Mutations in Chemosensory Cilia Cause Resistance to Paraquat in Nematode Caenorhabditis elegans*

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The relationship between oxidative stress and longevity is a matter of concern in various organisms. We isolated mutants resistant to paraquat from nematode Caenorhabditis elegans. One mutant named mev-4 was long-lived and showed cross-resistance to heat and Dyf phenotype (defective in dye filling). Genetic and sequence analysis revealed that mev-4 had a nonsense mutation on the che-11 gene, homologues of which are involved in formation of cilia and flagella in other organisms. The paraquat resistance was commonly observed in various Dyf mutants and did not depend on the daf-16 gene, whereas the extension of life span did depend on it. Expression of antioxidant enzyme genes seemed normal. These results suggest that chemosensory neurons are a target of oxidative stress and influence longevity dependent on the daf-16 signaling in C. elegans.

The life spans of animals are determined by both environmental and genetic parameters. Accumulating evidence in model organisms demonstrates the importance of genetic approaches with the findings that single gene mutations affect the life span in nematode Caenorhabditis elegans, fruit fly Drosophila melanogaster, and laboratory mice. The key to understanding longevity seems to lie in the network of cell maintenance systems that reduce accumulation of deleterious stresses. The life span of nematodes is controlled by the insulin-like signals from the nervous system (1–3). Such signals also seem to control life span of the fruit fly and mice (4–7). These results suggest that neuroendocrine pathways in the neurons constitute an important determinant of life span across phylogeny (8–11).

Various lines of evidence show that oxidative stress is a major damaging factor accelerating aging (12, 13). It is invoked by reactive oxygen species (ROS)† generated as chemical by-products of normal cellular metabolisms. Caloric restriction is shown to be beneficial in decreasing the production of ROS in metabolic pathways such as the mitochondrial electron transport system (13). Animals have evolved defense mechanisms against ROS; antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase work to eradicate ROS as a first aid (14). However, much remains to be understood as regards the defense mechanisms in diverse tissues of vertebrates. To facilitate understanding of the mechanisms, C. elegans and D. melanogaster are frequently used as a multi-cellular model organism because powerful genetic analysis is possible.

In C. elegans, longevity is affected by particular genes involved in dauer larvae formation (15–17), stress resistance (18–24), mitochondrial function (25–28), caloric restriction (29), reproduction (30–32), sensory perception (33), neurosecretory function (34), and chromatin silencing (35). Although multiple factors seem to be involved in the longevity, there exist a positive relationship between the capacity to resist oxidative stress and the longevity (12). Nonetheless, the target of oxidative stress is yet to be understood even in this model organism. To address this question empirically, we isolated mutants of C. elegans with altered sensitivity to oxidative stress using paraquat (methyl viologen) as a selecting agent. In this study, we report that one of the paraquat-resistant mutants with extended life span is defective in the che-11 gene that seems to be involved in the function of chemosensory cilia (33, 36). We also examined sensitivity to paraquat in various mutants of chemosensory perception.

EXPERIMENTAL PROCEDURES

Strains and Culture Conditions—The C. elegans strains used were obtained from the C. elegans Genetic Center. Worms were grown and maintained at 20 °C on NG plates seeded with Escherichia coli OP50 as a food source as described by Brenner (37) unless otherwise mentioned.

Mutant Isolation—L4 larvae of wild-type N2 were treated with 50 mM ethylmethane sulfonate for 4 h and cultured to bear F2 progenies. The worms were cultured singly on 96-well titer plates containing bacteria in liquid medium. These worms were allowed overnight to lay eggs, and mixtures of the eggs and hatched L1 larvae were transferred to fresh NG plates containing 0.4 mM paraquat. After incubation for 4–5 days, the plates were examined under a microscope to find adult worms. Eggs from these worms were prepared individually by treatment with alkaline hypochlorite as described previously (37) and placed on agar medium containing 0.4 mM paraquat to isolate worms that can grow under the selective conditions.

Genetic Analysis—Genetic crosses were performed as described previously (37). To assign a chromosome (LG V) to mev-4 locus, its linkage with the following genetic markers were examined: dpy-6(e11) for LG (linking group) I, rol-5(ce13) for LG II, dpy-16(e1) for LG III, unc-22(e66) for LG IV, dpy-1(e224) for LG V, and lon-2(e6178) for LG X. To regionally map mev-4 locus on LG V, three-factor crosses were carried out with the following combinations of the markers: dpy-11(e224) unc-42(e270), rol-4(e8) lin-25(n545), him-5(e1467) unc-76(e911), rol-4(e8) unc-61(e229), unc-42(e270) rol-4(e8), sma-1(e30) unc-76(e911), and unc-42(e270) lon-3(e1275).

