

Worm Breeder's Gazette 17(2)

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2002 Regional Meetings

Theresa Stiernagle, Bob Herman

Caenorhabditis Genetics Center, University of Minnesota, 250 Biological Sciences Center,
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2002 Regional Meetings

East Coast Worm Meeting
University of New Hampshire, Durham, NH
14 - 16 June, 2002
Organizer: John Collins, Department of Biochemistry and Molecular Biology, UNH.

European Worm Meeting
Paestum, (Salerno), Italy
18 - 21 May, 2002

The 3rd Japanese C. elegans Meeting
Nagoya University, Furo-cho, Chikusa-ku, Nagoya, Japan
6-8 August 2002
Organizer: Shin Takagi

Midwest Worm Meeting
St. Louis, Missouri
28 - 30 June, 2002
Organizer: Kerry Kornfeld

West Coast C. elegans Meeting
UCSD, San Diego, California, USA
10 - 13 August, 2002

European C. elegans meeting

The European C. elegans meeting 2002 will be held in Paestum, Italy from late afternoon of Saturday, May 18 until noon of Tuesday, May 21. The format of the meeting will be very similar to the previous ones.

The organisers are :
Paolo Bazzicalupo, Napoli, Italy (Local Organizer)
Thierry Bogaert, Ghent, Belgium
Barbara Conradt, Martinsried, Germany
Mario de Bono, Cambridge, UK
Marie-Anne Felix, Paris, France
Rik Korswagen, Utrecht, The Netherlands

The deadline for abstract submission, registration and payment will be around mid March. We are going to set up a website for information and registration and its address will appear on Leon Avery website. For more information, contact: ewm2002@iigb.na.cnr.it

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Theresa Stiernagle, Bob Herman

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1445 Gortner Avenue, St. Paul, MN 55108-1095

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New and improved *pie-1*-based vectors for maternal expression of transgenes

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We previously reported the construction of a *pie-1*-based vector for maternal expression of GFP fusion proteins in the germline and early embryos [Worm Breeder's Gazette 15(5): 18 (February 1, 1999)]. This vector was modified by Praitis et al., 2001 for use in bombardment-mediated transformation. We have now created new versions of these vectors that are compatible with Invitrogen's Gateway Recombination Cloning Technology. This technology bypasses the need for restriction enzymes and allows for the directional cloning of virtually any ORF into the *pie-1* vectors.

For expressing ORFs in the germline:

pID2.02:

unc-119 rescuing fragment/*pie-1* promoter-gateway destination cassette B-3'utr of *pie-1*
(suitable for bombardment, Praitis et al., 2001)

For expressing GFP-ORF fusions in the germline:

pKR2.40:

pie-1 promoter-GFP- gateway destination cassette B -3'utr of *pie-1*
(suitable for complex arrays, Kelly et al., 1997)

pID3.01B:

unc-119 rescuing fragment / *pie-1* promoter-GFP- gateway destination cassette B - 3'utr of *pie-1*
(suitable for bombardment, Praitis et al., 2001)

Anyone interested in these vectors should write to Geraldine at gseydoux@jhmi.edu.

Rab gene nomenclature

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Rab genes are a large family of small GTPases that regulate vesicular trafficking in cells. In vertebrates around 60 Rab genes have been identified. *C. elegans* contains at least 28 Rab genes. Since the identification of vertebrate Rabs is now essentially complete, it is now possible to relatively confidently define the vertebrate homolog of most *C. elegans* Rab genes (Pereira-Leal and Seabra. 2001 J. Mol. Biol. 313 889-901). At the request of Jonathan Hodgkin, I have now assigned formal names to the 22 Rab genes for which a clear vertebrate homolog can be identified. Six remaining putative Rab genes have not been assigned names. The assignments were made using the analysis of Pereira-Leal and Seabra as a foundation. I then confirmed that the predicted coding regions were very likely accurate by identifying the *C. briggsae* homolog (which in most cases is >95% identical to the *C. elegans* protein). This analysis revealed that several of the predicted Rab sequences in the database are incorrect (specifically, rab-8, rab-33 and rab-39). The rab-28 gene structure remains questionable as the gene is longer than most Rab genes by 25 amino acids and the N-terminal region is much less highly conserved than the rest of the gene. However, the proper structure is not obvious from my analysis. A table compiling general information on the protein sequences of both *C. elegans* and *C. briggsae* Rab homologs, representative cDNAs, and accession numbers for both genomic and protein sequences is available at <http://thalamus.wustl.edu/nonetlab/NMimages/genedatafold/Rabgenes.html>

Proposed *C. elegans* *rab* gene nomenclature

Proposed name	cosmid name	vertebrate homolog
<i>rab-1</i>	C39F7.4	Rab1
<i>rab-2</i>	F53F10.4	Rab2
<i>rab-3</i>	C18A3.6	Rab3
	not present	Rab4
<i>rab-5</i>	F26H9.6	Rab5
<i>rab-6.1</i>	F59B2.7	Rab6
<i>rab-6.2</i>	T25G12.4	Rab6
<i>rab-7</i>	W03C9.3	Rab7
<i>rab-8</i>	D1037.4	Rab8
	not present	Rab9
<i>rab-10</i>	T23H2.5	Rab10
<i>rab-11.1</i>	F53G12.1	Rab11
<i>rab-11.2</i>	W04G5.2	Rab11
<i>rab-14</i>	K09A9.2	Rab14
<i>rab-18</i>	Y92C3B.3	Rab18
<i>rab-19</i>	Y62E10A.9	Rab19
<i>rab-21</i>	T01B7.3	Rab21
<i>rab-27</i>	Y87G2A.4	Rab27
<i>rab-28</i>	Y11D7A.4	Rab28
<i>rab-30</i>	Y45F3A.2	Rab30
<i>rab-33</i>	F43D9.2	Rab33
<i>rab-35</i>	Y47D3A.25	Rab35
<i>rab-37</i>	W01H2.3	Rab37
<i>rab-39</i>	D2013.1	Rab39
Not assigned	C33D12.4	
Not assigned	4R79.2	
Not assigned	K02E10.1	
Not assigned	F11A5.4	
Not assigned	F11A5.3	
Not assigned	C56E6.2	

The volume of freezing solution affects survival rate

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Introduction

In reverse genetics using transposon or chemical mutagen, recovery from freezing stock is one of the important steps to isolate deletion mutants. Effective isolation of deletion mutants requires a "good" library, which has a high survival rate as same as a high mutation rate. Although mutagenesis and PCR conditions have been optimized previously, the effect of freezing condition on the survival rate has not been fully investigated. Here, we report that the volume of freezing solution affects survival rate. Particularly, the survival rate dramatically decreased in small volume.

Materials and Methods

N2 Bristol strain was used. Three or four adult worms were placed on a seeded 60 mm NGM plate and cultured at 20 °C for 5 days until bacterial lawn became almost invisible. Eight or ten plates were used for experiment 1 or experiment 2. Freshly starved L1 larvae (and adults) were washed from the plates with M9 buffer into a 15 ml plastic tube. After low speed centrifugation, the supernatant was removed and an equal volume of 2 x freezing solution was added. The aliquot (worm solution) was mixed gently and transferred into 2 ml freezing vials. In experiment 1, each set of vials contains various volume of worm solution, but all vials contain about 50,000 worms. In experiment 2, each set of vials contains various volume of worm solution, in which a density of worms was about 50 worms/ μ l. The vials were placed in holes drilled into a styrofoam block without a lid. The block was placed in the -80 °C freezer for overnight. In the next day, vials were thawed and the contents of each tube were plated onto a seeded 60 mm NGM plate. Two days later, the number of surviving worms on each plate was counted and the survival rate was determined (average \pm SD, n=3).

