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Aging: Antagonistic Pleiotropy Supported by Gut Eating

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A new study has found that, in the nematode worm *Caenorhabditis elegans*, biomass conversion from the intestine to yolk, mediated by autophagy and insulin/IGF-1 signaling, promotes reproduction in early life but aging in late life.

Humans have a dream of a healthy life with extended longevity, as illustrated by diverse tales about the 'fountain of youth' across the world. A dictionary definition of aging is 'the process of growing old', but is getting old inevitable? Could we overcome the progress of aging? What is the mechanism of aging? Various approaches are being taken to address these questions, but the answers remain unclear. A series of longevity regulatory mechanisms have been discovered through molecular genetics studies in yeast, *Caenorhabditis elegans*, *Drosophila melanogaster* and mice, involving molecular pathways such as those involving insulin/IGF-1 signaling, mTOR signaling, AMPK signaling, mitochondrial signaling, sirtuins and signals from the reproductive system [1]. At the same time, theories have been proposed for understanding aging; for example, in the damage theory, aging is explained as an accumulation of cellular damage due to internal or external factors; and in the programmed theory, it is proposed that aging proceeds on a determined time schedule specific for a given species [2,3]. In this issue of *Current Biology*, Ezcurra *et al.* [4] report new evidence to support the hyper-function theory, aging is a result of which wild-type genes with positive effects in early life have negative effects in late life because of their continued action throughout life (hyper-function), and follows antagonistic pleiotropy in which genes evolve to enhance organism fitness in early life but allow or promote senescence later in life [5,6].

In their new study, Ezcurra *et al.* [4] found that in *C. elegans*, biomass conversion from the intestine to yolk promotes reproduction early in life but aging later in life, and that this is mediated by autophagy and insulin/IGF-1 signaling. In a survey of age-related senescent pathologies reported previously [7–12], including oocyte clustering, gonadal atrophy, pharyngeal deterioration, intestinal atrophy, and the accumulation of pseudocoelomic lipoprotein pools (PLPs), the authors found that the development of intestinal atrophy and PLPs strongly correlates with aging and they chose these two senescent phenotypes for further investigation. PLPs are known to contain yolk proteins, and their accumulation results from continued production of lipoproteins after cessation of egg-laying [8,9].

In their new work, Ezcurra *et al.* [4] show that PLP accumulation is accelerated upon knocking down, by RNA interference (RNAi), the oocyte yolk uptake receptor encoded by the gene *rme-2*, and that PLPs do not accumulate in males that do not produce yolk proteins. They further confirmed that PLPs co-localize with vitellogenin, which increases its level by seven-fold in early adulthood. Accordingly, they found that the triglyceride content level, together with the lipid organelle area, increase eight-fold in the body cavity of *C. elegans* over its lifetime. Together, the authors suggest that this age-dependent accumulation of PLPs is a result of the hyper-function of lipoprotein production and is an interesting form of pathological senescent obesity in *C. elegans* (Figure 1).

Strikingly, the seven-fold increase of vitellogenin results in it constituting 30–40% of total worm proteins. How does *C. elegans* supply this large amount of lipoproteins later in life when their feeding almost ceases completely after day 9 of adulthood [13]? In *C. elegans*, the intestine not only acts as a digestive organ but also plays crucial roles in lipid metabolism, including yolk production. Given the close correlation between intestinal atrophy and PLP accumulation during aging, Ezcurra *et al.* [4] hypothesized that the intestine consumes its own biomass to sustain the capacity for yolk production. In support of this hypothesis, they found that inhibiting yolk production suppresses not only PLP accumulation but also intestinal atrophy. They also found that, although PLP accumulation and intestine atrophy are not observed in wild-type males, these two senescent pathologies could both be induced by introducing ectopic yolk production in males. On the other hand, the age-associated increase of bacterial growth inside the intestinal lumen is not related to the induction of intestinal atrophy.

