IUBMB *Life*, 60(5): 315–322, May 2008

Critical Review

Mechanisms of Aging and Energy Metabolism in *Caenorhabditis elegans*

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Summary

Aging studies on diverse species ranging from yeast to man have culminated in the delineation of several signaling pathways that influence the process of senescent decline and aging. While understanding these interlinked signal-transduction cascades is becoming even more detailed and comprehensive, the cellular and biochemical processes they impinge upon to modulate the rate of senescent decline and aging have lagged considerably behind. This fundamental question is one of the most important challenges of modern aging research and has been the focus of recent research efforts. Emerging findings provide insight into the facets of cellular metabolism which can be fine-tuned by upstream signaling events to ultimately promote longevity. Here, we survey the mechanisms regulating aging in the simple nematode worm *Caenorhabditis elegans*, aiming to highlight recent discoveries that shed light into the interface between aging signaling pathways and cellular energy metabolism. Our objective is to review the current understanding of the processes involved and discuss mechanisms that are likely conserved in higher organisms.

IUBMB *Life*, 60(5): 315–322, 2008

Keywords aging; adipose tissue; *Caenorhabditis elegans*; caloric restriction; dauer larva; germline; hormone; insulin; lifespan; longevity; reproduction.

INTRODUCTION

Research on simple model organisms such as *Caenorhabditis elegans*, *Drosophila melanogaster*, and *Saccharomyces cerevisiae* has led to remarkable progress in understanding the molecular pathways that modulate aging and senescence (*1–4*). The free-living soil nematode *C. elegans* has led research on the genetic regulation of aging in part because of its relatively short lifespan and the capacity for self-fertilization which facilitates the generation of genetically homogenous populations. A multitude of single-gene mutations altering lifespan have been identified in *C. elegans* and other species, providing evidence that aging can be modulated by evolutionary conserved regulatory pathways (*4*). These pathways normally control growth, reproduction, stress response, and energy metabolism.

In the nematode, neuroendocrine signaling, nutritional sensing, and mitochondrial functions have been shown to play important roles in the determination of lifespan. In this review, we focus on the role of insulin signaling in aging and the mechanisms by which insulin signals are translated through downstream effector kinases and transcriptional factors to modulate lifespan. In addition, we discuss physiological conditions that affect aging, including dietary restriction, altered mitochondrial function, and reduced protein translation, aiming to highlight links between different pathways that reveal an integrated network of interactions, which coordinates the aging process.

THE INSULIN SIGNALING PATHWAY

Aging in *C. elegans* is mainly controlled by a neuroendocrine system, the Insulin/Insulin Growth Factor 1 (IGF-1) signaling pathway (IIS), which also modulates lifespan in flies and mammals, indicating that this pathway is a universal longevity regulator (*5–7*). The *C. elegans* Insulin/IGF-1 pathway was first genetically identified through studies of the dauer larva formation (Daf) process. Dauer is an alternative nematode developmental stage induced by harsh environmental conditions such as starvation, high population density, or high temperature. Under normal conditions, *C. elegans* develops to the reproductive adult through four larval stages (L1–L4) in 3 days. However, when conditions are adverse, larvae arrest normal 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 post-dauer lifespan is not affected by the duration of the dauer stage (*8*). The

Received 28 December 2007; accepted 5 February 2008
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ISSN 1521-6543 print/ISSN 1521-6551 online
DOI: 10.1002/iub.66

Insulin/IGF-1 pathway is required for reproductive growth and metabolism, as well as normal lifespan. In addition to insulin signaling, the TGF-β-like pathway also regulates the choice between reproductive growth and dauer entry (*9*) and has recently been implicated in the aging process (*10*).

The IIS pathway was first linked to aging in *C. elegans*, when mutations in two genes, *age-1* and *daf-2* encoding components of the pathway, were found to dramatically extend the lifespan of the worm (*6*). Numerous subsequent investigations have led to the discovery of many additional genes affecting longevity via the IIS pathway.

How does the Insulin/IGF-1 pathway coordinate physiological processes to influence the aging rate? *C. elegans* senses environmental cues through ciliated sensory neurons. The *C. elegans* genome contains more than 30 insulin-like ligands that might mediate input to the DAF-2 insulin receptor in response to environmental cues, such as nutritional status or growth conditions (*11, 12*). Insulin-like peptides (ILP) can act as either agonists or antagonists on DAF-2 to regulate metabolism, reproductive growth, and lifespan. ILPs are mainly expressed in neurons, although they are also found in intestine, epidermis, muscle, and gonad. A likely mechanism for the neuroendocrine control of aging is that environmental cues control the production and release of ILPs from sensory cells, thereby influencing the physiology of the organism. Cell ablation or mutations abrogating sensory neurons extend the lifespan of *C. elegans* (*13, 14*). Thus, it is plausible that sensory perception affects lifespan, at least in part, by influencing the activity of the insulin signaling pathway. However, these manipulations appear to have complicated interactions with the Insulin/IGF-1 pathway (*14*).