Analysis of Brood Size—The eggs were prepared and allowed to hatch by overnight incubation in S-basal buffer. Hatched L1 larvae

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‡ The abbreviations used are: ROS, reactive oxygen species; SOD, superoxide dismutase; FITC, fluorescein isothiocyanate; IFT, intraflagellar transport.
were transferred to NG plates and incubated to develop to L3–L4 larvae. Individual worms were transferred to fresh plates every 24 h, and the numbers of laid eggs were scored until the worms ceased to lay eggs.

**Assay of Sensitivities to Stresses**—Sensitivity to paraquat was determined as described by Ishii et al. (38) with a slight modification. The eggs, instead of L1 larvae, were placed on growth medium containing various concentrations of paraquat. After incubation for 4–5 days, the number of adult worms was scored. Sensitivity to thermal stress was determined as described by Lithgow et al. (20). Briefly, L1 larvae were cultured on NG plates for 4 days. Then 50 adult worms were incubated at 36 °C on fresh NG plates, and their survival was examined at intervals. Similarly, 50 adult worms were placed on bacteria-free plates and exposed to UV light (40 J/m2) as described by Murakami and Johnson (39). Then they were transferred to NG plates and examined for their survival during subsequent culture at 20 °C.

**Assay of Life Span**—Life span was determined as described by Ishii et al. (38). L1 larvae were allowed to hatch by overnight incubation in S buffer and transferred to NG plates to develop to L4 larvae. A hundred of the L4 larvae were transferred to NG plates supplemented with 0.3 mM paraquat, and none reached adulthood in the presence of 0.3 mM paraquat, and none reached adulthood in the presence of 0.4 mM paraquat within 4 days. In contrast, all of the mutant worms grew normally under these conditions, and more than half of them grew to adulthood even in the presence of 0.6 mM paraquat. The mean and maximum life spans of mev-4 were 30% and 20% longer on averages than those of N2, respectively, when cultured at 20 °C (Fig. 1A). When cultured at 26 °C, they were 15 and 23% longer than those of N2, respectively (data not shown).

Then we investigated sensitivity to thermal stress and UV light, both typical stress markers in *C. elegans*. When incubated at 36 °C, mean and maximum survival times were significantly longer in mev-4 than in N2 (Table I). When cultured at 26 °C, they were 15 and 23% longer than those of N2, respectively (data not shown).

**Characterization of the Mutated Gene in mev-4**—The paraquat-resistant trait was genetically recessive and inherited to progeny in a Mendelian fashion. Linkage analysis revealed that the trait was concordant with the genetic marker *dpy-11* located on LG V. Therefore, we regionally mapped *mev-4* locus on LG V using three factor crosses with appropriate genetic markers. We obtained the following results: (*dpy-11 unc-2)* (8/8) *mev-4*; *mev-4* (14/14) (rol-4 lin-25 him-5 unc-76); *mev-4* (4/4) (rol-4 unc-61); *unc-42* (15/18) *mev-4* (3/18) rol-4, *sma-1* (1/20) *mev-4* (19/20) *unc-76*, and (*unc-42 lon-3*) (29/29) *mev-4*. Thus, *mev-4* mutation was mapped to a region close to *lon-3*.

**RESULTS**

**Isolation and Characterization of mev-4 Mutant**—To isolate mutants with altered sensitivity to oxidative stress, we used paraquat as a selective agent. This herbicide is known to generate superoxide radicals in a living cell and confer oxidative stress in various organisms including *C. elegans* (38, 44). We screened a total of ~2,500 F2 worms born from the wild-type N2 worms that had been mutagenized with ethylmethane sulfonate and isolated several mutants capable of vigorously growing on the selective plate. Among them, we successfully characterized one mutant named *mev-4*(qka5000) after purifying its mutation by backcrossing five times to N2 worms.

This mutant was highly resistant to paraquat (Fig. 1A). For example, N2 worms hardly grew to adulthood in the presence of 0.3 mM paraquat, and none reached adulthood in the presence of 0.4 mM paraquat within 4 days. In contrast, all of the mutant worms grew normally under these conditions, and more than half of them grew to adulthood even in the presence of 0.6 mM paraquat. The mean and maximum life spans of mev-4 were 30% and 20% longer on averages than those of N2, respectively, when cultured at 20 °C (Fig. 1A). When cultured at 26 °C, they were 15 and 23% longer than those of N2, respectively (data not shown).