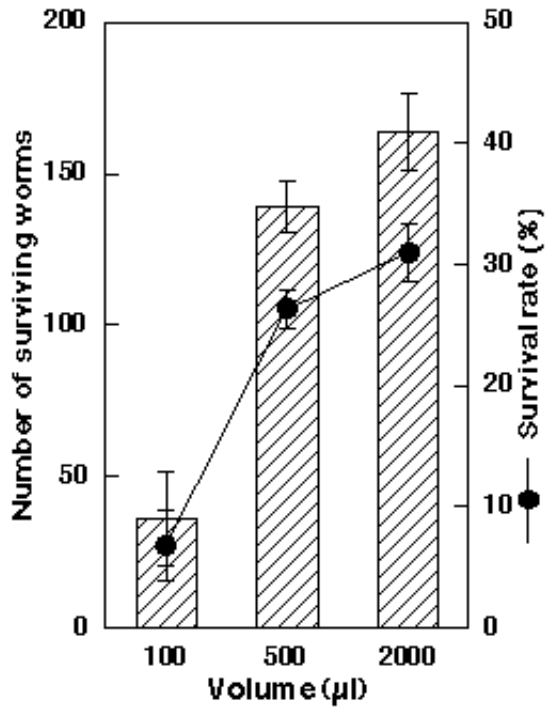
Results and Discussion

Small volume (100 μ l) of worm solution showed the lowest survival rate (Experiment 1). The survival rate of 100 μ l was 4 times lower than those of 500 μ l or 2000 μ l. In experiment 1, volume of worm solution and density of worms were both changed. In experiment 2, survival rate were determined in various volumes with the same worm density to determine which factor affects survival rate. Small volume (100 μ l) also showed the lowest survival rate, and 500 μ l of volume showed a relatively high survival rate but large SD (Experiment 2). Over 1000 μ l of volume resulted in stable and high survival rates. A relatively low density of worms seems to give a better survival rate.

Standard freezing methods recommend that the rate of temperature decrease should be slow (about 1 °C/min). We assume that the rate of temperature decrease depends on the volume of worm solution and that the temperature in small volume probably decrease rapidly. On construction of freezing library of mutagenized worms, 200 μ l PCR tubes or 96-well plates were often used to save the space in a freezer. However, our results showed that small volume of freezing worm solution would result in a large decrease of survival rate. We suggest that the rate of temperature decrease should be controlled carefully, in order to achieve better efficiency for isolating deletion mutants from the frozen library with small volume.

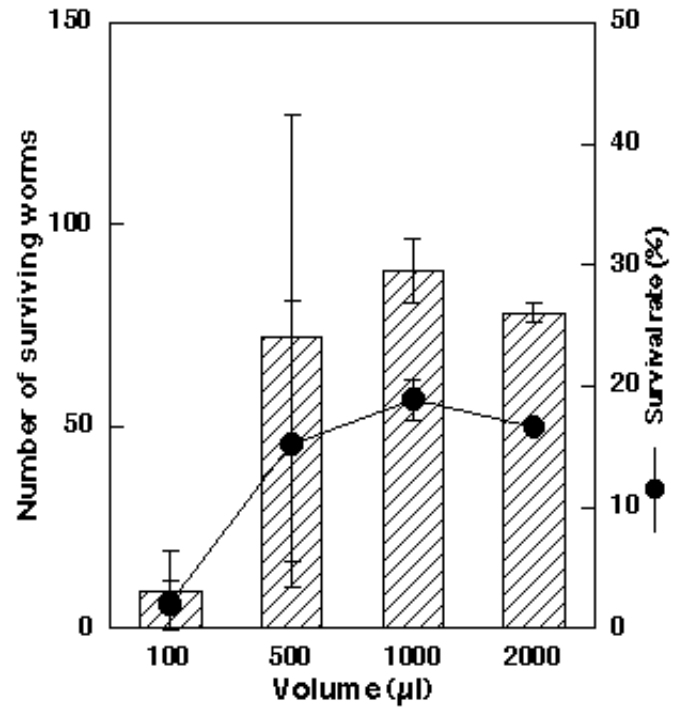
Experiment 1

Volume of worm solution	Number of surviving worms	Survival rate
100 μ l	36.2 \pm 15.4	6.9 \pm 2.9
500 μ l	139.0 \pm 8.3	26.4 \pm 1.6
2000 μ l	163.7 \pm 12.5	31.0 \pm 2.4



Experiment 2

Volume of worm solution	Number of surviving worms	Survival rate
100 μ l	9.4 \pm 9.6	2.0 \pm 2.0
500 μ l	71.9 \pm 55.4	15.3 \pm 11.8
1000 μ l	88.7 \pm 8.0	18.9 \pm 1.7
2000 μ l	78.1 \pm 2.4	16.7 \pm 0.5



A Potential Function for the Carboxy-Terminal Domain of SMG-4 as a Nuclear Export Sequence Regulated by Phosphorylation

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Since the identification of *smg-4*, questions of how the domains of the protein may function to mediate mRNA surveillance have remained. In spite of the beautiful results with the human orthologues, hUpf3p and hUpf3-X, showing these nucleocytoplasmic shuttling proteins bind with Y14 to mRNAs 20nt upstream of exon-exon boundaries [Kim, V. N. et al. (2001) *Science* 293: 1832-1836, and Lykke-Andersen, J. et al. (2001) *Science* 293: 1836-1839], and in an RNP in association with CBP80 help mediate a 'pioneer' round of translation [Ishigaki Y et al. (2001) *Cell* 106:607-617], the domains responsible for these activities are not yet fully elucidated. Although overall sequence identity between the worm and human proteins is only 20%, there is 64% sequence similarity over one 336 a.a. stretch, and many potential functional domains are highly conserved. Interestingly, part of the most conserved domain (Aronoff, R. et al. (2001) *Gene* 268:153-164), similar to an RNP-1 -like RNA binding motif and essential for rescue of *smg-4* mutant animals, is spliced out from one variant, hUpf3delta, of the two human genes. Complex regulation of the encoded protein products is probable.

