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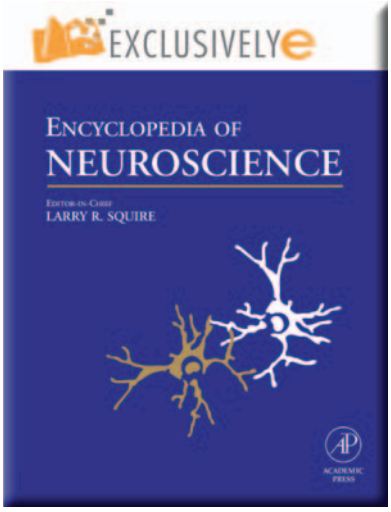

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Aging: Invertebrate Models of Normal Brain Aging

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Introduction

The free-living soil nematode *Caenorhabditis elegans* has been extensively used for studying the genetic regulation of aging, in part because of its short life span and genetic homogeneity. In the nematode, neuroendocrine signaling, nutritional sensing, and mitochondrial functions have been shown to play important roles in the determination of life span. However, aging in *C. elegans* is mainly controlled by a neuroendocrine system, the DAF-2/insulin signaling pathway, which also regulates the life span of flies and mammals, indicating that this pathway is a universal longevity regulator.

The insulin signaling pathway in *C. elegans* was first genetically identified for its effects on dauer larva formation (DAF). Dauer is an alternative developmental stage induced by harsh environmental conditions such as starvation, high population density, or high temperature. Under normal conditions *C. elegans* develops to reproductive adulthood through four larval stages (L1–L4), in 3 days. However, when conditions are adverse, larvae arrest development at the second molt, to enter the dauer stage. Dauers do not feed, are resistant to stress, and can survive up to several months. Dauer larvae are considered to be nonaging because postdauer life span is not affected by the duration of the dauer stage. In addition to insulin signaling, another neuronal pathway that regulates the choice between reproductive growth and dauer entry is the DAF-7 transforming growth factor-β (TGF-β) pathway.

The DAF-2 insulin/insulin-like growth factor-1 (IGF-1) receptor pathway is required for reproductive growth and metabolism, as well as for normal life span. *C. elegans* has a single transmembrane insulin receptor kinase, DAF-2. Upon ligand binding to DAF-2, the kinase domain of the receptor phosphorylates and activates AGE-1, which is a phosphatidylinositol 3-kinase (PI3K). Activated AGE-1 PI3K generates 3-phosphoinositides (PtdIns-3,4-P2 and PtdIns-3,4,5-P3), which are second messengers required for activation of downstream kinases. Downstream kinases include pyruvate dehydrogenase kinase and serine/threonine kinases (PDK-1, AKT-1, and AKT-2), which are protein kinase B (PKB) proteins. These protein kinases regulate the forkhead (FOXO) transcription factor DAF-16, which translocates to the nucleus depending on its phosphorylation level. Phosphorylated DAF-16 remains inactive in the cytoplasm, while upon dephosphorylation it enters the nucleus and exerts its effects on transcription. Thus, the insulin signaling pathway functions to block the nuclear localization of DAF-16. An antagonist of the DAF-2/AGE-1 signaling pathway is the DAF-18 phosphatase and tensin homolog (PTEN) lipid phosphatase (**Figure 1**).

Neuronal Insulin-Like Signaling

Mutations in *daf-2*, *age-1*, or in other genes positively regulated by *daf-2* result in constitutive developmental arrest at the dauer stage. Reducing the activity of genes that antagonize insulin signaling, such as *daf-18* PTEN or *daf-16* FOXO, suppresses the dauer-constitutive phenotype of insulin signaling mutants. While severe mutations in the insulin pathway induce dauer arrest, a milder reduction of insulin signaling results in longer life span. For example, when temperature-sensitive *daf-2* and *age-1* mutants are grown at the permissive temperature until past the dauer arrest decision point, and then shifted to higher temperatures, *daf-2* and *age-1* mutants show increased life span that is dependent on DAF-16. DAF-16 is the main downstream target and major effector of DAF-2/insulin-like signaling regulating *C. elegans* life span. Signaling via the DAF-2/insulin-like receptor antagonizes the FOXO transcription factor DAF-16 by promoting its phosphorylation. Similar modulation of insulin-like signaling pathways in the fruit fly and mouse also modify life span.

