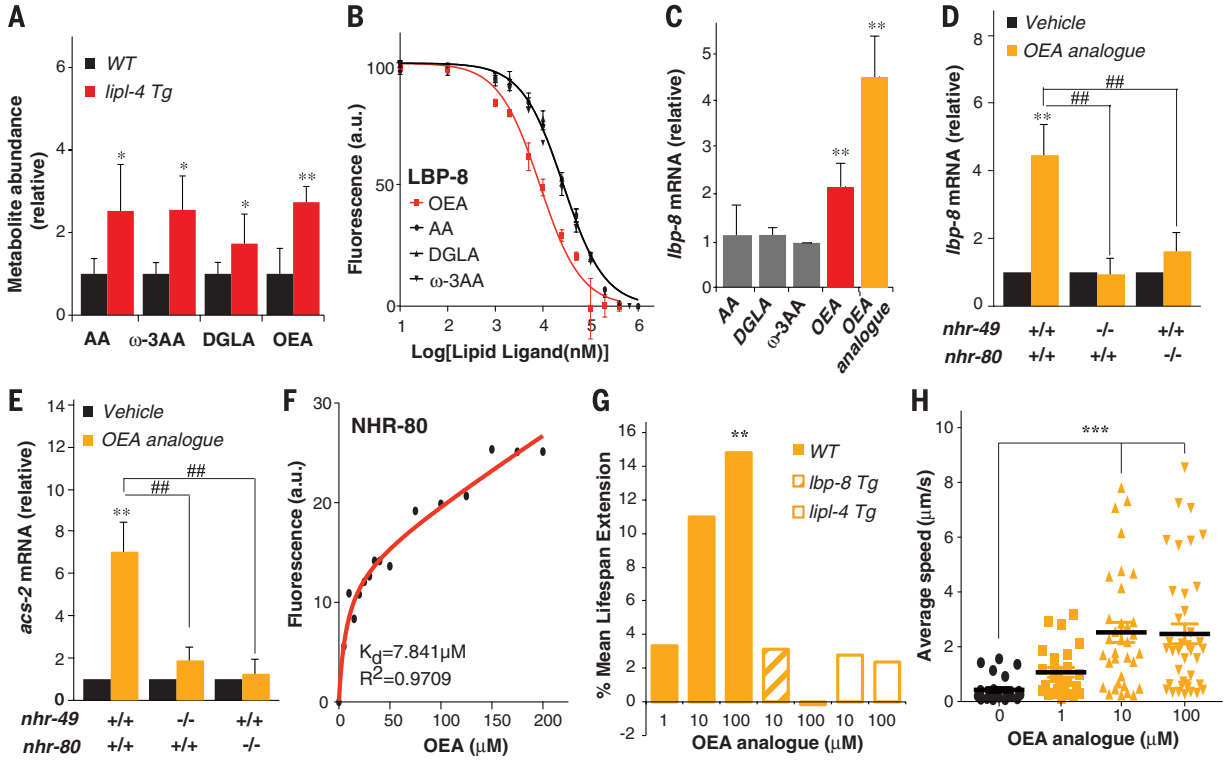


Fig. 3. Nuclear receptors act in lysosomal longevity signaling. (**A** and **B**) With adult-only RNAi inactivation of *nhr-49* or with the *nhr-80(tm1011)* loss-of-function mutation, the mean life spans of *lipl-4 Tg* and WT are not significantly different. $P > 0.5$, log-rank test. (**C**) Increased mRNA amount of NHR-49 target gene *acs-2* is suppressed by the *nhr-49(nr2041)* or *nhr-80(tm1011)* loss-of-function mutation in *lipl-4 Tg*, and is absent in *lipl-4 Tg no SP*. (**D**) *acs-2* mRNA amount is increased in *lbp-8 Tg* but not in the transgenic strain expressing *lbp-8* without the N-terminal NLS (*lbp-8 Tg no NLS*). (**E**) Increased mRNA amount of *lbp-8* in *lipl-4 Tg* is suppressed by the *nhr-49(nr2041)* or *nhr-80(tm1011)* mutant. Error bars represent SD. $^{**}P < 0.01$ by Student's *t* test; $^{\#\#}P < 0.01$ by two-way analysis of variance (ANOVA).