How, then, is the intestinal biomass converted to yolk in PLPs? Ezcurra *et al.* [4] discovered a new role of autophagy in regulating this conversion. Autophagy is a physiological process that recycles the damaged cellular components through the action of the products of a set of *atg* genes in *C. elegans*, and is known to be required for the longevity-promoting effects associated with insulin/IGF-1 signaling, mTOR signaling, sirtuins, and germline signals [14]. In this work, the authors, however, showed that the inactivation of the autophagy gene *atg-13* suppresses intestinal atrophy, PLP accumulation, and lipid redistribution at the same time, which suggests the requirement of autophagy in stimulating these age-associated pathologies.

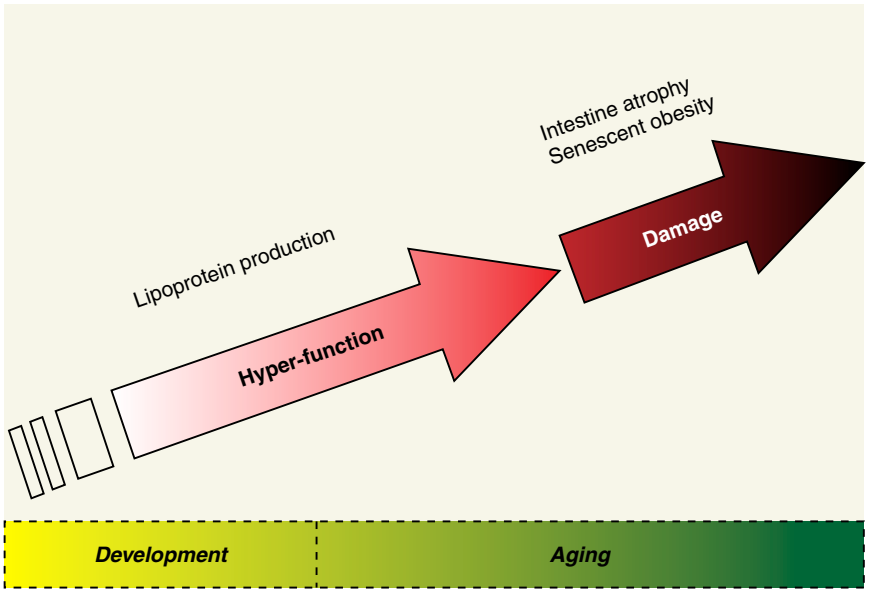

Figure 1. Run-on wild-type function promotes senescent morphologies.
In early lifetime, lipoprotein production uses gut biomass to enhance reproduction. However, age-dependent accumulation of PLPs, a result of hyper-function of lipoprotein production, causes senescent pathologies including intestine atrophy and senescent obesity to restrict late life fitness. (Adapted from Blagosklonny *et al.* [6].)

Furthermore, the fact that intestine-specific restoration of *atg-13* in its mutant resumes intestinal atrophy further supports the cell-autonomous action of autophagy.

Ezcurra *et al.* [4] also followed intracellular markers for the Golgi apparatus and early, late and recycling endosomes in the intestine during aging to examine autophagic consuming of endomembranes. They found that Golgi but not endosomal labeling is reduced with increasing age, and this age-associated decrease can be rescued by RNAi inactivation of *atg-13*. From these results, the authors conclude that the gut-to-yolk biomass conversion mediated by autophagy leads to senescent multimorbidity. Their new findings suggest that autophagy enhances the development of age-associated pathologies in *C. elegans*, seemingly contrary to the known protective functions of autophagy against aging [14,15]. Indeed, the authors observed a negative correlation between intestinal atrophy and lifespan, and further showed that RNAi inactivation of *atg-13* extends lifespan in a condition dependent manner at 25°C. On the other hand, knocking down yolk accumulation during development in the *atg-13* mutant leads to sterile phenotypes. Thus, the gut-to-yolk biomass conversion mediated by intestinal autophagy improves early-life reproductive fitness and exacerbates late-life senescent pathologies, suggesting an antagonistic pleiotropic effect.