The insulin/IGF-1 signaling pathway was first linked to aging in *C. elegans* when mutations in *daf-2* were found to double the life span of the worm. Subsequent investigations, aimed at identifying in which specific cells insulin signaling controls animal aging, supported a prominent role for the nervous system. In these studies, the life span of mosaic animals that had lost *daf-2* activity in different cell lineages was examined. After fertilization, the first cell division produces the AB and the P_1 cells. The AB descendants produce most of the neurons, the hypodermis, the pharynx, the excretory glands, and the vulva, while the P_1 descendants give rise to the muscles, the germ line, the somatic gonad, the hypodermal cells, a few pharyngeal cells, and a few neurons. AB mosaics, which had lost *daf-2* activity in the AB lineage but were *daf-2*(+) in the P_1 lineage, lived twice as long

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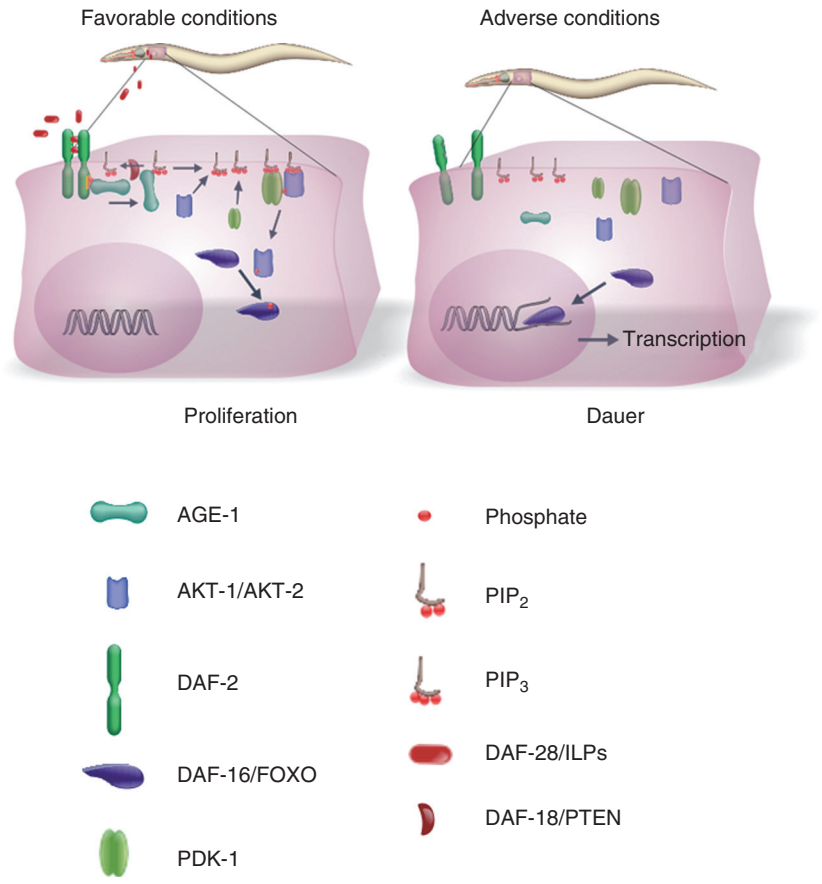

Figure 1 The *C. elegans* insulin-like signaling pathway genes regulate reproductive growth and aging. (Left): Under favorable growing conditions, insulin-like peptides (ILPs) are produced from sensory neurons, to promote the reproductive mode. Binding of ILPs to the DAF-2/insulin receptor results in the phosphorylation of AGE-1/PI3K. Activated AGE-1 generates the phosphoinositides required for the activation of downstream kinases (PDK-1 and AKT-1). This conserved signaling cascade phosphorylates the transcription factor DAF-16/FOXO, preventing its nuclear localization. Retention of DAF-16 in the cytoplasm leads to normal reproductive growth and aging. (Right): Under unfavorable conditions (e.g., crowding or starvation), insulin signaling is inhibited, resulting in the nuclear localization of DAF-16. In the nucleus, DAF-16 regulates the transcription of genes that induce dauer entry and extend life span. Protein nomenclature: AGE, advanced glycosylation end product; AKT, serine/threonine kinase; DAF, abnormal dauer formation; FOXO, forkhead transcription factors, group O; PDK, pyruvate dehydrogenase kinase; PIP, phosphoinositol phosphate; PTEN, phosphatase and tensin homolog. Illustration: Liesbeth de Jong.