DAF-2 is the single *C. elegans* transmembrane insulin receptor kinase (*15*). Upon binding of ILPs to DAF-2, the kinase domain of the receptor phosphorylates and activates AGE-1, a phosphatidylinositol 3-kinase (PI3K) (*16*). 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 effector kinases. Downstream kinases include PDK-1, SGK-1, AKT-1, and AKT-2 protein kinase B proteins (*17–19*). These protein kinases regulate the forkhead (FOXO) transcription factor DAF-16, which translocates to the nucleus depending on its phosphorylation level (*20–22*). Phosphorylated DAF-16 remains inactive in the cytoplasm, but 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/TEN lipid phosphatase (*23*). Reduced Insulin/IGF-1 signaling, increased DAF-18/PETEN activity, or stress conditions such as starvation, heat, or oxidative stress result in the nuclear localization of DAF-16/FOXO. In the nucleus, DAF-16 regulates expression of many genes, among others, genes involved in metabolism, immune defense, autophagy, and stress resistance (*24–27*).

In addition to the IIS kinase cascade, other kinases have been found to modulate DAF-16 activity. The c-Jun N-terminal kinase (JNK-1) is activated upon environmental stress and its overexpression in *C. elegans* results in life extension (*28*). JNK-1-mediated lifespan extension is DAF-16-dependent. JNK-1 phosphorylates DAF-16 and induces its translocation into the nucleus. JNK-1 overexpression further increases the lifespan of *daf-2* mutants, indicating that this kinase pathway acts in parallel to the PI3/AKT pathway. The MST (mammalian sterile 20-like) kinase also phosphorylates DAF-16 to regulate oxidative-stress responses and lifespan (*29*). MST is required for mutant *daf-2* longevity and its overexpression extends lifespan in a DAF-16-dependent manner. The AMP-activated protein kinase (AMPK) senses AMP/ATP ratios and is activated upon reduced energy levels. Knockout of the *C. elegans* homologue AAK-2 suppresses mutant *daf-2* longevity while its overexpression extends lifespan (*30*). Other kinases partially required for mutant *daf-2* longevity are the p38 MAP kinase and RAS signaling kinases (*31, 32*). Apart from phosphorylation, DAF-16/FOXO is also modulated by ubiquitination. The conserved E3 ubiquitin ligase RLE-1 regulates aging by polyubiquitination of DAF-16. RLE-1 deficient worms have increased levels of DAF-16, are stress resistant, and show a *daf-16*-dependent life extension (*33*).

Additional factors also regulate DAF-16/FOXO activity in the nucleus. Increased expression of the NAD^+-dependent protein deacetylase, sirtuin, increases the lifespan of yeast, worms, and flies (*34–36*). Deacetylation of FOXO by the mammalian homologue SIRT1 is a requirement for its nuclear localization (*37*). In *C. elegans*, lifespan extension conferred by extra copies of *sir-2.1* depends on DAF-16 and on 14-3-3 scaffold proteins. In response to stress, SIRT-2.1, 14-3-3, and DAF-16 form a complex that activates the DAF-16 target gene superoxide dismutase [*sod-3* (*38, 39*)]. Furthermore, the heat-shock transcription factor HSF-1, which is induced upon heat stress, mediates mutant *daf-2* longevity. HSF-1 overexpression extends lifespan in a DAF-16-dependent manner (*40*). In addition, SMK-1, a conserved nuclear factor, mediates longevity and DAF-16 nuclear localization in worms lacking the germline (*41*). Another transcriptional regulator of DAF-16 in worms and mammals is β-catenin/BAR-1, a component of the Wnt signaling pathway. β-Catenin physically interacts with DAF-16 and enhances the expression of *sod-3* (*42*). However, it is not known whether BAR-1 is required for the long life of Insulin/IGF-1 signaling mutants.

CALORIC RESTRICTION

Caloric restriction (CR), a significant reduction in calorie intake without essential nutrient deprivation, can slow the intrinsic rate of aging in yeast, nematodes, flies, rodents, and probably primates (*43*). The fascinating effects of dietary restriction include maintenance of most physiological processes in a youthful state and a delay in the occurrence and/or progression of age-associated disease. Little is actually understood about the mechanism by which reduced caloric intake is translated into

longevity. In rodents, the antiaging action of dietary restriction is dependent upon the reduced intake of calories, rather than reduction of the body fat content or metabolic rate (*44*).

If the life-prolonging stimulus is reduced calories, what are the molecules that "sense" this signal and convert it to the many physiological changes in calorie-restricted cells? In yeast, CR is mimicked by limiting media glucose levels or by genetic mutation of components of the cyclic AMP-dependent protein kinase A pathway. CR effects on yeast replicative capacity requires the activity of the SIR2 histone deacetlyase and NPT1, a gene required for production of NAD, the oxidized form of nicotinamide adenine dinucleotide. NAD availability plays an important role in signaling, and may affect several metabolic processes (*3*). In *C. elegans*, mutations in genes regulating feeding (*eat* genes) result in lowered food intake because of defects in pharyngeal function. The consequent, imposed dietary restriction significantly lengthens animal lifespan (*45*). Dietary restriction in worms can also be achieved by diluting their bacterial food. At optimum levels of dietary restriction, worms typically live 20–50% longer than fully fed animals.