One of the best-characterized longevity regulatory mechanisms is mediated by the *daf-2*/insulin/IGF-1 receptor signaling pathway [1]. The *daf-2* mutation extends lifespan and attenuates age-associated senescent pathologies, but shows a trade-off in reproduction [1,8,16]. Ezcurra *et al.* [4] suggest that the gut-to-yolk biomass conversion could explain the longevity effect of the *daf-2* mutation that negatively impacts reproduction by reducing yolk production but extends lifespan by delaying senescent pathologies. Therefore, *daf-2* is introduced as a gene that enhances reproductive fitness in early life, and consequently exaggerates senescent pathologies in late life to limit lifespan. This hyper-function mechanism may be typical for insulin/IGF-1 signaling, given its dual functions in driving tumor development in unfertilized oocytes by run-on embryogenesis and gonad atrophy by run-on germline apoptosis [11,17,18].

In support of their ideas, Ezcurra *et al.* [4] found that age-associated senescent morphologies are attenuated in the long-lived *daf-2* mutant, which is dependent on the FoxO transcription factor encoded by *daf-16*. Furthermore, in another long-lived *glp-4* mutant that lacks germline development, intestinal atrophy is also delayed in a *daf-16* dependent manner. Together, the authors suggest DAF-16/FoxO as a key mediator of the gut-to-yolk biomass conversion. Do DAF-16/FoxO and autophagy cooperate or act independently? The answer is not completely clear yet, but the authors found that, in the *daf-16* mutant, the inactivation of autophagy genes could still delay intestinal atrophy and extend lifespan, which would favor a parallel action of these two factors.

The new paper of Ezcurra *et al.* [4] provides new insights into the hyper-function theory, by revealing pathological senescent obesity from a continued action of a wild-type function to enhance early life reproduction and by characterizing the surprising role of autophagy in this antagonistic pleiotropic effect. Although there are different views regarding the *daf-2*-mediated longevity mechanism and the protective role of autophagy against aging, the hyper-function theory as supported in this new work should be also taken into consideration. As the authors mention, bone erosion in lactic mammals to supply sufficient calcium in milk is another example for such a hyper-function involving a wild-type function [19]. Further, antagonistic pleiotropy is also related to maintain polymorphic disease alleles in human [20]: for example, Huntington's disease is an autosomal dominant neurodegenerative disorder, but the patients show increased fecundity and decreased risk of certain cancers. Thus, the hyper-function theory with antagonistic pleiotropy can be applicable in more natural mechanisms including aging and disease models.

REFERENCES

1. Kenyon, C. (2010). The genetics of ageing. Nature *464*, 504–512.
2. Jin, K. (2010). Modern biological theories of aging. Aging Dis. *1*, 72–74.

3. López-Otín, C., Blasco, M.A., Partridge, L., Serrano, M., and Kroemer, G. (2013). The hallmarks of aging. Cell *153*, 1194–1217.

4. Ezcurra, M., Benedetto, A., Sornda, T., Gilliat, A.F., Au, C., Zhang, Q., van Schelt, S., Petrache, A.L., Wang, H., de la Guardia, Y., *et al*. (2018). C. elegans eats its own intestine to make yolk leading to multiple senescent pathologies. Curr. Biol. *28*, 2544–2556.

5. Williams, G.C. (1957). Pleiotropy, natural selection, and the evolution of senescence. Evolution *11*, 398–411.

6. Blagosklonny, M.V. (2006). Aging and immortality: quasi-programmed senescence and its pharmacologic inhibition. Cell Cycle *5*, 2087–2102.

7. Hughes, S.E., Huang, C., and Kornfeld, K. (2011). Identification of mutations that delay somatic or reproductive aging of Caenorhabditis elegans. Genetics *189*, 341–356.

8. Garigan, D., Hsu, A.L., Fraser, A.G., Kamath, R.S., Ahringer, J., and Kenyon, C. (2002). Genetic analysis of tissue aging in Caenorhabditis elegans: a role for heat-shock factor and bacterial proliferation. Genetics *161*, 1101–1112.

9. Herndon, L.A., Schmeissner, P.J., Dudaronek, J.M., Brown, P.A., Listner, K.M., Sakano, Y., Paupard, M.C., Hall, D.H., and Driscoll, M. (2002). Stochastic and genetic factors influence tissue-specific decline in ageing C. elegans. Nature *419*, 808–814.