as wild-type animals. Although genetic mosaic analyses of *daf-2* support the interpretation that DAF-2 signaling from the nervous system controls longevity, these experiments did not assign longevity control by *daf-2* to specific cell types. In a complementary approach, cell-type-restricted promoters were used to drive the expression of *daf-2* and *age-1* cDNAs in *daf-2* and *age-1* mutants, respectively. Transgenic expression of *daf-2* and *age-1* in neurons suppressed the life span extension phenotype of the corresponding *daf-2* and *age-1* mutants. Life span extension is not rescued when insulin signaling is restored in muscles or in intestinal cells. However, tissue-specific expression, genetic mosaic analysis, and RNA interference (RNAi) experiments indicate that *daf-16* FOXO activity in neurons accounts for not more than 20% of the longevity seen in *daf-16*(−); *daf-2*(−) double mutant animals. Instead, intestinal expression of *daf-16* is sufficient to extend the life span of these animals by 50–60%. These findings indicate that an intricate signaling network regulates aging in *C. elegans* and that neuronal insulin-like signaling controls life span by producing downstream signals that control aging of nonneuronal target tissues.

DAF-2 Insulin Receptor Function in the Nervous System

The *C. elegans* genome encodes more than 30 insulin-like ligands that might mediate input to the *daf-2* pathway through environmental cues, such as nutritional

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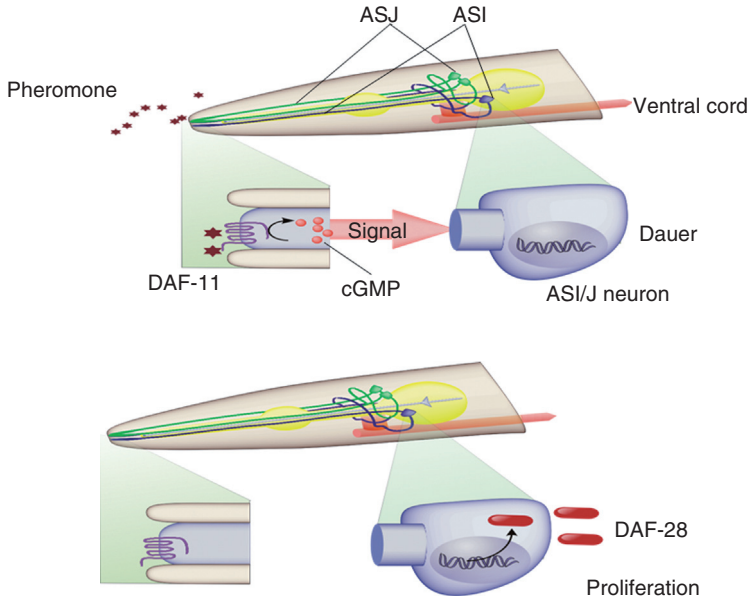

Figure 2 Sensory neurons couple environmental cues to the production of ILPs, such as DAF-28. In the ciliated sensory neurons ASJ and ASI, DAF-11/guanylyl cyclase transduces dauer pheromone signals to cyclic guanosine monophosphate (cGMP) gated ion channels to induce dauer arrest (upper panel). At low pheromone concentration, DAF-28 is produced to activate DAF-2/insulin signaling and reproductive growth (lower panel). Illustration: Liesbeth de Jong.

status or growth conditions. These insulin genes are mainly expressed in neurons, although they are also found in the intestine, epidermis, muscle, and gonad. Some of the insulin-like peptides (ILPs) have been shown to influence longevity. Thus, neuroendocrine control of aging may entail environmental cues that influence neuronal production of insulin-like ligands. For example, *daf-28* encodes an insulin-like protein, which when mutated causes dauer arrest and downregulation of DAF-2 signaling. *daf-28* is expressed in two sensory neurons (ASI and ASJ) that regulate dauer arrest. The presence of dauer pheromone is sensed by DAF-11/guanylyl cyclase, which in turn downregulates *daf-28*. Conversely, in the absence of dauer pheromone, DAF-28 is produced to induce reproductive growth (Figure 2). Although the dauer pheromone does not appear to influence aging, ILPs can act as either agonists or antagonists on DAF-2 to regulate metabolism, reproductive growth, and life span.

