

Insulin-like signaling pathway

The secret of genius is to carry the spirit of the child into old age, which means never losing your enthusiasm.
—Aldous Huxley

A&S300-002 Jim Lund

Genetic influences on aging

Genes influence aging

- Comparative and evolutionary studies.
- Population studies
 - Rose's *Drosophila* studies
 - Similar studies in other organisms.

Could single gene mutations that affect the rate of aging be found?

age-1

The first single gene mutation that extends lifespan was found in *C. elegans*.

Friedman and Johnson, 1987.

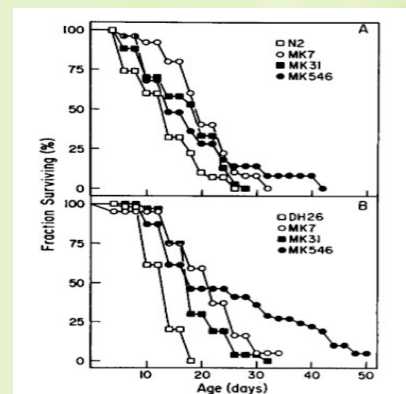
A Mutation in the *age-1* Gene in *Caenorhabditis elegans* Lengthens Life and Reduces Hermaphrodite Fertility

Cloned

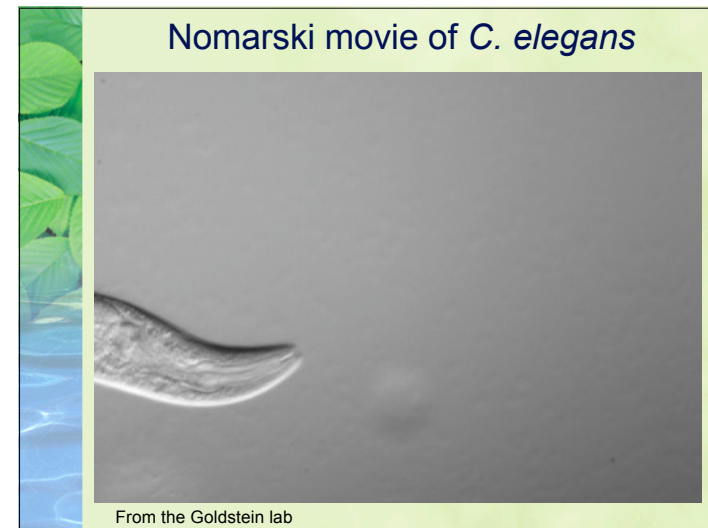
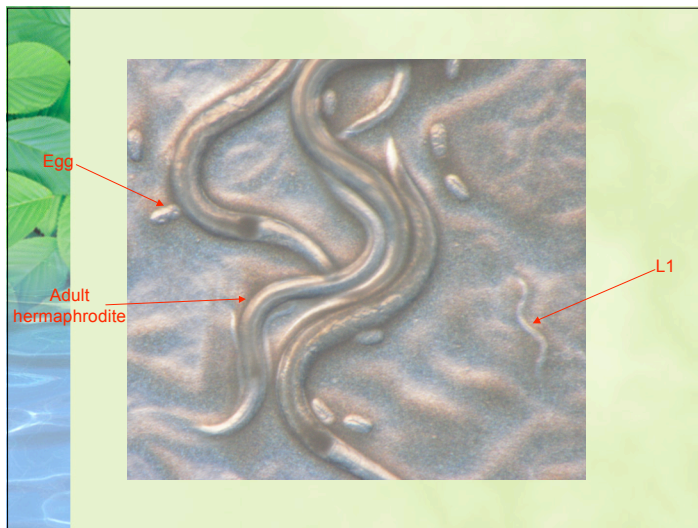
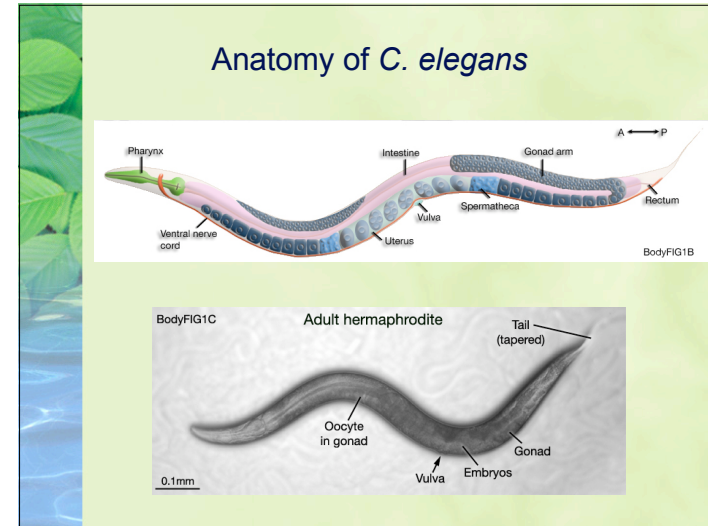
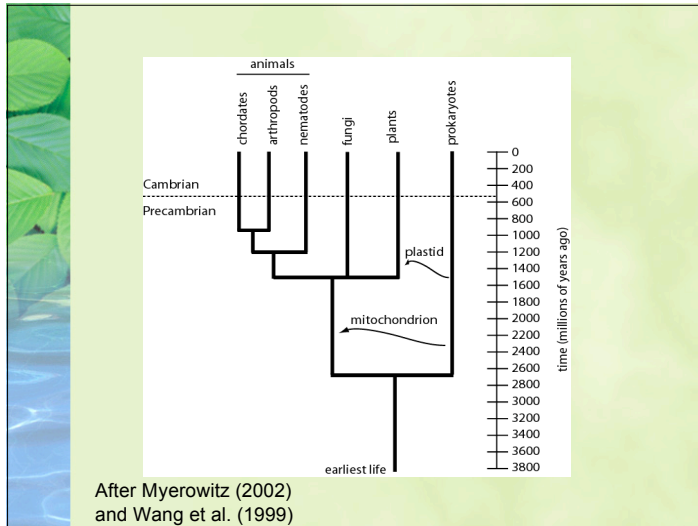
Morris et al., 1996