Fig. 4. OEA activates nuclear receptors and promotes longevity. (**A**) Increased levels of arachidonic acid (AA), ω-3 arachidonic acid (ω-3 AA), dihomo-γ-linoleic acid (DGLA), and OEA in *lipl-4 Tg* compared with WT. $^{*}P < 0.05$, $^{**}P < 0.001$, Welch's *t* test. (**B**) Decreased fluorescence derived from binding of 1-anilinonaphthalene-8-sulfonic acid (1,8-ANS) to LBP-8 by increasing OEA, AA, DGLA, and ω-3 AA competition. OEA has higher binding affinity than the other lipids by a factor of 3. (**C**) *lbp-8* mRNA amounts are increased in WT supplemented with OEA or the OEA analog, but not AA, DGLA, or ω-3 AA, $^{**}P < 0.01$, Student's *t test*. (**D** and **E**) mRNA amounts of *lbp-8* and *acs-2* are increased by OEA analog supplementation in WT, but not in the *nhr-49(nr2041)* or *nhr-80(tm1011)* mutant. $^{**}P < 0.01$, Student's *t* test. $^{\#\#}P < 0.01$, two-way ANOVA. (**F**) The intrinsic fluorescence intensity of GST-NHR-80 fusion proteins is decreased with increasing concentration of OEA [dissociation constant (K_d) of the binding reaction, 7.8 ± 4.1 μM]. R^2 is the coefficient of determination. (**G**) Supplementation of the OEA analog increases mean life span in WT, but not in *lipl-4 Tg* or *lbp-8 Tg*. $^{**}P < 0.01$, log-rank test. (**H**) Mean locomotion velocity is increased in WT treated with the OEA analog at 18 days of age. $^{***}P < 0.0001$, Student's *t* test. Error bars, SD. Error bars represent SD in (A) to (E), and in (H), standard error of the mean.

compartments for different functions (*4*, *5*). Of the nine *C. elegans* FABP homologs, only mRNA amounts of *lbp-8* were increased in *lipl-4 Tg* animals, but not in the *lipl-4 Tg no SP* strain (Fig. 1F). A green fluorescent protein (GFP) reporter strain showed that *lbp-8* was exclusively expressed in the intestine (fig. S5A). Both FLAG- and mCherry-tagged LBP-8 proteins were predominantly localized to intestinal lysosomes (Fig. 1, G to I, and fig. S5, B to J).

We also detected partial nuclear localization of LBP-8 in the intestine, which was enhanced in *lipl-4 Tg* animals (Fig. 2, A to G, and fig. S6, A to F). LBP-8 contains an N-terminal nuclear localization signal (NLS) (fig. S6G) and was present in both cytoplasmic and nuclear fractions of total worm lysate (fig. S6H). Both RNA interference (RNAi)–mediated depletion of LBP-8 and a newly isolated deletion mutant, *lbp-8(rax1)*, suppressed the life-span extension in *lipl-4 Tg* animals without affecting WT life span (Fig. 2H, fig. S7, and table S1). Thus, LBP-8 appears to be required for LIPL-4 lysosomal activity to confer longevity.

We found that a transgenic strain (*lbp-8 Tg)* constitutively expressing *lbp-8* had a 30% increase in mean life span compared with WT animals (Fig. 2I and table S1) and improved maintenance of physical activity in old age (fig. S3B). However, a transgenic strain that constitutively expresses LBP-8 lacking NLS (*lbp-8 Tg no NLS)* was excluded from nuclei and showed little or no life-span extension (fig. S8 and table S1). Thus, LBP-8 may function as a lysosomal lipid chaperone transducing lipid signals to the nucleus.

To test whether lysosomal signals might influence nuclear transcription, we screened several transcription factors implicated in longevity regulation (*6*–*11*). Nuclear hormone receptors *nhr-49* and *nhr-80*, previously demonstrated to physically interact (*10*), were both required for *lipl-4*– and *lbp-8*–mediated longevity. RNAi-mediated inactivation of *nhr-49* in adult worms shortened the life span of WT worms but also completely suppressed longevity extension in *lipl-4 Tg* and *lbp-8 Tg* worms (Fig. 3A, fig. S9A and table S1). The loss-of-function mutation *nhr-80(tm1011)* abrogated longevity extension without affecting the life span of WT worms (Fig. 3B, fig. S9B, and table S1). Neither *nhr-49* nor *nhr-80* is required for dietary restriction–induced longevity (*6*, *12*), which suggests that the LIPL-4–mediated longevity mechanism may act independently of dietary restriction. Concordantly, the longevity extensions by *lipl-4 Tg* and *eat-2(ad1116)*, a genetic model of dietary restriction in *C. elegans* (*13*), were additive (fig. S10).

acs-2 encodes an acyl-CoA synthetase required for mitochondrial β-oxidation and is a target gene of NHR-49 (*11*). *acs-2* transcription was increased more than 15-fold in *lipl-4 Tg* animals; this effect was dependent on *nhr-49* and *nhr-80,* and absent in the *lipl-4 Tg no SP* strain (Fig. 3C). Transcription of *acs-2* was also increased more than 10-fold in *lbp-8 Tg* but not in *lbp-8 Tg no NLS* animals (Fig. 3D). Thus, LIPL-4–induced activation of NHR-49 and NHR-80 can be reproduced by nuclear action of LBP-8. Transcriptional increase of *lbp-8* by *lipl-4 Tg* was in turn mediated by NHR-49 and NHR-80 (Fig. 3E).