In support of this notion, mutations in two genes involved in Ca^{2+}-regulated secretion (*unc-64*, encoding syntaxin, and *unc-31*, encoding calcium-dependent activator protein for secretion, or CAPS), result in an increased life span that is dependent on *daf-16*. *unc-31* is expressed exclusively in neurons, and although *unc-64* is expressed in many secretory tissues, including the nervous system and the intestine, it is the function of *unc-64* in neurons that influences aging. In mammals, insulin secretion by β cells in the pancreas is a Ca^{2+}-regulated process. Therefore, a possible explanation is that the life span extension of *unc-64* and *unc-31* mutants is due to decreased secretion of a DAF-2 insulin-like ligand. Alternatively, *unc-64* and *unc-31* could regulate neurotransmitter input to other insulin-producing cells.

It has also been suggested that oxidative damage to neurons may be a primary determinant of life span. Loss of DAF-2 activity results in the activation of the FOXO transcription factor DAF-16, which controls the expression of antioxidant enzymes, such as superoxide dismutase (SOD) and catalase. Increased expression of these and possibly other free-radical-scavenging enzymes may protect neurons from oxidative damage. Thus, neuronal *daf-2* signaling might regulate animal life span by controlling the integrity of specific neurons that secrete neuroendocrine signals that might regulate the life span of target tissues. In support of this hypothesis, overexpression of Cu/Zn SOD exclusively in *Drosophila* motor neurons extends life span.

DAF-16 Targets

An important question that arises is how the insulin/IGF-1 pathway ultimately regulates aging. As noted earlier, the DAF-16/FOXO transcription factor is a downstream effector of insulin signaling and regulates a wide range of physiological responses by altering the expression of genes involved in metabolism and energy generation, as well as antimicrobial and cellular stress response genes (Table 1).

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Table 1 Proteins implicated in neuroendocrine control of *C. elegans* life span, encoded by genes under control of the DAF-16/FOXO, transcription factor

Protein	*Brief description*
SOD-3	Manganese superoxide dismutase
CTL-1	Cytosolic catalase
CTL-2	Peroxisomal catalase
GST-4	Glutathione-*S*-transferase
MTL-1	Metallothionein-related cadmium-binding protein
OLD-1	Putative receptor tyrosine kinase
SCL-1	Secreted protein with sperm-coating protein (SCP) domain
LYS-7	Lysozyme
LYS-8	Lysozyme
DOD-1	Member of the cytochrome P450 family
DOD-13	Member of the cytochrome P450 family
DOD-16	Cytochrome P450, involved in the oxidation of arachidonic acid to eicosanoids
FAT-7	Involved in the biosynthesis of polyunsaturated fatty acid
DOD-11	Putative alcohol dehydrogenase
GPD-2	Glyceraldehydes-3 phosphate dehydrogenase
DAO-3	Putative tetrahydrofolate dehydrogenase/cyclohydrolase
DOD-14	Alcohol dehydrogenase
DOD-15	UDP-glucuronosyl and UDP-glucosyl transferases
GCY-6	Putative guanylyl cyclase
GCY-18	Guanylate cyclase catalytic domain
VIT-2	Vitellogenin
VIT-5	Vitellogenin
PES-2	Unknown function, putative role in ubiquitin-mediated protein degradation
PEP-2	Oligopeptide transporter
HSP16	Heat shock protein family
SIP-1	Heat shock protein
INS-7	Insulin/insulin-like growth factor-1 peptide
PNK-1	Pantothenate kinase
MRP-5	Adenosine triphosphate-binding protein, member of the subfamily C transporters