The proline rich carboxy-terminal domain of SMG-4 is particularly intriguing, with its alternatively spliced extension and some similarity to a regulatory domain of MAP-4, containing hallmarks of a substrate for phosphorylation. The recent report of a proline rich domain responsible for nuclear export that is regulated by phosphorylation [Catez et al. (2002) *MCB* 22: 1126-1139], caused me to reexamine the SMG-4 sequence. It is clear that sequence identity (although only 15.5% overall) is shared between the two proteins (see Figure), and conserved elements include potential MAP Kinase sites. Perhaps when *smg-4* is phosphorylated in this domain, it will be actively exported along with its associated RNP to the cytoplasm. Whether the virus coopts the mRNA surveillance machinery in its lifecycle is a new question raised by this apparent similarity.

```

1  M T D S K D G H V K V V L R R L P K Y M T E H E V L E Q I S P L P E E V I G T Y smg-4
1  M S Q T - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - us11

41  F H P A N F S F D R C A Y A T L T V N F S E Y C D S M M E F E R R F D G Y I F V smg-4
5  - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - - us11

81  D S R G N D S A A V V E A A S N Q N F A K C D R N R M K E D T R V G A I L T D K smg-4
5  - - - - - Q P P A P V G P G D P D V Y L K - - - - - - - - - - - - - - - - - - us11

121 Y Y L D F C K K L E E E R A I P I L T L E Q Q I R K L N Q P D D A R T Q I D K M smg-4
21 - - - - - - - - - - - - - - - G V P S A G M - - H P R G V H A P R - - - - - - - - us11

161 E T P L V K Y F F E K E T G K R R D Y D A R R Q R R D E K R A E K R D K V D K F smg-4
37 - - - - - - - - - - - - - - - G H P R M I S G P P Q R G D N D Q A A G Q C G - - - - us11

201 E K H K N V L D I L M K P S V P M A S T S A T T S K K D L K K E K P M T E K E K smg-4
60 - - D S G L L R V G A D T T I S K P S E A V - - - - - - - - - - - - - - - - - - us11

241 E R W E K Q D A K R K E R N M I R K Q K F L D E K K K K H E E R E Q D G P R V P smg-4
80 - - - - - - - - - - R P P T I P R T P R V P R E P R V P R P P R E P R E P R V P us11

281 R D K K K E R L A K P P R P S P A K T V G E Q Q G E D W I K K L T D P K S A P M smg-4
110 R A P R D P R V P R D P R D P R - - - - - - - - - - - - - - - - Q P R S P R - us11

321 K K K H D L S V T T K L N K E T D T R P R T A P S S T K L P T R A T T S N H P K smg-4
132 - - - - - - - - - - - - - - - E P R S P R E P R S P R E P R T P R T P R E P R us11

361 R P S T A P N H smg-4
156 T A R G S V us11

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Figure: Alignment of HSV-1 US11 protein and SMG-4 protein.

If the serine at position 129 of the US11 sequence is mutated to phenylalanine the protein is retained in nucleoli.

Worm finance

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Hodgkin and Barnes (*Proc R Soc Lond B Biol Sci* **246**(1315): 19-24, 1991) described a weak *tra-3* mutant that produces 53% more progeny than the wild-type. This large increase in productivity comes at a price: a 4% increase in the minimum life cycle. The *tra-3* mutant produces sperm for 2.6 hours longer than the wild-type, explaining both the large increase in average brood size (from 327 to 499) and the small increase (from 64.4 to 67.0 hours) in life cycle. Once oogenesis begins, progeny are produced at a rate of 5.3 per hour until the sperm supply gives out.

How can the costs and benefits of a trade-off like this be evaluated? The problem is precisely analogous to one that arises in the field of corporate finance. Suppose you have a choice between two investments. Each requires an initial outlay of \$1.00. The first (wild-type) will return \$5.30 per hour after a delay of 64.4 hours up to a total of \$327. The second (*tra-3*) will return \$5.30 per hour after a delay of 67 hours, but will continue up to a total of \$499. Although at first glance it appears that *tra-3* is the better long-term investment, this conclusion ignores the time value of money: money received early is more valuable because it can be reinvested for a profit. (Similarly, a worm hatched early contributes more to population growth than one hatched later, because in the intervening time the early worm can produce progeny.)

The internal rate of return is used to compare the long-term potential of such investments. If all receipts are immediately reinvested, the value of the total investment rapidly approaches an exponential growth steady-state $v = (1 + r)^t$. Over the long-term an investment with higher r will outperform an investment with lower r . r is calculated as follows. Each investment is described as a series of cash flows. For the wild-type these are -\$1 at time 0 (negative because it is an expenditure), \$1 at 64.4 h, \$1 at 64.6 h, , \$1 at 125.9 h. r is then the positive root of the equation $0 = \sum c_i(1 + r)^{-t_i}$, where c_i is the i^{th} cash flow and t_i the time at which it occurs. The doubling time τ_2 is $\ln 2 / \ln(1 + r)$. Financial calculators and spreadsheet programs such as Excel have built-in functions for calculating IRRs given a series of cash flows.

The key assumption in this analysis is that returns can be reinvested. In the biological context, this means that each newly hatched worm has the same opportunities for growth as its parent. In its natural environment *C. elegans* is generally thought to be r -selected; that is, it competes on the basis of rapid reproduction in the presence of abundant resources. Under these circumstances strains with the highest population growth rate will do best.

The table below gives the growth rates calculated from life history parameters measured by Hodgkin and Barnes. This analysis predicts that wild-type will outgrow *tra-3*: the wild type's 4% time advantage is more important than *tra-3*'s 53% yield advantage. Hodgkin and Barnes measured relative population growth rates in an "eating race" in which the time a population derived from a single worm required to eat a defined large quantity of food was measured. Wild-type finished the race in 2.8 ± 0.6 % less time than *tra-3*, in excellent agreement with the 3.0% difference in predicted doubling times.

Statistic	wild-type	<i>tra-3</i>	optimum (201 sperm)
IRR (r)	6.99% hourly	6.78% hourly	7.09% hourly
doubling time (τ_2)	10.25 h	10.56 h	10.13 h
dauers/worm	0.327	0.360	0.306

If there is a trade-off between time and yield, there ought to be an optimum brood size that produces the maximum internal rate of return. To test this prediction, Hodgkin and Barnes measured the brood sizes of 15 independent wild isolates. Finding a tight distribution ranging from 235 to 353, they concluded. "The races appear strikingly similar in self-fertility, despite the diversity of their geographic origins, suggesting that a brood of about 300 self-progeny is a universal optimum for this species." Using Hodgkin and Barnes's measured trade-off rate of 66 sperm/h, I find the optimum brood size to be 201, predicted to grow 1.3% faster than wild-type. 201 is outside the range of normal brood sizes, implying that something is missing from the analysis. It is possible that life history parameters in the wild are subtly different from those measured by Hodgkin and Barnes in the lab. However, there is an alternative explanation: that slower growth provides an advantage when resources become limiting.

Opportunities for extremely rapid growth are brief, both in financial markets and in ecological niches. For instance, at an hourly growth rate of 7% a single worm would grow to a mass larger than Alan Greenspan in less than 3 weeks--it is unlikely that a worm ever encounters a food concentration of that size in the wild. Like a venture capitalist making a rapid growth investment, r -selected organisms need an exit strategy: a way to recoup the gains of rapid growth in a form that can be preserved when a recession strikes. For *C. elegans*, this is the dauer larva. When food runs out, older worms are more valuable than young ones. Eggs and first-stage larvae are likely to die within a week; second-stage larvae can become dauer larvae and survive for months: older larvae can become adults, and adults can support the growth of a new generation by becoming bags of worms, probably to the point where at least some can become dauer larvae. There are more older worms in a slow-growing population than a rapidly growing one. Assuming no death among reproductive or prereproductive age worms, the proportion of the population older than age t is $(1 + r)^{-t}$. Thus when food runs out, a slow-growing population has an advantage. To get an idea of the possible magnitude of this effect, assume eggs and first-stage larvae produce no dauers on starvation, second through fourth-stage larvae produce one dauer each on starvation, and adults produce 10 dauers on starvation. The results are in the last row of the table.