10. McGee, M.D., Weber, D., Day, N., Vitelli, C., Crippen, D., Herndon, L.A., Hall, D.H., and Melov, S. (2011). Loss of intestinal nuclei and intestinal integrity in aging C. elegans. Aging Cell *10*, 699–710.

11. de la Guardia, Y., Gilliat, A.F., Hellberg, J., Rennert, P., Cabreiro, F., and Gems, D. (2016). Run-on of germline apoptosis promotes gonad senescence in C. elegans. Oncotarget *7*, 39082–39096.

12. Palikaras, K., Mari, M., Petanidou, B., Pasparaki, A., Filippidis, G., and Tavernarakis, N. (2017). Ectopic fat deposition contributes to age-associated pathology in Caenorhabditis elegans. J. Lipid Res. *58*, 72–80.

13. Huang, C., Xiong, C., and Kornfeld, K. (2004). Measurements of age-related changes of physiological processes that predict lifespan of Caenorhabditis elegans. Proc. Natl. Acad. Sci. USA *101*, 8084–8089.

14. Rubinsztein, D.C., Mariño, G., and Kroemer, G. (2011). Autophagy and aging. Cell *146*, 682–695.

15. Gelino, S., Chang, J.T., Kumsta, C., She, X., Davis, A., Nguyen, C., Panowski, S., and Hansen, M. (2016). Intestinal autophagy improves healthspan and longevity in C. elegans during dietary restriction. PLoS Genet. *12*, e1006135.

16. DePina, A.S., Iser, W.B., Park, S.S., Maudsley, S., Wilson, M.A., and Wolkow, C.A. (2011). Regulation of Caenorhabditis elegans vitellogenesis by DAF-2/IIS through separable transcriptional and posttranscriptional mechanisms. BMC Physiol. *11*, 11.

17. Wang, H., Zhao, Y., Ezcurra, M., Benedetto, A., Gilliat, A.F., Hellberg, J., Ren, Z., Galimov, E.R., Athigapanich, T., Girstmair, J., *et al*. (2018). A parthenogenetic quasi-program causes teratoma-like tumors during aging in wild-type C. elegans. Aging Mech. Dis. *4*, 6.

18. McGee, M.D., Day, N., Graham, J., and Melov, S. (2012). cep-1/p53-dependent dysplastic pathology of the aging C. elegans gonad. Aging *4*, 256–269.

19. Hopkinson, J.M., Butte, N.F., Ellis, K., and Smith, E.O. (2000). Lactation delays postpartum bone mineral accretion and temporarily alters its regional distribution in women. J. Nutr. *130*, 777–783.

20. Carter, A.J., and Nguyen, A.Q. (2011). Antagonistic pleiotropy as a widespread mechanism for the maintenance of polymorphic disease alleles. BMC Med. Genet. *12*, 160.

Animal Communication: Learning by Listening about Danger

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A variety of animals eavesdrop and learn to use other species' alarm calls to avoid predators. Superb fairy-wrens, when hearing unfamiliar calls together with known alarm calls, can learn to associate these new calls with danger.

Hearing someone scream "Fire!" immediately conjures up a vision of bright orange flames, perhaps even a house or apartment building burning down. You might not have the same reaction to hearing "Dóiteáin", unless you happen to live in Galway, Ireland. But if you have a friend that speaks Gaelic, it might be useful to know that this means the exact same thing as "Fire!" before your own house burns down. Each animal species speaks a different 'language', yet it is not uncommon for animals to listen in on the vocal signals of others. Eavesdropping between different species, 'heterospecifics', has been documented in many different species, from insects to whales. The majority of eavesdropping examples have focused on alarm calls and it isn't hard to imagine how knowing that a predator is nearby would be useful information for other species with similar ecologies and shared predators. There are dozens of examples of animals eavesdropping on heterospecific alarm calls [1], both across closely related (e.g., a songbird eavesdropping on another songbird's alarm calls) and unrelated species (e.g., a songbird eavesdropping on a monkey's alarm calls). But how do animals actually know what the calls of other species mean? In a new paper in this issue of *Current Biology*, Dominique Potvin, Robert Magrath and colleagues [2] document for the first time an intriguing method by which an animal learns to recognize other species calls as alarm calls.

Alarm calls can transmit important information about predators [3–6]