SOD is one of the most effective intracellular enzymatic antioxidants. This antioxidant enzyme catalyzes the dismutation of superoxide anions (O_2^-) to oxygen (O_2) and to the less reactive species, hydrogen peroxide (H_2O_2). *sod-3* encodes one of two manganese-containing SODs. It is localized in the mitochondrial matrix and is abundant in neural tissues. *sod-3* was one of the first recognized targets of DAF-16. *sod-3* mRNA is increased in *daf-2* mutants and undetectable in the absence of DAF-16; microarray experiments show that expression of this gene is at least tenfold higher in wild-type worms compared to DAF-16-deficient mutants. Moreover, SOD-3 is upregulated in long-lived strains, such as *age-1* and *daf-2* mutants, and in response to exogenously imposed oxidative stress in a DAF-16-dependent manner. Therefore, increased detoxification from damaging free radicals by this enzyme may contribute to life span extension.

DNA microarray analysis shows that *daf-16* affects the expression of stress response genes, the products of which directly influence aging. For example, expression of the catalase genes *ctl-1* and *ctl-2*, the glutathione-*S*-transferase gene *gst-4*, and the small heat shock protein genes increases when the activity of *daf-2* is reduced, whereas the expression of these genes decreases with the reduction of *daf-16* activity. All of these genes function to promote longevity, probably by preventing or repairing oxidative and other forms of macromolecular damage.

The gene *mtl-1*, which encodes the basally expressed form of metallothionein, is another known target of DAF-16. Metallothioneins are small cysteine-rich, metal-binding proteins protecting cells against heavy metal toxicity and reactive oxide species (ROS)-associated damage. They are induced under a variety of stress conditions, such as conditions involving metal ions, inflammation, glucocorticoids, or oxidative stress. The expression of metallothionein genes is increased in *daf-2* mutants, compared to wild-type animals. Elevated levels of these proteins as well as antioxidant enzymes are expected to decrease ROS-associated damage and hence extend life span.

An additional downstream signaling factor that is regulated by insulin/IGF-1 signaling and promotes longevity is OLD-1, a transmembrane tyrosine kinase. OLD-1 expression is increased in long-lived *daf-2* and *age-1* mutants. This increase is dependent

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on DAF-16. Moreover, OLD-1 is necessary for the increased longevity of *daf-2* and *age-1* mutants and its overexpression increases life span and stress resistance. *old-1* mutations render animals more sensitive to ultraviolet light, starvation, and heat stress. These results point to a positive regulatory role for OLD-1 in life span and stress resistance.

The gene *scl-1* (which encodes sperm-coating protein (SCP)-like extracellular protein) is another target of DAF-16 that is essential for life span extension. SCL-1 has an SCP domain and is homologous to the mammalian cysteine-rich secretory protein (CRISP) family. These proteins enter the secretory pathway and are either released or anchored extracellularly by a transmembrane domain or a glycophosphatidylinositol (GPI) anchor. Expression of *scl-1* is elevated in long-lived *daf-2* and *age-1* mutants and is required for their extension of life span, since downregulation of *scl-1* reduces both life span and stress resistance of these animals. However, *scl-1* is not expressed in *daf-16* mutants. *scl-1* expression correlates with dauer morphogenesis; *scl-1* expression increases (fivefold) as worms enter dauer morphogenesis and decreases (four- to sevenfold) during dauer exit. This implicates *scl-1* in both aging and dauer formation. CRISP family proteins are involved in host defense systems in various organisms, and several functions have been postulated for SCP domain proteins, including cell adhesion, ligand function, protease inhibition, and other enzymatic activities. SCP proteins function in a variety of biological processes that involve signaling, which can be reconciled with SLP-1 being a secreted protein. However, the biochemical function of SCL-1 remains unknown.

DNA microarray analysis has also revealed a number of other *daf-2*/*daf-16*-regulated genes with substantial effects on life span. These include antimicrobial genes encoding lysozymes (*lys-7* and *lys-8*). Lysozymes are upregulated in *daf-2* mutants, and RNAi with these genes suppresses longevity of *daf-2* mutants. Consistently, *daf-2* mutants are resistant to bacterial pathogens. Other genes induced in *daf-2* and repressed in *daf-16* mutants encode proteins potentially involved in the synthesis of steroid or lipid-soluble hormones (e.g., cytochrome P450s, estradiol dehydrogenases, esterases, alcohol/short-chain dehydrogenases, and UDP-glucuronosyltransferases), and genes involved in fatty acid desaturation.