Then we investigated sensitivity to thermal stress and UV light, both typical stress markers in *C. elegans*. When incubated at 36 °C, mean and maximum survival times were significantly longer in mev-4 than in N2 (Table I). When adult worms were irradiated with UV light and cultured until all died. The mean and maximum survival values were not significantly different between mev-4 and N2 (Table I). We also examined fecundity in the mutant and N2 because the reproduction system is shown to affect longevity in *C. elegans* (30–32). N2 and mev-4 laid 276 ± 15 (n = 19) and 280 ± 25 (n = 11) eggs, respectively, thereby showing no difference between these strains.

**Characterization of the Mutated Gene in mev-4**—The paraquat-resistant trait was genetically recessive and inherited to progeny in a Mendelian fashion. Linkage analysis revealed that the trait was concordant with the genetic marker *dpy-11* located on LG V. Therefore, we regionally mapped *mev-4* locus on LG V using three factor crosses with appropriate genetic markers. We obtained the following results: (*dpy-11 unc-2*) (8/8) *mev-4*; *mev-4* (14/14) (rol-4 lin-25 him-5 unc-76); *mev-4* (4/4) (rol-4 unc-61); *unc-42* (15/18) *mev-4* (3/18) rol-4, *sma-1* (1/20) *mev-4* (19/20) *unc-76*, and (*unc-42 lon-3*) (29/29) *mev-4*. Thus, *mev-4* mutation was mapped to a region close to *lon-3*.
locus. This region contains che-11 locus. che-11 exhibits a defect in chemosensory perception because of irregular sensory ciliary segments with the extension of the life span (33, 36). Therefore, we tested a possibility that mev-4 is allelic to che-11. As expected, the chemosensory neurons of mev-4(qa5000) were not stained or very weakly stained with FITC similar to che-11(e1810), whereas those of N2 were clearly stained (Fig. 2). Consistent with this finding, they showed a defect in osmotic avoidance (not shown). In addition, che-11 was found to be resistant to paraquat as mev-4 (Fig. 3A). We thus constructed worms (rol-4 mev-4/che-11) heterozygous for mev-4 and che-11 mutations and found that this heterogenote was as resistant to paraquat as mev-4 (data not shown). These results suggest that the two mutants are identical.

Based on the above data, we sequenced the che-11 gene (C27A7.4) that contains an open reading frame of 4,260 bp encoding a putative protein of 1,419 amino acids (Sanger Center web site and Ref. 45). The open reading frame of mev-4 was found to have a transition from G to A at position 2,474, which results in conversion of 825Trp (TGG) to a stop codon (TAG). che-11(e1810) mutant also had a transition from C to T at position 2,464, resulting in the conversion of 822Gln (CAA) to a stop codon (TAA) (Fig. 4). This putative protein is homologous to human hypothetical protein KIAA0590 with 29.9% identity and 55.4% similarity and Drosophila protein CG11838 with 24.0% identity and 49.4% similarity. This protein is also homologous to IFT140 protein involved in intraflagellar transport (IFT) in Chlamydomonas reinhardtii (45). In Chlamydomonas, the biochemically identified IFT particle is composed of 16 polypeptides that can be classified into two complexes: complex A containing four polypeptides and complex B containing 12 polypeptides. IFT140 constitutes one of the complex A proteins with TRP motifs necessary for protein-protein interaction (46–48). Similar to mev-4/che-11, other cilial mutants in C. elegans seem to have a defect in its possible IFT complex proteins (45).