This analysis reveals a second trade-off. A fast-growing organism can exploit resources more rapidly than a slow-growing one--this is an advantage in direct head-to-head competition for the same food source. However, a slow-growing population converts growth into lasting benefits more efficiently, an advantage when opportunities for growth are limited, or when the population can obtain exclusive access to a resource pool, either by luck or by erecting barriers to competition. This trade-off results from the greater survivability of older worms. Although the mechanisms that allow older worms to survive appear at first to be specific consequences of *C. elegans* physiology and response to starvation, it is plausible that trade-offs of this type would be common: that mature, stable organisms or investments are better able to survive an unfavorable environment than young, rapidly growing ones.

A DAF-2 pathway regulates muscle protein degradation by antagonizing Ras-Raf-MEK-MAPK signaling

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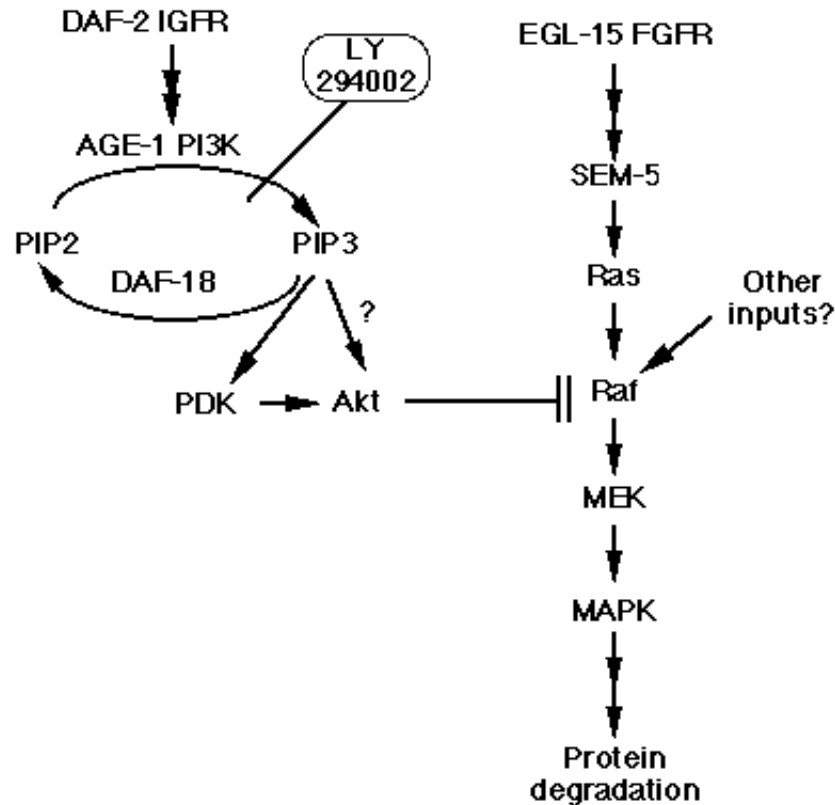
We have been using the non-myofibrillar myosin:: β -galactosidase fusion protein produced by *ccls55(unc-54::lacZ)* to "report" on protein degradation in muscle. This protein is stable in well-fed wild-type animals, but its degradation is induced by starvation, by acute disruption of cholinergic signaling (e.g., *cha-1(p1182^{ts})* animals) [1], or by activation of the Ras-MAPK pathway either directly (e.g., *let-60(ga89^{ts})* [2]) or indirectly (*clr-1(e1745^{ts})* activation of EGL-15 FGFR). Protein degradation induced by starvation or denervation is distinct from Ras-induced degradation on three grounds: (a) Reduction-of-function mutations in *mek-2* (MEK) or *mpk-1* (MAPK) suppress Ras-induced but not starvation/denervation-induced degradation; (b) Proteasome inhibitors block starvation/denervation-induced but not Ras-induced degradation; (c) The nAChR agonist levamisole blocks starvation/denervation-induced but not Ras-induced degradation.

Because of the well-known effects of insulin and Insulin-like Growth Factor (IGF) in promoting protein anabolism in mammalian muscle, we have now explored a possible role in muscle for the signaling pathway downstream of the DAF-2 IGFR homologue. We find that well-fed *daf-2(e1370^{ts})* or (*m41^{ts})* animals degrade the pre-existing reporter protein when shifted to nonpermissive temperature. Specifically, animals grown until mid-adulthood at 16°C and then shifted to 25°C showed a time-dependent loss of reporter activity and protein. Similarly, reporter degradation was observed when *age-1(hx546^{ts})* mutants were shifted to 25°C or when wild-type animals were treated with the PI-3-kinase (AGE-1) inhibitor LY-290042 [3]. This protein degradation appears to utilize pre-existing signaling cascades and proteases, inasmuch as degradation can still be triggered after treatment with the protein synthesis inhibitor cycloheximide.

The expression of *age-1⁺* in muscle is known to affect lipid storage [4]. We infer that AGE-1 affects muscle protein degradation by intra-muscular action, because expression of *age-1⁺* from the *unc-54* promoter (constructs kindly provided by C. Wolkow & G. Ruvkun) is sufficient to block protein degradation in the muscles of *age-1* null-mutant animals. Protein degradation induced by *daf-2(m41^{ts})* or LY-294002 is also prevented when the downstream signaling pathway is activated by either (a) a *daf-18* reduction-of-function mutation that permits accumulation of the AGE-1 product PtdIns-P₃; or (b) gain-of-function mutations *pdk-1(mg142)* or *akt-1(mg144)*. However, the reduction-of-function mutation *pdk-1(sa709)* is not sufficient to trigger protein degradation, suggesting either that PDK-1 can activate AKT-1 but is not required for AKT-1 activation, or that *sa709* mutants retain sufficient PDK-1 function to activate AKT-1. Thus, IGFR-PI3K-(PDK)-Akt signals oppose protein degradation in muscle. In contrast to the way this pathway functions in controlling dauer larva formation, here the target of AKT-1 is not the forkhead-class transcription factor DAF-16, since degradation in LY-294002-treated animals is not blocked by the loss-of-function mutation *daf-16(mgDf50)*.

What is the relevant target of AKT-1 action in muscle? Inhibitory phosphorylation of mammalian Raf by Akt has been reported [5], the mutation of presumptive Akt phosphorylation sites in LIN-45 Raf affects vulval development [6], and we had noted a low-frequency MuV phenotype in *daf-2(m41)* animals. These observations prompted us to test if the Ras-Raf-MEK-MAPK pathway was the target of negative regulation by the IGFR-PI3K-Akt pathway in worm muscle. Indeed, we found that reduction-of-function mutations *soc-2(n1774)*, *lin-45(sy96)*, *mek-2(ku114)* or *mpk-1(n2521)* suppressed protein degradation in response to

LY-290042 treatment, but *let-60(n2021)* did not. Conversely, increased activity of the DAF-2 pathway is sufficient to block protein degradation induced by EGL-15 activation (*clr-1(e1745^{ts})*; *daf-18(e1375)* animals). Thus, our results suggest that DAF-2 signals via AGE-1, PDK-1 and AKT-1 to inhibit LIN-45 Raf and protein degradation in muscle. They also imply that in normal adult muscle there is incoming signal to Raf, passed to subsequent steps in the cascade only when the balancing Akt inhibition of Raf is released.



Does the DAF-2 pathway affect the response to starvation? We find that starvation-induced reporter protein degradation is normal in *daf-2(e1370^{ts})* animals grown at 20°C then shifted to 25°C at the onset of starvation. However, the same mutants grown from L3 on at 25°C are at least partially resistant to reporter degradation in response to starvation at 25°C. These observations appear to reflect the excess lipid storage in *daf-2* mutants at 25°C. We have noted in wild-type that the onset of protein degradation about 8 hr. after starvation corresponds approximately to the time required to exhaust stored lipid in the intestine (by Sudan Black staining). Furthermore, we observed normal starvation-induced protein degradation in *age-1(hx546^{ts})* animals grown at 20°C to adulthood then starved at 25°C, and in wild-type animals treated with LY-290042 from the time of starvation. We infer that DAF-2 signaling does not directly regulate muscle proteolysis in response to starvation.

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***C. elegans* SEK-1 MAPKK regulates locomotion by functioning downstream of UNC-43 CaMKII**

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C. elegans UNC-43, the type II Ca²⁺ and calmodulin-dependent protein kinase (CaMKII), acts upstream of the NSY-1 MAPKKK-SEK-1 MAPKK-MAPK pathway to establish asymmetric cell fate decision in olfactory AWC neuron (Sagasti *et al.*, 2001; Tanaka-Hino *et al.*, 2002). UNC-43 also regulates several other neuronal functions including locomotion. In fact, the *unc-43(gf)* gain-of-function causes severe Unc phenotype. Although the GOA-1/EGL-30 heterotrimeric G protein network is involved in UNC-43-mediated regulation of locomotion, other components acting downstream of UNC-43 in the pathway are still unknown. We have determined whether the SEK-1 MAPKK is also involved in the UNC-43 locomotory function. In contrast to *unc-43(gf)* single mutants, *unc-43(gf);sek-1(lf)* double mutant animals exhibited almost normal movement pattern. Thus, the *sek-1* loss-of-function mutation can suppress the movement defect of *unc-43(gf)*. Next, we examined the effect of the activated *sek-1* mutation (*sek-1-STDD*; Tanaka-Hino *et al.*, 2002) on the locomotion. When *sek-1-STDD* was expressed by the *jkk-1* promoter (Kawasaki *et al.*, 1999) in N2 wild-type animals, they showed severe Unc phenotype similar to *unc-43(gf)*. This Unc phenotype was suppressed by the *goa-1(lf)* mutation. These results suggest that SEK-1 functions downstream of UNC-43 and upstream of GOA-1 to regulate proper movement.