Genes with expression decreased in *daf-2* mutants and increased in *daf-16* mutants include those (*gcy-6* and *gcy-18*) encoding two receptor guanylate cyclases that are expressed in neurons. Further, RNAi with these genes prolongs life span, indicating a role for insulin signaling in sensing the environment. Other genes in this group include vitellogenin genes (*vit-2* and *vit-5*; yolk protein/apolipoprotein-like) and some genes for proteases and metabolic enzymes, such as amino- and carboxypeptidases; also included are *pes-2* (encoding a protein associated with ubiquitin-mediated protein degradation) and an amino oxidase gene, an aminoacylase gene, and an oligopeptide transporter (*pep-2*) gene. Inhibition of several of these genes results in life span extension, leading to the suggestion that the life span extension of *daf-2* mutants may involve reduced turnover of specific proteins.

Studies utilizing computational tools have also identified putative DAF-16 transcriptional targets. The genomes of both *C. elegans* and *Drosophila* were surveyed for genes with DAF-16 binding sites. Orthologous genes identified were further examined in wild-type and *daf-2* mutants animals; *pnk-1* and *mrp-5* were among several putative targets. *pnk-1* encodes a pantothenate kinase that is involved in the biosynthesis of coenzyme A, which is key to fat metabolism. This gene is upregulated in *daf-2* mutants, and RNAi inactivation results in a dramatic decrease of life span of both wild-type and *daf-2* mutant worms. *daf-2* mutants have increased fat storage, which may reflect *pnk-1* upregulation. *mrp-5* encodes an adenosine triphosphate-binding cassette C transporter. Proteins of this family modulate the secretion of insulin and participate in the transport of glutathione and nucleoside analogs. Inactivation of this gene by RNAi extends life span. It has been proposed that MRP-5 could affect aging by regulating the secretion of insulin or the transport of glutathione, an enzyme required for the antioxidant defense of the organism.

It is known that both heat shock and reduced insulin signaling trigger the nuclear localization of DAF-16, where it promotes the expression of small heat shock protein (*shsp*) genes (e.g., *hsp-16.1*, *hsp-16.49*, *hsp-12.6*, and *sip-1*). The *C. elegans* transcription factor, heat-shock factor-1 (HSF-1), is also required for the life span extension, as observed in *daf-2* mutants. HSF-1 acts in response to heat stress and reduced insulin signaling to activate the expression of *shsp* genes, together with DAF-16. Interestingly, overexpression of the gene encoding HSP70F increases longevity, similar to overexpression of the *shsp* gene *hsp-16*. Heat shock proteins are involved in reparation of misfolded or damaged proteins and are essential for recovery of cells after heat treatment. This indicates that protein misfolding and aggregation are important factors in aging.

In addition to inducing the expression of genes involved in several processes, DAF-16 can also act as a transcriptional repressor. For example, DAF-16 inhibits the expression of *ins-7*. This gene encodes an

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insulin/IGF-1 peptide. Its expression is repressed in animals with reduced DAF-2 activity and is elevated in animals with reduced DAF-16 activity. RNAi for *ins-7* increases the life span of wild-type animals and the frequency of dauer formation. Thus, INS-7 behaves as a putative DAF-2 agonist. It is hypothesized that when DAF-2 is active, it inhibits the activity of DAF-16, which allows *ins-7* to be expressed. The production of INS-7 leads to further activation of DAF-2. However, when DAF-2 activity is reduced, DAF-16 is activated and inhibits the expression of *ins-7*.

Sensory Input and Neuroendocrine Signaling

C. elegans senses environmental cues through ciliated sensory neurons. Large numbers of genes required for the development and function of *C. elegans* sensory neurons have been identified. In addition to disrupting sensory neuron function, mutations in some of these genes increase life span.