In addition, when CHE-11 protein was expressed using a che-11::gfp construct in C. elegans, GFP fluorescence was found in IFT particles in sensory neurons (45, 49). Taken together, we conclude that mev-4 is defective in the function of chemosensory cilia.
exhibited strong resistance to paraquat although mec-8 and dyf-1 che-6 and ASE-mediated chemotaxis and axon outgrowth (53, 54). che-1 tax-4 seem to have normal cilia but have a defect in AWC- and daf-10 have a defect in the socket and/or sheath cells. mec-8 and in chemosensory perception makes worms resistant to spite some ambiguities, the results demonstrate that a defect che-12 (e1812) (36) showed marked resistance to paraquat. De- e1812 with their resistance to paraquat, because one of such mutants to uptake FITC into chemosensory neurons. However, levels of normal culture conditions, and che-14 tax-2 showed significant extension of life span. Therefore, the paraquat-resistant trait in mev-4(qa5011) is not affected by the daf-16 mutation. We crossed mev-4(qa5000) to daf-16(m26) unc-75(e950) double mutant to obtain the mev-4 daf-16 unc-75 triple mutant. The triple mutant was extremely resistant to paraquat, whereas the daf-16 unc-75 double mutant and the daf-16 single mutant were significantly more sensitive to paraquat than N2 (Fig. 3A). Therefore, the paraquat-resistant trait in mev-4 was not affected by the daf-16 mutation. The same result was obtained in che-11(e1810). Then we examined life spans of the above mutants (Fig. 3B). The double mutant mev-4 unc-75 showed significant extension of life span. However, the mev-4 daf-16 unc-75 triple mutant showed a normal level of life span. Similar results were ob- tained in che-11. Therefore, the extension of life span in mev-4 and che-11 depend on the DAF-16 activity, demonstrating that the paraquat resistance can be uncoupled with the extension of life span.

Antioxidant Enzyme Genes—We examined mRNA levels for major antioxidant enzymes in mev-4 and N2. The levels for

| Mutant       | Paraquat resistance | Lifespan | FITC uptake | Genetic defect |
|--------------|---------------------|----------|-------------|----------------|
| N2           | –                   | 1.0      | +           | ASE function   |
| che-1(p679)  | –                   | ND       | ND          | Sensory cilia  |
| che-2(c1033) | ++                  | 1.4      | –           | Sensory cilia  |
| che-3(p801)  | ++                  | 2.0      | –           | Sensory cilia  |
| che-5(c1073) | –                   | ND       | ND          | ASE function   |
| che-6(c1126) | –                   | ND       | ND          | ASE function   |
| che-7(c1128) | –                   | ND       | ND          | ASE function   |
| che-9(e75)   | –                   | ND       | ND          | ASE function   |
| che-10(e1809)| ++                  | ND       | –           | Sensory cilia  |
| che-10(qa5011) | ++                  | 1.2      | –           | Sensory cilia  |
| che-11(e1810)| ++                  | 1.5      | –           | Sensory cilia  |
| che-12(e1812)| ++                  | ND       | –           | Sheath cells   |
| che-13(e1805)| ++                  | 1.5      | –           | Sensory cilia  |
| che-14(e1960)| –                   | ND       | –           | Socket and sheath cells |
| oms-1(p880)  | ++                  | 1.4      | –           | Sensory cilia  |
| oms-3(p892)  | ++                  | 1.6      | –           | Sensory cilia  |
| oms-5(p813)  | ++                  | 2.2      | –           | Sensory cilia  |
| oms-6(p811)  | ++                  | 1.6      | –           | Sensory cilia  |
| daf-6(e1377)| ++                  | 1.3      | –           | Socket and sheath cells |
| daf-10(e1387)| ++                  | 1.6      | –           | Sensory cilia  |
| daf-19(m88)  | –                   | 1.5      | –           | Sensory cilia  |
| mec-1(e968)| +                   | 1.0      | –           | Fasciculation  |
| mec-6(c98)   | –                   | 1.6      | –           | Fasciculation  |
| tax-2(p691)  | +                   | 1.2      | ND          | Axon guidance  |
| tax-4(p787)  | –                   | 1.9      | ND          | Axon guidance  |
| dyf-1(mn335) | ++                  | ND       | –           | SHE function   |
| dyf-2(m160)  | ++                  | ND       | –           | SHE function   |
| dyf-2(m881)  | ND                  | ca.1.8   | –           | SHE function   |
| dyf-3(m185)  | ++                  | ND       | –           | SHE function   |
| dyf-4(m158)  | ++                  | ND       | –           | SHE function   |
| dyf-5(m400)  | ++                  | ND       | –           | SHE function   |
| dyf-6(m175)  | ++                  | ND       | –           | SHE function   |
| dyf-7(m537)  | ++                  | ND       | –           | SHE function   |
| dyf-8(m539)  | ++                  | ND       | –           | SHE function   |
| dyf-9(m1513)| ++                  | ND       | –           | SHE function   |
| dyf-10(e389)| ++                  | ND       | –           | SHE function   |
| dyf-11(mn392)| ++                  | ND       | –           | SHE function   |
| dyf-12(sa127)| ++                  | ND       | –           | SHE function   |
| dyf-13(mn396)| ++                  | ND       | –           | SHE function   |

* The phenotypes were determined as described under “Experimental Procedures.” ND, not determined. –, +, ++, and +++ denote that worms did not reach adult food or did on the fifth, fourth, and third days, respectively, during a 5-day incubation on medium containing paraquat.