A phosphatidylinositol-3-OH kinase family member regulating longevity and diapause in *Caenorhabditis elegans*.

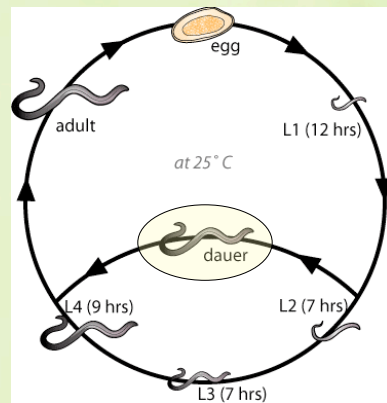
age-1



Lifespan 50% longer than wild-type N2 worms.

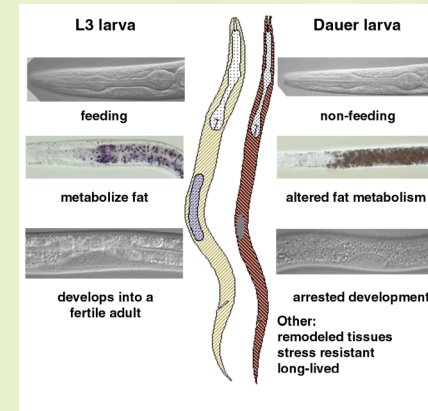


C. elegans life cycle



Dauer larvae live at least 7 times longer than normal

C. elegans larval phenotypes



Dauer larvae live at least 7 times longer than normal

Courtesy of M.Tan

Kenyon et al., 1993: *daf-2*

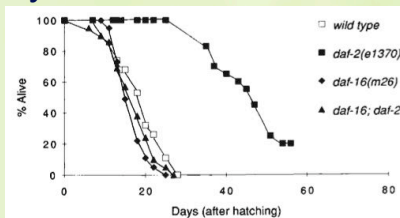


FIG. 4 The longevity of *daf-2* mutants is blocked by *daf-16(m26)*, a dauer-defective mutation in a gene that acts downstream of *daf-2* in dauer formation. Lifespans were determined in parallel for N2, *daf-2(e1370)* and *daf-16(m26)* single mutants as well as *daf-16(m26); daf-2(e1370)* double mutants. Mean lifespans were 17 days for *m26* ($n = 37$); 17 days for *m26; e1370* ($n = 42$); and 19 days for N2 ($n = 19$). For *daf-2(e1370)*, $n = 20$. The lifespan differences between N2, *daf-16* and *daf-16; daf-2* were not significantly different from one another (for example, for N2 versus *daf-16*, $\chi^2 = 1.68$; $0.19 < P < 0.21$), whereas differences between these three strains and *daf-2* were statistically significant (for example, for *daf-2* versus *daf-16*, $\chi^2 = 50.6$; $P < 0.00001$).