Amphids are gustatory and olfactory neurons located at the *C. elegans* head. Gustatory neurons sense dauer pheromone, food, and amino acids in the environment. Olfactory neurons are responsible for sensing food-derived substances and volatile chemicals. To define which of these cells are involved in the regulation of life span, individual cells were ablated by a focused laser microbeam. Ablation of gustatory neurons revealed that only a specific subset (ASI and ASG, and not ADF, ASJ, and ASK) may influence life span. This was also the case for the olfactory neurons (AWA and AWC), since only the ablation of AWA extended life span, whereas, ablation of AWC had no effect. This was further confirmed by using mutants with specific defects in these neurons. Combined ablation of gustatory and olfactory neurons results in greater longevity, compared to ablation of either gustatory or olfactory neurons alone, suggesting that these neurons function in distinct pathways to control life span. Many mutations abrogating sensory neurons, including putative chemosensory receptors, extend the life span of *C. elegans*, largely in a *daf-16*-dependent manner. The life span extension caused by gustatory neurons depends on *daf-16*, indicating that these neurons might modulate the *daf-2* pathway. However, in the case of olfactory neurons, effects on life span are only partly dependent on *daf-16*. Many sensory neurons in *C. elegans* produce ILPs. Therefore, it is plausible that perception affects life span by influencing the activity of the insulin signaling pathway. However, these mutations show complicated interactions with the insulin/IGF-1 pathway. Double mutants did not live longer than the *daf-2* single mutant; instead their life span was shorter. This may indicate that sensory control of life span is only partially dependent on the *daf-2* pathway. Likewise, some gustatory and olfactory neurons enhance, whereas others reduce, longevity. Therefore, environmental signals that affect life span may be relayed by a *daf-2*-independent pathway.

A possible additional mechanism for influencing life span by sensory inputs is the regulation of lipid accumulation. *C. elegans* mutant strains with defects in neuroendocrine signaling show increased fat accumulation and extended life span. This is the case for *daf-2* insulin receptor mutants, the tryptophan hydroxylase *tph-1* serotonin defective mutant, and the *tub-1* (tubby ortholog) mutant. In *C. elegans*, *tub-1* is expressed in sensory neurons and *tph-1* is expressed in serotonergic neurons. In addition, a genome-wide RNAi screen identified several genes involved in food sensation and neuroendocrine signaling that, when knocked down, resulted in aberrant fat accumulation. These include genes for glutamate and dopamine receptors, as well as chemoreceptor and olfactory receptor genes. Consistently, *C. elegans* mutants with either structural or functional defects in nine specific ciliated neurons show increased fatty acid accumulation in the intestine. Interestingly, some mutations that increase lipid accumulation also lengthen life span. Thus, ciliated neurons may sense environmental cues and express neuropeptides and insulin ligands to regulate metabolism and life span. However, while the insulin signaling pathway is a major regulator of *C. elegans* fat storage (*daf-2* mutants show increased lipid accumulation), fat accumulation in these sensory mutants is independent of DAF-16/FOXO.

Other Neuroendocrine Mechanisms

In a chemical screen aimed at identifying drugs that delay aging, anticonvulsant medications were found to extend worm life span Anticonvulsants modulate neural activity in mammals and act presynaptically to modulate neuromuscular activity in the worm. Interestingly, anticonvulsants significantly increase the life span of *daf-2* loss-of-function mutants as well as that of *daf-16* mutants. This finding suggests that neural activity regulates aging by an additional mechanism independent of insulin-like signaling Similarly, these compounds further increased the life span of animals with mutations in genes important for the function of sensory neurons (*osm-3* and *tax-4*) and neurotransmission (*unc-31*, *unc-64*, and *aex-3*), highlighting the intricacy of the neuronal pathways that might be involved in the regulation of nematode aging.