Kawasaki M., Hisamoto N., Iino Y., Yamamoto M., Ninomiya-Tsuji, J., Matsumoto, K. A *Caenorhabditis elegans* JNK signal transduction pathway regulates coordinated movement via type-D GABAergic motor neurons. *EMBO J.*, 18: 3604-3615 (1999).

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Tanaka-Hino, M., Sagasti, A., Hisamoto, N., Kawasaki, M., Nakano, S., Ninomiya-Tsuji, J., Bargmann, C. I., Matsumoto, K. SEK-1 MAPKK mediates Ca²⁺ signaling to determine neuronal asymmetric development in *C. elegans*. *EMBO Rep.*, 3: 56-62 (2002).

***C. elegans* p38 MAPK cascade mediates arsenical stress response**

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Arsenic is one of the heavy metals that are harmful to living organisms and is known to induce multiple stress responses. It has been reported that arsenic selectively activates p38 MAP kinase (MAPK) in mammalian cultured cells, but the relationship between p38 and arsenical resistance in multicellular organisms remained to be determined. To address this, we have studied the role of the p38 MAPK pathway on arsenical-induced cellular response in *C. elegans* as a model system. In wild-type N2 worms, sodium arsenite strongly induced activation of *C. elegans* p38 PMK-1. RNAi of *pmk-1* lowered the resistance of animals to arsenite. Thus, p38 MAPK is involved in arsenical stress response. Recently, we have identified SEK-1 MAPKK which functions upstream of PMK-1 (Tanaka-Hino et al., 2002). Consistent with this, PMK-1 activation in response to arsenical stimulus was lost in *sek-1* null mutants and the *sek-1* mutant animals were hypersensitive to sodium arsenite. The SEK-1 MAPKK regulates asymmetrical development of AWC neurons by acting downstream of UNC-43 CaMKII and NSY-1 MAPKKK (Sagasti et al., 2001; Tanaka-Hino et al., 2002). In *nsy-1* loss-of-function mutants arsenite-induced activation of PMK-1 partially decreased and the mutant animals showed partial sensitivity to sodium arsenite. However, the *unc-43* loss-of-function mutation had any effects on neither PMK-1 activation nor sensitivity induced by arsenic treatment. Taken together, these results suggest that the NSY-1-SEK-1-p38 MAPK pathway regulates arsenical stress response in a manner independent of UNC-43. Furthermore, in this pathway other MAPKKK(s) may function upstream of SEK-1 MAPKK redundantly with NSY-1.

Sagasti, A., Hisamoto, N., Hyodo, J., Tanaka-Hino, M., Matsumoto, K., Bargmann, C. I. The CaMKII UNC-43 activates the MAPKKK NSY-1 to execute a lateral signaling decision required for asymmetric olfactory neuron fates. *Cell*, 105: 221-232 (2001).

Tanaka-Hino, M., Sagasti, A., Hisamoto, N., Kawasaki, M., Nakano, S., Ninomiya-Tsuji, J., Bargmann, C. I., Matsumoto, K. SEK-1 MAPKK mediates Ca²⁺ signaling to determine neuronal asymmetric development in *C. elegans*. *EMBO Rep.*, 3: 56-62 (2002).

A JNK/UNC-16 signaling complex regulates synaptic vesicle localization through a conventional kinesin in *C. elegans*

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The c-Jun N-terminal kinase (JNK) of the MAP kinase (MAPK) superfamily is involved in various stress responses and apoptosis in mammal. The *C. elegans* JNK cascade is composed of JNK-1 (MAPK) and JKK-1 (MAPKK). The JNK-1 pathway functions in type-D GABAergic motor neuron and modulates coordinated locomotion. The *C. elegans unc-16* gene encodes a protein homologous to mammalian JSAP1/JIP3, which acts as a scaffold protein in the JNK pathway by binding with MLK (MAPKKK), MKK7 (MAPKK) and JNK3 (MAPK). Like JSAP1/JIP3, UNC-16 physically interacts with JNK-1 and JKK-1, forming a JNK signaling module. *unc-16(ju79)*, *jnk-1(gk7)*, and *jkk-1(km2)* mutant animals exhibit mislocalization of synaptic vesicle marker SNB-1::GFP in L1 DD motor neurons. This suggests that the JNK-1 pathway containing UNC-16 regulates synaptic vesicle localization.

To understand the mechanism regulated by UNC-16, we screened for UNC-16-binding proteins using yeast two-hybrid system. One of the isolated genes is *klc-2* encoding a kinesin light chain. Co-immunoprecipitation experiments reveal that KLC-2 associates with UNC-16 and UNC-116 kinesin heavy chain when they are co-expressed in mammalian cells. We constructed the *klc-2(km11)* mutation that produces a truncated form of the KLC-2 protein lacking its C-terminal portion. The mutant animals exhibit Unc and weak Dpy phenotypes. Similar to *unc-16(ju79)*, *jnk-1(gk7)*, and *jkk-1(km2)* mutants, the SNB-1::GFP marker is mislocalized along the dorsal DD processes in the *klc-2(km11)* L1 larvae. These results raise the possibility that the UNC-16-JNK-1 pathway regulates synaptic vesicle localization through phosphorylation of KLC-2 in *C. elegans*.

***atp-2* Controls Development in a Cell Nonautonomous Manner**

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The growth and development of an organism are energy-dependent and rely on the mitochondrial respiratory chain (MRC) as the major source of ATP. The MRC is made up of 5 protein complexes, and its biogenesis requires the coordinate expression of genes from both the nuclear and the mitochondrial genomes. A defective MRC has been implicated in a wide variety of human diseases including diabetes, myopathies, neuromuscular and heart diseases.

We are developing the nematode, *Caenorhabditis elegans* as a model system for studying mitochondrial diseases. We have previously isolated a MRC mutation in the *atp-2* gene encoding the active site β subunit of the ATP synthase. The *ua2* mutation is a deletion and is homozygous lethal: *atp-2(ua2)* animals hatch and develop through 2 larval stages before arresting at the L3 stage.

We are performing mosaic analysis to determine whether losses of the wild type *atp-2* gene in certain cells or tissues can prevent development beyond the L3 stage. We have generated several strains of the genotype *atp-2(ua2); svDp1{sDp3[atp-2(+)]-svEx12[unc-4(+)-sur-5::gfp]}* (*svDp1* is a gift from Dr. S. Tuck). Mosaic animals are identified by screening plates for candidates with less intense fluorescence as observed in the dissecting microscope. They are then examined with the compound microscope to identify the exact nature of their losses. We have mainly focused on early duplication losses (i.e. losses in the AB, ABa, ABp, P₁, P₂, EMS, E, MS, C, and D(P₃) lineages; the *sur5::gfp* reporter is not expressed in the germ line, which is derived from P₃). Animals with a loss in one or more of the AB, ABp, P₁, P₂, EMS, MS, C and D(P₃) precursor cell all arrest at L3, whereas a loss in either ABa or E gives rise to both L3 arrested and L4/adult worms. Our data suggests that *atp-2* controls development cell nonautonomously and may be involved in the production or the regulation of a global, developmental signal required for the L3-to-L4 transition.

Analysis of *cdh-3* upstream regulatory region to find sequences necessary for expression

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EGL-38 is a Pax transcription factor important for the development of several organs in *C. elegans*, including the hindgut. Two genes are known to act downstream of *egl-38*: *lin-48* and *cdh-3*. Genetic studies indicate that *lin-48* and *cdh-3* are part of two separate pathways. The two genes also function differently, as LIN-48 is responsible for the specification of cell fates, while CDH-3 coordinates development and epithelial morphogenesis^{1,2}. Previous studies have shown that *lin-48* is a direct target for EGL-38³. To investigate whether *cdh-3* might also be a target of EGL-38, we have characterized its upstream regulatory sequence.