* Values relative to N2 (1.0) were shown using data (33) except for che-10(qa5011) and dyf-2(m881).

* The data of mev-4(qa5011) identical to che-10.

* The data in Ref. 64.

Paraoquat Sensitivity in Chemosensory Mutants—We tested sensitivity to paraquat in the following mutants in chemosensory perception (Table II) (36, 50–52). daf-19 lacks all cilia. che-2, che-13, oms-1, oms-5, and oms-6 have a deletion in the middle and/or distal segments of cilia. che-3, che-11, and daf-10 have reduced or irregular ciliary segments. che-12, che-14, and daf-10 have a defect in the socket and/or sheath cells. mec-1 and mec-8 have a defect in amphid cilia fasciculation. tax-2 and tax-4 seem to have normal cilia but have a defect in AWC- and ASE-mediated chemotaxis and axon outgrowth (53, 54). che-1 and che-6 seem to have a defect in ASE sensory neuron function (54, 55). dyf-1 to dyf-13 can not uptake FITC, possibly because of chemosensory cilial dysfunction.

An outstanding finding is that most of the above mutants exhibited strong resistance to paraquat although che-14, daf-19 and mec-8 did not (Table II). daf-19 grew very poorly under normal culture conditions, and che-14 showed a weak activity to uptake FITC into chemosensory neurons. However, levels of the residual activity to uptake FITC did not clearly correlate with their resistance to paraquat, because one of such mutants che-12(e1812) (36) showed marked resistance to paraquat. Despite some ambiguities, the results demonstrate that a defect in chemosensory perception makes worms resistant to paraquat.

Effects of daf-16 Pathway—Many mutants of C. elegans with extended life span are shown to depend on DAF-16 activity (17, 31–33, 35, 56, 57). The daf-16 gene encodes a forkhead transcription factor and plays a key role in expression of genes involved in formation of dauer larvae and tolerance to various stresses (58, 59). In fact, extended life span, resistance to oxidative stress, and up-regulation of the sod-3 gene in daf-2 mutants are not observed on daf-16 backgrounds (17, 60). We thus examined whether the phenotypes of mev-4 were affected by coexistence of a daf-16 mutation.

We crossed mev-4(qa5000) to daf-16(m26) unc-75(e950) double mutant to obtain the mev-4 daf-16 unc-75 triple mutant. The triple mutant was extremely resistant to paraquat, whereas the daf-16 unc-75 double mutant and the daf-16 single mutant were significantly more sensitive to paraquat than N2 (Fig. 3A). Therefore, the paraquat-resistant trait in mev-4 was not affected by the daf-16 mutation. The same result was obtained in che-11(e1810).

Then we examined life spans of the above mutants (Fig. 3B). The double mutant mev-4 unc-75 showed significant extension of life span. However, the mev-4 daf-16 unc-75 triple mutant showed a normal level of life span. Similar results were obtained in che-11. Therefore, the extension of life span in mev-4 and che-11 depend on the DAF-16 activity, demonstrating that the paraquat resistance can be uncoupled with the extension of life span.

Antioxidant Enzyme Genes—We examined mRNA levels for major antioxidant enzymes in mev-4 and N2. The levels for...
C. elegans, and these mutants become resistant to paraquat because of the inability to uptake paraquat into chemosensory neurons. Laser-assisted ablation of chemosensory neurons in amphid has revealed that they are not necessary for the post-embryonic viability of worms, and disruption of all of them leads to constitutive formation of dauer larvae (54, 63). When worms were cultured in the presence of paraquat for more than a week, the majority of them died instead of becoming dauer larvae. This implies that paraquat may damage the entire nervous system.

Many mutants in chemosensory cilia showed extended life spans depending, at least in part, on the DAF-16 activity (33). DAF-16 seems to be activated in the ciliary structure mutants because it specifically accumulates in the nuclei of these mutants (61). The extended life span in mev-4/che-11 can be explained in this context. On the contrary, the paraquat resistance did not depend on DAF-16, indicating that these two phenotypes in mev-4/che-11 are uncoupled. Furthermore, resistance to heat shock did not always cause extension of life span in the worms. For instance, other mutants such as mev-6(qa5006) and mev-7(qa5007) were resistant to both paraquat and thermal stress, but they were not long-lived. Therefore, paraquat or heat tolerance does not directly correlate with longevity, despite the fact that resistance to stress generally favors extended longevity in many organisms (64).