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The reproductive system also regulates aging in *C. elegans*. Ablation of the two germ line precursor cells, as well as mutations that reduce germ line proliferation, remarkably extend the *C. elegans* life span. This life span extension requires the presence of the somatic gonad, since ablation of both germ line and somatic gonad has no effect on life span. The life span extension of germ-line-ablated animals depends on DAF-16/FOXO and may be mediated hormonally, since it also depends on DAF-12, a nuclear hormone receptor, and DAF-9, a cytochrome P450 involved in the production of steroid hormones (3-keto sterols) that function as DAF-12 ligands. Another gene required for the increased life span associated with germ line loss is *kri-1*. The *kri-1* gene encodes a conserved protein with ankyrin repeats and is expressed in pharynx and intestine. Germ line ablation results in the nuclear localization of DAF-16 in the intestine (the worm's adipose tissue), and intestinal expression is sufficient to account for the observed longevity. KRI-1 and to a lesser extent DAF-12 and DAF-9 are required for the DAF-16 nuclear localization in the intestine of germ-line-defective animals. However, although loss of DAF-2 receptor activity promotes the nuclear localization of DAF-16 in many tissues, including the intestine, DAF-16 localization is not dependent on KRI-1, DAF-12, or DAF-9. Moreover, *kri-1* RNAi completely suppresses the life span extension of germ line mutants, while it has no significant effect on wild-type or *daf-2* mutants, indicating that modulation of life span by KRI-1 is specific to the reproductive-signaling pathway. Thus, the role of lipophilic hormones and KRI-1 on the nuclear localization of DAF-16 is germ line specific and independent of insulin signaling. Therefore, the germ line might possess a specific endocrine system to influence aging.

Nevertheless, neuronal and gonadal endocrine signaling mechanisms appear to interact in a complex manner. Somatic gonad ablation prevents the life span extension of germ-line-ablated wild-type animals, but it does not completely prevent life span extension in animals that lack olfactory neurons. Similarly, germ line ablation further extends the life span of *daf-2* mutants independently of whether or not the somatic gonad is present.

Concluding Remarks

The nervous system performs the task of sensing and integrating environmental cues into coordinated physiological responses that will ensure maximal survival and reproductive fitness. In *C. elegans*, food availability, temperature, and a secreted pheromone are some of the sensory inputs that regulate the decision of entering the metabolically active reproductive mode or shifting to the nonreproducing, nonfeeding dauer larva stage, with large amounts of stored fat.

Despite its apparent simplicity, *C. elegans* has a surprisingly sophisticated neuroendocrine system that regulates development, metabolism, and life span. Both, insulin-like and TGF-β signaling pathways act in parallel to regulate development and metabolism, with the insulin-like signaling pathway playing a major role in life span regulation. Importantly, the regulation of life span by insulin/IGF signaling is conserved across taxa, and reduction of insulin signaling has been shown to extend life span in worms, flies, and mammals. Similarly, the physiological processes involved in the aging process also appear to be conserved. For example, signals from the reproductive system also influence life span in mammals, and dietary restriction has been shown to extend life span in a wide variety of organisms. Likewise, sensory perception could also regulate life span in higher organisms, since blocking the sense of taste reduces insulin secretion in mammals, and the smell of food increases insulin levels in humans.

How physiological processes are coordinated by neuroendocrine signaling to meet the biological demands of an organism is still not completely understood. More than 30 ILPs are encoded in the *C. elegans* genome, some of which are agonists and others of which are antagonists. Some have been shown to influence aging, but many remain to be functionally characterized. It is of fundamental importance to understand which cells or tissues emit or receive signals to coordinate the aging process at the level of the whole organism. *C. elegans* has been instrumental for the discovery of conserved molecular pathways regulating aging. Its relatively short life span and its amenability for genetic and molecular analyses make it an ideal organism to pursue these studies further, aiming to ultimately understand why and how animals age.

See also: Aging of the Brain; Gene Expression in Normal Aging Brain; Insulin-Like Growth Factor Signaling and Actions in Brain; Neuroendocrine Aging: Pituitary Metabolism; Vesicular Neurotransmitter Transporters.

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Relevant Websites

http://www.arclab.org – Aging Research Centre.

http://www.afar.org – American Federation for Aging Research.

http://www.ncoa.org – National Council on Aging.

http://www.nia.nih.gov – National Institute on Aging (U.S. National Institutes of Health).

http://sageke.sciencemag.org – Science of Aging Knowledge Environment, an interdisciplinary repository of issues related to aging (American Association for the Advancement of Science).

http://www.geron.org – The Gerontological Society of America.