In comparison studies between *C. elegans* and *C. briggsae*, we found that there are five domains of consensus sequence within a 1000bp region upstream of the start ATG of *cdh-3*. We chose to focus on these areas, reasoning that these were the most likely spots for protein binding. We constructed clones including different amounts of upstream sequence driving expression of the green fluorescent protein (gfp) and injected them into animals to study their expression.

From this data (Table 1), we found that two regions are important for expression of *cdh-3* in the seam cells and hindgut cells. Deletion of the region between 677 and 555 eliminated expression in the seam cells and deletion of the region between 555 and 526 eliminated expression in both seam cells and the cells of the hindgut. To confirm the function of these two regions, we generated point mutations in the reporter gene with the 824bp upstream sequence (Table 2). A clone with a mutation in the more distal site (pSS1) was not expressed in seam cells but maintained hindgut expression. In contrast, clones with a mutation in the more proximal site (pSS20) or in both sites (pSS21) were not expressed in either cell type. This indicates that the proximal element is important for expression in both cell types.

GATA-binding factors have been shown to play a role in seam cell development^{4,5}, and the distal region contains a block of sequence conserved between *C. elegans* and *C. briggsae* that includes a GATA sequence motif. In contrast, although EGL-38 plays a role in *cdh-3* hindgut expression, the conserved sequence in the more proximal 555-526 region does not resemble the binding site for Pax proteins. Thus we suspect the relationship between *egl-38* and *cdh-3* is indirect.

¹ Pettit et al., 1996 Development

² Chamberlin et al., 1999 Genetics

³ Johnson et al., 2001 Development

⁴ Page et al., 1997 Genes and Development

⁵ Koh and Rothman, 2001 Development

Table 1

Upstream sequence in clone (bp)	Expression in hindgut (F+U cells)	Expression in seam cells	n
824	66.5%	96%	82
677	48.5%	65%	95
555	64%	0%	58
526	0%	0%	33
467	0%	0%	31

Table 2

clone	Expression in hindgut	Expression in seam cells	n
pSS1	84%	3%	37
pSS20	0%	0%	38
pSS21	0%	0%	38

Functional and comparative studies of *Pax-2/5/8* genes in *Caenorhabditis elegans* and *Caenorhabditis briggsae*

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Pax transcription factors play an important role in organ development in animals. Pax factors are subdivided into four subclasses based on sequence similarity and the presence of other sequence motifs. In *C. elegans* there are five Pax genes with one member for three of the subclasses but two *Pax 2/5/8* members: *egl-38* and *K06B9.5* (1). Although these two genes are highly similar in their coding region and bind similar DNA targets (2) they are not functionally redundant. *egl-38* is essential for viability, and mutations can disrupt development of distinct organs, including the hindgut and the egg-laying system (3). We hypothesize that the unique functions of *egl-38* and *K06B9.5* result from differences in expression pattern between the two genes.

To test this idea, we have investigated the expression pattern of *K06B9.5*. We generated reporter transgenes by tagging the 3' end of *K06B9.5* with *gfp*. We found that these transgenes express in two cell types: The PVC neurons in the tail and the D cells of the vulva (vulD). To confirm that the vulD expression is specific to cell type rather than position, we have crossed the *K06B9.5::gfp* transgenes into vulval lineage mutants (Table 1). In wild type two vulval cells express *K06B9.5::gfp*, with one vulD produced from each of the 2° lineages of P5.p and P7.p. In *lin-15* mutants we frequently observe additional ectopic expression coincident with cells that produce ectopic 2° lineages. In addition, the expression in P7.p-derived cell is missing or misplaced in some *lin-17* mutants consistent with the expected lineage defects. Using a deletion analysis, we have localized sequences important for vulD expression to 150bp of the *K06B9.5* promoter. Preliminary RNAi experiments indicate that both *egl-38* and *K06B9.5* are affected by double-stranded RNA from either gene. Currently we are trying to study the function of *K06B9.5* alone by expressing sense and antisense RNA under the control of *K06B9.5* promoter and tagging *K06B9.5* with the activator VP16, and with the *engrailed* repressor domain.

To better understand the relationship between *egl-38* and *K06B9.5*, we have isolated the *Pax-2/5/8* family gene from *C. briggsae* and found that there is only one copy of this gene in this species. This result is confirmed by the recent completion of the *C. briggsae* genome sequence. A sequence comparison between the genes between *C. elegans* and

C. briggsae indicate that *C. elegans egl-38* and *K06B9.5* are more similar to each other than to the *C. briggsae Pax-2/5/8* gene, suggesting *egl-38* and *K06B9.5* result from a gene duplication subsequent to the divergence of the *C. elegans* and *C. briggsae* lineages. We have generated a GFP reporter transgene for the *C. briggsae Pax-2/5/8* gene. In the larva, this transgene is expressed in two tail neurons (PVC), two neurons in the head, uterine and D cells in the vulva. Characterization of embryonic expression is ongoing. RNAi of this gene in *C. briggsae* showed defects in egg-laying, hindgut, tail morphology and a low level of larval lethality.

Table 1

Genetic background	No of vulval cells expressing K06B9.5::GFP transgene				
	0	1	2	3	4
N2 (Wild Type)			30		
<i>lin-15(n309)</i>			4	19	3
<i>lin-17(n671)</i>		3	20 + 5 ^a		

^a Two cells express but P7.p derived cell is misplaced.

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124 : 3919-3928

Like in *C. elegans*, Many GATA Factors in *C. briggsae* are in Redundant Groups

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A surprising finding from studies of the *C. elegans* GATA factors has been that most occur in functionally overlapping pairs. The ectodermal GATAs *ELT-5/EGL-18* and *ELT-6* share overlapping function (Koh and Rothman, 2001). The GATAs *MED-1,2* specify MS and E fates, *END-1,3* specify E fate, and *ELT-2* and *ELT-7* elaborate intestinal fate in the E descendants. The availability of genome sequences for *C. briggsae* has enabled us to identify all the GATA factors predicted to be encoded by its genome, and in particular ask whether any are found in similar pairs as in *C. elegans*.

The *elt-2* and *elt-7* genes have clear homologs (McGhee lab, K. Strohmaier and J.R, unpublished). The putative *elt-5/egl-18* and *elt-6* homologs are adjacent genes transcribed in the same direction, just as they are in *C. elegans*. We have identified a similar pair of MED-like GATA factors in *C. briggsae* that both appear to be encoded by a single, intronless ORF, and which both have putative SKN-1 binding sites just 5' to the coding region (properties similar to the *C. elegans* genes). Like *Ce-med-1*, a transgene reporter of *Cb-med-1* is expressed in the early EMS lineage in *C. elegans*. Unlike *Ce-med-1,2*, which are on separate linkage groups, *Cb-med-1* and *-2* are adjacent to one another in an inverted, divergently-transcribed orientation. As expected from an independent, recent origin of each duplication, the predicted *Ce-med-1,2* and *Cb-med-1,2* gene products are more similar within each species than between them. The results with *end-1* and *end-3* were similar. The *end-3* gene in *C. elegans* is located ~30 kbp to the right of *end-1*. In *C. briggsae*, however, there are **two** *end-3* homologs a similar distance away from a single *end-1* homolog. Like *Cb-med-1,2*, the two *end-3*-like genes are adjacent, in inverted orientation and divergently transcribed. RT-PCR analysis confirmed that *Cb-end-1* and the two *Cb-end-3* genes are expressed, while cross-species transgene rescue and heat shock experiments in *C. elegans* shows that these genes are expressed in the E lineage, and can specify endoderm fate. Therefore, the regulation of the *end* genes, and the activity of their gene products, has been conserved. The high degree of sequence identity between the two *C. briggsae* *end-3* homologs suggests that they arose from a recent duplication, while the intra-species divergence between the *end-1,3* genes suggests that they arose from a much earlier event. We conclude that among the entire suite of *C. elegans* and *C. briggsae* GATA factors, redundancy via gene duplication arose multiple times both before and after the *C. elegans/C. briggsae* evolutionary split.