Mean lifespan 130% longer than wild-type N2 worms.

Kenyon et al., 1993: *daf-2*

daf-2:

- A member of the Daf gene class, a gene that controls dauer formation in *C. elegans*.

- Acts through downstream gene *daf-16*.

- *daf-2; daf-16* double mutants have wt lifespans.

Dorman et al., 1995:

- *daf-2(e1370); age-1(hx546)* mutant does not live longer than the *daf-2* single mutant.

- *age-1* lifespan extension also dependent on *daf-16*.

Daf genes

Malone et al., 1996:

- *Daf-28*, 12-13% lifespan extension.
- Upstream of *daf-16*.

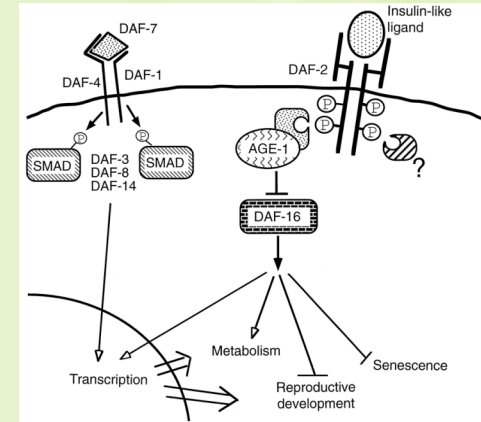
***age-1* cloned:**

- A phosphatidylinositol-3-OH kinase family member regulating longevity and diapause in *Caenorhabditis elegans* (Morris et al., 1996).

***daf-2* cloned:**

- Homolog to human Insulin receptor and IGF-1 (Kimura et al., 1997), Ruvkun lab.

Daf pathways: TGF- β and Insulin-like



Kimura et al., 1997

Daf genes

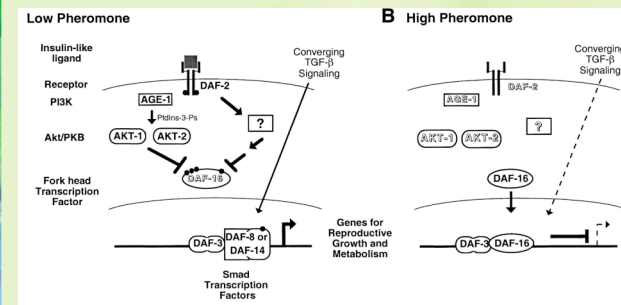
***daf-16* cloned:**

- An HNF-3/forkhead family transcription factor (Ogg et al., 1997; Lin et al., 1997), Ruvkun and Kenyon labs.

***akt-1* and *akt-2*:**

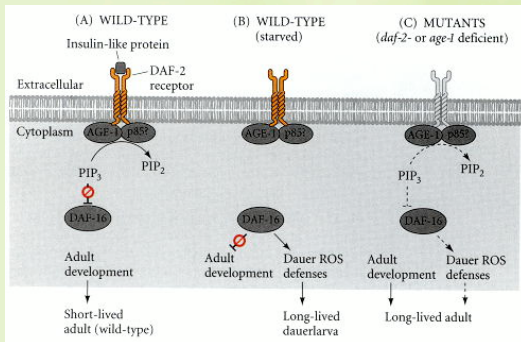
- Two Akt/PKB homologs, serine/threonine kinases, are downstream of *age-1* in the pathway (Paradis and Ruvkun, 1998).
- Found by homology: Akt/PKB known to be activated by phosphoinositol-3-kinase in human.

Daf pathways with *akt-1* and *akt-2*



Paradis and Ruvkun, 1998

C. elegans insulin-like signaling pathway



Effect of insulin-like signaling on lifespan and development.

Daf genes

daf-18 cloned:

- A homolog of the human tumor suppressor PTEN.
- Acts between AGE-1 and AKT (Ogg and Ruvkun, 1998).

ins-18/Ceinsulin-1:

- A homolog of human insulin.
- Activates signaling through *daf-2*, the insulin-like receptor.

C. elegans has 38 insulin homologs, but only one homolog of the insulin receptor!

Insulin-like signaling pathway in *C. elegans*

