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Eat your proteins—live longer

Doctors suggest that decreasing stress, reducing our caloric intake and exercising will extend our lives. Eating our protein, literally, through a process called autophagy, may also help us live longer.

Autophagy is an environmentally and hormonally regulated cellular process in which portions of the cell cytoplasm are sequestered into double-membraned autophagosomes and delivered to degradative organelles for breakdown and recycling. For example, during starvation, autophagy generates amino acids from cytoplasmic polypeptides for use in the synthesis of proteins essential for survival. Autophagy also plays a role in developmental processes that require substantial cellular or tissue remodeling. Furthermore, autophagy in mammals is induced by protein caloric restrictions, which, in turn, may extend life. Now, Melendez *et al.* (*Science*, **301**, 1387–1391; 2003) show that the reversible arrest of *Caenorhabditis elegans* in dauer, a stage of development in which metabolism downshifts and lifespan increases, requires a functional autophagy process.

Entry into dauer is controlled by different cell signaling, including insulin-like pathways. A loss-of function mutation in *daf-2*, an insulin-like tyrosine kinase receptor gene, produces a constitutive dauer phenotype in *C. elegans*. During growth at higher temperatures these worms exhibit the distinct morphological features observed during dauer larval development. Photomicrographs of wild-type and mutant animals grown at 25 °C show that *daf-2* mutants have a constricted and elongated body and pharynx (top row) and a lateral rigid cuticle (bottom row, arrow). Furthermore, staining for fat deposition (middle row) indicates that *daf-2* mutant worms have increased fat storage. Close examination of seam cells, a hypodermal cell type known to be important for some of the morphological changes in dauer, shows that mutant worms have a significant increase in late-stage autophagic vacuoles (arrow heads).

To determine if autophagy was essential for dauer arrest, Melendez *et al.* used RNA interference to knockdown autophagy genes, specifically *(bec-1)*, in the *daf-2* worms. These animals have an abnormal dauer phenotype in which the body and pharynx (third column) are less constricted and elongated than in worms with normal dauer (second column). Furthermore, the *daf-2;bec-1 (RNAi)* animals with abnormal dauer store less fat than *daf-2* mutants (second row), and their seam cells (third row) have no autophagic vacuoles . These results indicate that *bec-1* is essential for the formation of dauer. Melendez *et al* show that at least five other *C. elegans* orthologs of yeast and mammalian autophagy genes are required for normal dauer morphogenesis in these worms.

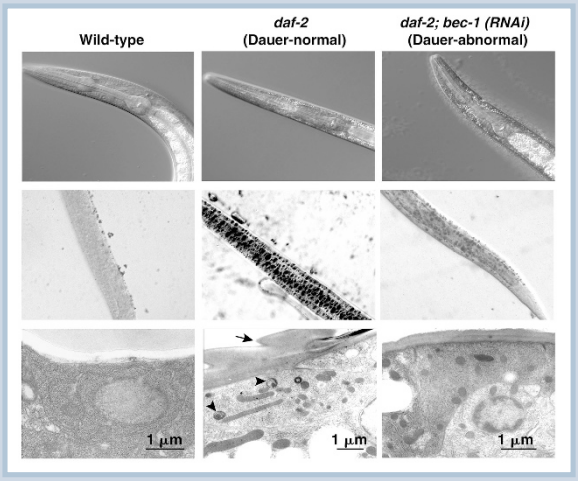

Figure modified and printed with permission from Melendez *et al.*

Are these autophagy genes, specifically *bec-1,* also important for extension of lifespan? During reproductive growth (15 °C) *daf-2* worms live longer (~48 days) than wild-type nematodes (~28 days). Animals with an inactive autophagy process, *daf-2;bec-1(RNAi)* worms, have shortened lifespans (~24 days). Furthermore, normal dauer worms can live at 25 °C for extended periods and resume growth once they return to non-stressful environment. In contrast, animals with a defect in autophagy die within two days and never recover from stress when returned to reproductive growth conditions. Hence, both lifespan extension and maintenance of dauer arrest requires *bec-1* and active autophagy.

Yeast and humans have homologs of *bec-1* and use the autophagy process during development and stress responses. The data presented by Melendez *et al.* suggest that in eukaryotes such as ourselves, eating our own proteins may regulate normal lifespan processes controlled by the insulin-like signaling pathway, as it does in nematodes. The molecular mechanism by which the autophagic process helps us live longer is not yet understood but is certain to pique the interest of many scientists.

Evelyn Jabri