EGL-32 may be a Sperm Protein that Regulates Egg Laying through the TGF- β Pathway

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A TGF- β related signaling pathway regulates dauer larval development and egg laying in *C. elegans*. Mutations in *daf-7* ligand, *daf-1* type I receptor, *daf-4* type II receptor, and *daf-8* and *daf-14* Smads result in Dauer-constitutive/Egg-laying defective animals (1). These mutations are suppressed for both defects by mutations in *daf-3* and *daf-5* (2). We are interested in the role of this pathway in egg laying. Two other genes that affect egg laying, *egl-4* and *egl-32*, are also implicated in this pathway by their suppression by *daf-3* and *daf-5* (3). Mutations in *egl-4* also have a weak Dauer-constitutive phenotype (4). Mutants of *egl-32* are the only known mutants to be suppressed by *daf-3* and *daf-5* that are Egg-laying defective, but not Dauer-constitutive.

Mutants of *egl-32* retain about twice as many eggs as wild type animals: 30 instead of 14. Experimental evidence suggests that EGL-32 is a sperm protein that regulates egg laying in *C. elegans*. It has 3 close homologs, all of which are found in *C. elegans*. EGL-32 and its 3 closest homologs have been shown to be highly expressed in sperm (5). *egl-32(n155)* is a temperature sensitive mutation. Temperature shift assays reveal that L4 is the critical stage for EGL-32 inactivation. The L4 stage does not correspond to the time when eggs are laid, but when hermaphrodites produce sperm. Furthermore, the introduction of wild type sperm, by mating, into *egl-32* animals results in a reduction in the number of eggs retained, and an increase in the number of eggs laid. The introduction of *egl-32* sperm into wild type animals, by mating, causes wild type animals to lay fewer eggs and retain more eggs, many of which are at the comma stage or later.

It has previously been described that meiotic maturation and ovulation in *C. elegans* is regulated partially by sperm (6). In female mutants, oocytes fail to undergo meiotic maturation and sheath cell contraction, which is necessary for ovulation, is irregular (7). Introduction of sperm, by mating, causes oocytes to complete maturation and sheath cells to begin to contract regularly, allowing ovulation. It has recently been found that the major sperm protein (MSP) supplies the signal for oocyte maturation and ovulation (6) in *C. elegans*. It is possible that a mechanism also exists to coordinate the time of fertilization with the time of egg laying to insure that eggs are not laid too soon or too late. It is possible that this mechanism functions either directly or indirectly through the TGF- β pathway. Further experiments will be done to test this hypothesis.

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Evidence for constitutive reduction of insulin/ IGF signalling in males

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When maintained in isolation to prevent attempted mating, N2 males live ~20% longer than hermaphrodites (1). Solitary male but not hermaphrodite lifespan is further enhanced by a range of uncoordinated (*unc*) mutations. It was first proposed that this was because these mutations prevented life-shortening behaviour, even in solitary males (1). We have since found, however, that the male *unc* lifespan effect is limited to neuronal *unc* mutations and is not seen in muscle *uncs* (10 mutants tested, data not shown). Thus, many defects affecting the nervous system retard ageing in males but not hermaphrodites.

One possibility is that this reflects sex differences in the neuroendocrine regulation of ageing. Dauer formation is regulated by interacting genetic pathways, involving insulin/IGF signalling (IIS) and TGF-beta signalling, with a parallel and/or regulatory cGMP component. Dauer constitutive (*Daf-c*) mutations in the IIS pathway increase adult lifespan, while those in the TGF-beta/ cGMP pathways do not. Wild-type males form dauers more readily than hermaphrodites in response to dauer pheromone (2), as do several *Daf-c* mutants (3). Could it be that wild-type males are both longer-lived and more likely to form dauers than hermaphrodites because IIS is constitutively reduced in males? We investigated whether (a) the male bias to dauer formation and (b) the intrinsic male longevity were dependent on IIS. For this we looked at dauer formation and lifespan ratios of the two sexes in a range of IIS, TGF-beta and cGMP mutants.

(a) Dauer formation: Progeny from mated hermaphrodites were raised at a temperature that gave a mix of dauers and non-dauers. The sex of non-dauers and recovered dauers was scored, and the overall ratio of male: hermaphrodite dauer formation was determined (Table).

Strain	Temp (°C)	MH dauer ratio	N*	Strain	Temp (°C)	MH dauer ratio	N*
N2	25	1.20	309 (1)	<i>daf-4(m592)^b</i>	22.5	2.60	2453 (3)
<i>daf-2(m41)^a</i>	20	0.82	2486 (3)	<i>daf-1(m40)^b</i>	22.5	4.89	469 (1)
<i>daf-2(e1370)^a</i>	22.5	1.04	1116 (2)	<i>daf-8(m85)^b</i>	17	9.53	1031 (1)
<i>daf-2(e1365)^a</i>	22.5	0.48	2644 (2)	<i>daf-11(m47)^c</i>	15	1.67	209 (1)
<i>daf-2(e1368)^a</i>	22.5	0.49	4421 (2)	<i>daf-16(mgDf50); daf-1(m40)^{ab}</i>	22.5	3.26	3596 (2)
<i>pdk-1(sn709)^a</i>	26	0.66	858 (2)				

* Number of worms scored (number of trials); ^aIIS mutant; ^bTGF-beta mutant; ^ccGMP/ TGF-beta mutant

There was a marked male bias to dauer formation in wild type, as previously seen (2), as well as in the TGF-beta and cGMP mutants. However, either no bias or a hermaphrodite bias was observed in IIS mutants. This indicates that the increased tendency of males towards dauer formation is dependent on IIS. However, when partial dauer formation was measured in a *daf-16; daf-1* double mutant, the male bias as seen in dauer formation by the *daf-1* single mutant was only slightly reduced. This implies that a complex interplay of IIS and TGF-beta signalling may be involved.

(b) Survival analysis: When lifespan was measured under identical conditions (monoxenic liquid culture) for *daf-2* and *daf-16* mutants, the increased N2 male longevity was no longer apparent, with hermaphrodites living slightly longer than males (data not shown). The increased male longevity still remained in *pdk-1(sn709)*, however. These results suggest that increased male longevity is dependent on *daf-2* signalling via *daf-16*, but that this might not act via *pdk-1*.

Altogether, these results are consistent with a constitutive reduction of IIS in males, leading to increased dauer formation and longevity.

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The superoxide dismutase mimetic EUK-8 shortens lifespan

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If the free radical theory of aging is correct, augmentation of antioxidant defenses should retard ageing and increase lifespan. Yet over the years, studies of administration of antioxidants to model organisms have not generally fulfilled this prediction. By contrast, a recent report demonstrated that synthetic catalytic antioxidants increase lifespan in *C. elegans*, on average by 44% (1). The antioxidants used were the salen manganese compounds EUK-8 and EUK-134 which have superoxide dismutase (SOD) activity *in vitro* and *in vivo*. The effect was seen over a 0.05 - 10 mM range, and was not dose dependent. These findings provide robust support for the view that free radical damage is a primary cause of ageing.