The mutants in chemosensory cilia show abnormalities not only in chemotaxis but also in dauer formation. In these mutants, their chemosensory cilia cannot sense outside signals, but their neurons can work normally. In these situations, worms may take actions as if they are under starved or unfavorable conditions because they may transmit to tissues those signals that there are no chemical attractants or foods. Thus, the absence of chemosensory signals may cause a caloric restriction state or a dauer-like state, although food intake and behaviors seem normal (33). If so, it is no wonder that a mutation in chemosensory cilia can affect metabolism, stress resistance, and longevity in C. elegans. Recently, it was reported that multiple genes involved in metabolism and stress resistance act downstream of DAF-16 and affect longevity in the nematode (65, 66).

Finally, most of the paraquat-resistant mutants showed a defect in chemosensory ciliary functions, but not all of them showed extension of life span. We examined the life spans in more than 50 paraquat-resistant mutants and found that ~20% of them were long-lived. Revealing a signal from chemosensory neurons that causes extension of life span will be important for understanding aging in higher eukaryotes.

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REFERENCES
1. Morris, J. Z., Tissenbaum, H. A., and Ruvkun, G. (1996) Nature 382, 536–539
2. Kimura, K. D., Tissenbaum, H. A., Liu, Y., and Ruvkun, G. (1997) Science 277, 842–846
3. Walkow, C. A., Kimura, K. D., Lee, M. S., and Ruvkun, G. (2000) Science 290, 147–150
4. Clancy, D. J., Gens, D., Harshman, L. G., Oldham, S., Stocker, H., Haefen, E., Leever, S. J., and Partridge, L. (2001) Science 292, 104–106
5. Tatar, M., Kopelman, A., Epstein, D., Tu, M. P., Yin, C. M., and Garfinkel, R. S. (2001) Science 292, 107–110
6. Holzenberger, M., Dupont, J., Ducos, B., Leneuve, P., Gleen, A., Even, P. C., Cervera, and Le Bourc, Y. (2003) Nature 421, 182–187
7. Blumer, M., Kahn, B. E., and Kahn, C. R. (2003) Science 299, 572–574
8. Brown-Borg, H. M., Borg, K. E., Meliska, C. J., and Bartke, A. (1996) Nature 384, 33
9. Flurkey, K., Papaconstantinou, J., Miller, R. A., and Harrison, D. E. (2001) Proc. Natl. Acad. Sci. U. S. A. 98, 6748–6751

* M. Fujii, Y. Matsumoto, and D. Ayusawa, unpublished results.
20. Lithgow, G. J., White, T. M., Melov, S., and Johnson, T. E. (1995) Proc. Natl. Acad. Sci. U. S. A. 92, 7540–7544

21. Murakami, S., and Johnson, T. E. (1998) Curr. Biol. 8, 1091–1094

22. Lee, S. S., Kennedy, S., Tolonen, A. C., and Ruvkun, G. (2003) Development 130, 1215–1224

23. Barsyte, D., Lovejoy, D. A., and Lithgow, G. J. (2001) J. Comp. Neurol. 435, 435–451

24. Ogg, S., Paradis, S., Guttlieb, S., Patterson, G. I., Lee, L., Tissenbaum, H. A., and Ruvkun, G. (1997) Nature 389, 994–999

25. Honda, Y., and Honda, S. (1999) FASEB J. 13, 1385–1393

26. Lin, K., Hsin, H., Libina, N., and Kenyon, C. (2001) Nat. Genet. 28, 139–145

27. Parkes, T. L., Elia, A. J., Dickinson, D., Höflerik, A. J., Phillips, J. P., and Boulianne, G. L. (1998) Nat. Genet. 19, 171–174

28. Bargmann, C. I., and Horvitz, H. R. (1991) Science 251, 1243–1246

29. Munoz, M. J., and Riddle, D. L. (2003) Genetics 163, 171–180

30. Murphy, C. T., McCarroll, S. A., Bargmann, C. I., Fraser, A., Kamath, R. S., Ahringer, J. J., and Kenyon, C. (2000) Nature 424, 277–283

31. Lee, S. S., Kennedy, S., Tolonen, A. C., and Ruvkun, G. (2003) Science 300, 644–647
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