To identify lipid molecules that might function in this lysosome-to-nucleus lipid signaling, we performed high-throughput metabolomic profiling analyses on WT and *lipl-4 Tg* worms. Among 352 metabolites detected, 71 had significantly altered abundance in *lipl-4 Tg* animals (table S2). Long-chain fatty acids and their derivatives are likely binding partners of FABPs (*4*). Thus, we focused our analysis on three C20 fatty acids—arachidonic acid, ω-3 arachidonic acid, and dihomo-γ-linolenic acid—and oleoylethanolamide (OEA), an *N*-acylethanolamine fatty acid derivative (Fig. 4A and table S2). In fluorescence-based binding assays, all four lipids bound to LBP-8, and the binding affinity of OEA for LBP-8 was 3 times that of the fatty acids (Fig. 4B).

Next, we tested the effects of the four lipids on transcription when directly applied to WT adult worms. We also used an OEA analog, KDS-5104, that is more resistant to hydrolysis than OEA (*14*). Only OEA and its analog were sufficient to increase the transcription of *lbp-8* in WT worms, and the analog exerted a stronger effect (Fig. 4C). After 3 hours of treatment with the OEA analog, transcription of *lbp-8* and *acs-2* was increased more than 4- and 7-fold above the control levels, respectively (Fig. 4, D and E). This effect was abrogated in the *nhr-49(nr2041)* or *nhr-80(tm1011)* mutant (Fig. 4, D and E). Thus, accumulation of OEA in response to LIPL-4 may act to promote transcription via NHR-49/NHR-80.

To test whether OEA directly binds to NHR-49 or NHR-80, or both, we measured intrinsic fluorescence changes of glutathione *S*-transferase (GST)–NHR fusion proteins in the presence of OEA. OEA binding significantly decreased the fluorescence intensity of the NHR-80 fusion protein in a dose-dependent manner [equilibrium dissociation constant (K_d) of 7.8 μM] (Fig. 4F). In a differential protease-sensitivity assay, chymotrypsin digestion of [^{35}S]NHR-80 in the presence of the OEA analog resulted in protease-resistant fragments of approximately 45 and 35 kD (fig. S11), which indicated direct binding between NHR-80 and the OEA analog. However, no binding was detected between NHR-49 and OEA or the OEA analog (fig. S12). Thus, NHR-80 appears to act as a direct nuclear receptor of OEA and NHR-49 may function as a cofactor of NHR-80.

N-Acylphosphatidylethanolamine–specific phospholipase D (NAPE-PLD) mediates OEA synthesis (*15*). In *C. elegans*, *nape-1* and *nape-2* encode NAPE-PLD (*16*). The *nape-1(tm3860)* loss-of-function mutation suppressed the life-span extension in *lipl-4 Tg* and *lbp-8 Tg* by half (fig. S13 and table S1). Additionally, a loss-of-function mutant *lipl-4 (tm4417)* reduced the longevity of *lbp-8 Tg* by 68% (fig. S14), which supports the possibility that LIPL-4 activity promotes the generation of longevity-promoting OEA carried by LBP-8.

Direct treatment of WT worms with the OEA analog prolonged life span (Fig. 4G and table S1) and improved physical activity maintenance in aged animals (Fig. 4H). In contrast, neither *lipl-4 Tg* nor *lbp-8 Tg* life span was affected by OEA analog supplementation (Fig. 4G and table S1), which suggests that OEA may promote longevity by the same mechanism as occurs in *lipl-4 Tg* and *lbp-8 Tg* animals. Note that OEA supplementation decreased life span in the *nhr-80(tm1011)* mutant (fig. S15 and table S1), which indicated that OEA requires NHR-80 to promote longevity, and it can have detrimental effects in the absence of NHR-80. Thus, OEA may act as a lipid messenger to transduce lysosome-to-nucleus signaling in promoting longevity.

Overall, our studies suggest that bioactive lipid messengers and lipid chaperones link lysosomal activity and nuclear transcription to promote longevity. All the components of this lysosome-to-nucleus signaling pathway are well conserved in mammals. Notably, mammalian peroxisome proliferator–activated receptor α is activated by OEA (*17*), whereas NHR-80 is homologous to mammalian HNF4, which suggests that different nuclear receptors bind the same ligands despite divergent ligand-binding domains. Considering that FABPs are quite promiscuous in ligand binding (*4*), there may be other lipid molecules binding to LBP-8 and functioning in this longevity pathway.

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/347/6217/83/suppl/DC1
Materials and Methods
Figs. S1 to S16
Tables S1 and S2
References (*19*–*23*)

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Editor's Summary

Lysosomes signal the nucleus to control aging

Folick *et al.* propose a mechanism by which a lysosomal enzyme influences nuclear events that control longevity in the worm (see the Perspective by Shuo and Brunet). Increased expression of the lysosomal acid lipase LIPL-4 increased longevity, and this effect depended on the presence of the lysosomal lipid-binding protein LBP-8. LBP-8 acts as a chaperone that helps carry lipds to the nucleus. The authors identified the fatty acid oleoylethanolamide (OEA) as a potential signaling molecule whose transport to the nucleus could activate nuclear hormone receptors and transcription factors NHR-49 and NHR-80. The transcriptional targets of NHR-49 and NHR-80 in turn regulate longevity.

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