Hoping to use EUK-8 as an experimental tool to investigate mechanisms of ageing, we tested its effect on lifespan in *C. elegans*. EUK-8 was obtained from the same source as the Melov *et al.* study (Eukarion Inc., Bedford, MA, USA), and also from the Dept. of Pharmacy and Biological Science, University of Brighton, UK (R.G. Faragher and F. Fucassi). We examined the effect on lifespan of 0.05mM, 0.5mM and 5mM EUK-8, using methods as described (1). Worms were maintained in monoxenic liquid culture, either singly in 50-70 μ l of S medium containing an *E. coli* concentration of 5×10^8 /ml - 1×10^9 cells/ml, in 96 well microtitre plates; or in groups of approximately 20 in shallow plate culture. Medium was replenished at 2-3 day intervals. We examined effects on N2 hermaphrodites (2 trials, 661 animals) and males (2 trials, 132 animals), and nulliparous *fog-2(q71)* females (3 trials, 389 animals). In the case of the N2 hermaphrodite studies, the *E. coli* OP50 stock used was newly obtained from the *Caenorhabditis* Genetics Center.

In all trials we observed a dose-dependent reduction in longevity. For example, in a representative trial using N2 hermaphrodites, mean lifespans (20°C) were as follows: Control, 20.0 \pm 0.6 days; 0.05mM EUK-8, 20.6 \pm 0.5 days; 0.5mM, 14.7 \pm 0.4 days; and 5.0mM, 3.8 \pm 0.1 days (average sample size per test, 84 animals; range 72-100). We also measured the effect of EUK-8 on fertility in self-fertilizing hermaphrodites. As previously seen (1), no major reduction in fertility resulted from treatment with 0.05mM or 0.5mM EUK-8 (progeny numbers: control, 159 \pm 36 [S.D.], $N=54$ broods counted; 0.05mM, 151 \pm 38, $N=56$; 0.5mM, 143 \pm 33, $N=61$; when animals are raised from hatching liquid culture, brood sizes are reduced relative to those of animals maintained on agar plates). However, in 5mM EUK-8 brood size fell to 14 \pm 7 ($N=11$) (figures are means from four separate trials).

Thus, in our hands, EUK-8 did not increase lifespan, but rather, proved to be mildly toxic. It remains unclear whether the failure of EUK-8 to increase lifespan is because a) increased SOD activity does not retard ageing in *C. elegans*; b) EUK-8 does not have SOD activity in *C. elegans*; or c) EUK-8 is not taken up by worms (however, the dose-dependent reduction of lifespan seen suggests that EUK-8, or a derivative of it, is entering the worms). One possibility is that EUK-8 is inactivated by *E. coli*. With this in mind, we tested the effect of EUK-8 on axenically cultured N2 hermaphrodites (2). However, under these conditions a similar dose-dependent shortening of lifespan was seen. Mean lifespans for a representative trial are: Control, 33.8 \pm 0.8 days; 0.05mM EUK-8, 33.5 \pm 0.7 days; 0.5 mM, 24.8 \pm 1.1 days; and 5.0mM, 5.5 \pm 0.3 days (2 trials, 288 animals; note that culture in axenic medium increased lifespan, as previously observed). Thus, the toxicity of EUK-8 is not the result of an unusual interaction between EUK-8 and *E. coli*.

The reason for the differences between our results and those previously reported remain unclear. Our findings will only be fully interpretable when it is known whether administration of EUK-8 to *C. elegans* results in increased intracellular SOD levels, and protection against superoxide.

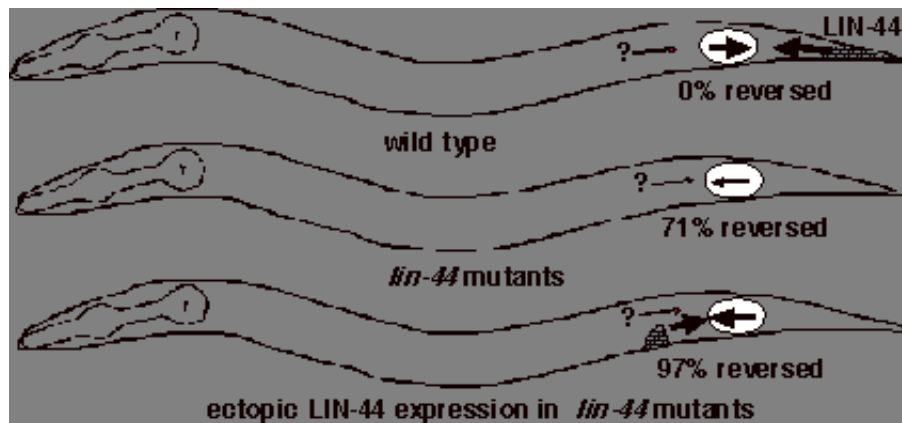
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Instructive roles of LIN-44/Wnt in the regulation of cell polarity

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Asymmetric cell division is a fundamental mechanism to produce cellular diversity during development. To divide asymmetrically, mother cells must have polarities. In *C. elegans*, polarities of mother cells are often regulated by *wnt* genes. In early development, a polarity of the EMS blastomere is regulated by *mom-2/wnt* (1, 2). During postembryonic development, polarities of V5 and T cells are regulated by *egl-20/wnt* and *lin-44/wnt*, respectively (3, 4). In *egl-20* and *lin-44* mutants, polarities of the V5 and T cell divisions, respectively, are often reversed. *egl-20* and *lin-44* are expressed posteriorly to their target cells (4, 5). We have previously proposed that LIN-44 activates LIN-17/Frizzled receptor at the posterior but not anterior side of the T cell to give them a posterior directed polarity (6). The polarity reversal phenotype in *lin-44* mutants could be caused by an unidentified signal (wnt?) expressed anteriorly to the T cell. If the hypothesis is correct, posterior expression of wnt must be important. However, Whangbo et al. showed that ectopic expression of *egl-20* in pharynx can rescue the polarity reversal of V5 in *egl-20* mutants, suggesting that *egl-20* has only permissive roles in the regulation of the V5 cell polarity (3). To examine this is also the case for *lin-44*, we expressed *lin-44* similarly in pharynx using the *myo-2* promoter to find that it did not affect the T cell phenotype in *lin-44* mutants. Because pharynx may be too far from the T cell, we next expressed *lin-44* just anterior to the T cell using the *egl-5* promoter (expressed in cells around the rectum). Surprisingly, the polarity reversal phenotype in *lin-44* mutants was enhanced from 71% to 97% by the *egl-5::lin-44* transgene. The results show that the T cell can recognize direction of the LIN-44 signal, and strongly suggest that LIN-44 instructs direction of cell polarity.



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An attempt to slow aging in *C. elegans*. 24. No positive effect of streptomycin with ascorbic acid

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The purpose of this study was to investigate the effect of different concentrations of streptomycin sulphate in presence of ascorbic acid (concentration 1:10⁴) in water solutions on the nematode life span in reproductive period. In this experiment streptomycin sulphate was used in following dilutions: 1:10¹, 1:10², 1:10³, 1:10⁴, 1:10⁵, 1:10⁶ and 1:10⁷. Three adult animals (3 - 5 days old) were kept in microtitre wells containing 0.5 ml of liquid medium (with *E. coli* and without ascorbic acid) during 4 hours, then they were discarded and newborn larvae were transferred in next wells (without streptomycin sulphate in medium) every day (one worm in one well) beginning from third day. Then, from 3th to 10th day, these worms were transferred every day in next wells containing medium with streptomycin sulphate in any concentration. This investigation was carried out in temperature +21°C and in the darkness.

The obtained results are presented in the following table.

Concentration of streptomycin sulphate	n	Longevity (days)	
		Mean±S.E.	Maximal
Control	12	12.8±1.1	18
1:10 ³	12	13.7±0.7	21
1:10 ⁴	12	14.0±0.6	23

Conclusion: If streptomycin sulphate solution in presence of ascorbic acid was applied to *C. elegans*, it was not able to increase significantly ($P>0.05$) their mean longevity in comparison with control.

Acknowledgment: The author wishes to express his thanks to CGC for providing C. elegans (Bristol, N2) and E. coli OP50.

An attempt to slow aging in *C. elegans*. 25. No positive effect of atorvastatin calcium

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The purpose of this study was to investigate the effect of atorvastatin calcium in water solutions on the nematode life span. In this experiment atorvastatin calcium was used in following dilutions: 1:10⁴, 1:10⁵, 1:10⁶, 1:10⁷ and 1:10⁸. Three adult animals (3 - 5 days old) were kept in microtitre wells containing 0.5 ml of liquid medium (with *E. coli* and without atorvastatin calcium) during 4 hours, then they were discarded and newborn larvae were transferred in next wells (without atorvastatin calcium in medium) every day (one worm in one well) beginning from third day. Then, from 3th to 10th day, these worms were transferred every day in next wells containing medium with atorvastatin calcium in any concentration. This investigation was carried out in temperature +21°C and in the darkness.

The obtained results are presented in the following table.

Concentration of atorvastatin calcium	n	Longevity (days)	
		Mean±S.E.	Maximal
Control	12	220.33±1.91	27
1:10 ⁴	12	220.42±1.84	28
1:10 ⁵	12	220.35±1.87	27
1:10 ⁶	12	220.25±1.70	28
1:10 ⁷	12	218.50±1.46	28
1:10 ⁸	12	221.50±1.70	27

Conclusion: If atorvastatin calcium solution was applied to *C. elegans*, it was not able to increase significantly ($P>0.05$) their mean longevity in comparison with control.

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