How does CR retard aging? Low calorie intake is correlated with reduced oxidative damage. Thus, the beneficial effects of dietary restriction upon lifespan may depend upon its ability to ameliorate oxidative stress by reducing protein oxidation. In addition, dietary restriction has been associated with elevated protein turnover (*46*). A recent study confirms earlier reports that protein synthesis and degradation rates decline with age in liver tissue, and this decline is retarded by CR (*47*). These findings indicate that elevation of protein turnover and the consequent maintenance of a healthy protein pool, free of oxidant damage, is one of the lifespan-extending capacities of CR. The molecules that mediate this regulation are of clear interest for antiaging interventions.

Recent research in C. elegans has revealed that two evolutionarily conserved transcription factors (PHA-4 and SKN-1) are required for lifespan extension under dietary restriction (*48, 49*). These regulators may coordinate physiological responses to dietary restriction. PHA-4, which was originally described for its role in specifying the pharynx in worm embryos, is a member of the forkhead family of transcription factors, and is very similar to mammalian FOXA proteins. In mammals, FOXA proteins have developmental roles, and regulate glucose metabolism later in life. *pha-4* mutant animals do not respond to dietary restriction. By contrast, mutants lacking DAF-16/FOXO still showed a normal response to dietary restriction, indicating that longevity induced by restricted food intake is DAF-16/FOXO independent. Thus, PHA-4/FOXA appears to be specific for dietary restriction-mediated longevity, whereas DAF-16/FOXO is involved in regulating longevity induced by insulin/IGF-1 signaling. A conserved nuclear factor SMK-1 is required for longevity in both pathways (*49*).

SKN-1 is related to mammalian NRF2 transcription factors. Similar to PHA-4, the nematode SKN-1 functions early in embryonic development, where it specifies the formation of the intestine and related tissues. Lack of SKN-1 specifically abolishes dietary-restriction-induced longevity over a wide range of food concentrations without affecting lifespan extension through reduction of insulin/IGF signaling (*48*). The *skn-1* gene is expressed in the intestine and a single pair of neurons known as the ASIs.

SKN-1 function in the ASI neurons, and not in the intestine, is required for the effects of dietary restriction longevity. Moreover, dietary restriction increases *skn-1* expression specifically in these two neurons. Therefore, dietary restriction activates a highly regulated process, rather than passive metabolic changes. Interestingly, ASIs are sensory cells that integrate cues from the environment and produce various hormonal signals that are relayed to the whole body. It is tempting to speculate that these signals coordinate organism-wide physiological responses to dietary restriction.

MITOCHONDRIAL DYNAMICS

Mitochondria are involved in key aging-associated processes, such as cellular metabolism and ATP synthesis. It is, therefore, not surprising that mitochondrial dysfunctions influence the rate of aging. Paradoxically, however, in many cases, unpaired mitochondrial function results in increased lifespan. The first identified long-lived mitochondrial mutant carried lesions in the nuclear gene *clk-1* (*50*), which encodes a mitochondrial protein involved in ubiquinone biosynthesis. Thereafter, a mutation in the *isp-1* gene, encoding the Rieske iron-sulfur subunit of complex III of the electron transport chain (ETC), was also found to increase lifespan (*51*). Other genetic mutations in mitochondrial proteins that increase lifespan include *gro-1* and *lrs-2*, an isopentenylphosphat:tRNA transferase and a leucine tRNA synthase, respectively (*52, 53*). Moreover, loss-of-function mutations in the ETC components *nuo-1*, *atp-2*, and *frh-1* increase nematode lifespan, while causing developmental arrest at the L3 larval stage (*54, 55*). A genetic mutation in *tpk-1*, a thiamine pyrophosphokinase which affects TCA cycle components, also increases the lifespan (*56*). In addition to genetic mutations, genome-wide RNAi screens have identified many other genes coding for mitochondrial proteins, and reduction of the synthesis of these proteins results in increased lifespan. These include mostly components of the ETC and ATP synthase, TCA cycle enzymes, and mitochondrial carrier proteins (*52, 57–60*).

What is the mechanism by which reduced mitochondrial function translates into increased lifespan? Mitochondria are major producers of reactive oxygen species (ROS) as a result of electron misplacement along the ETC. The free radical theory of aging postulates that ROS cause aging by damaging DNA, lipids, and proteins. In view of this theory, one possibility is that mitochondrial mutations might result in reduced rate of living and decreased ROS production (*51*). In other cases, ETC dysfunction might result in increased electron leakage and ROS production, which consequently activates an adaptive hormetic response. That is, in response to mild stress, defense mecha-

nisms will be activated resulting in oxidative stress resistance and life extension (*61*). Although a handful of data support the oxidative damage theory of aging, recent data put the correlation between oxidative stress and aging into question. Life-extending mitochondrial RNAi interventions respond differently to oxidative stress challenges (*52, 62*), indicating lack of correlation between protein oxidation levels and life extension in mitochondrial mutants (*63*). Moreover, measurable increase in oxidative damage due to reduced detoxification does not shorten the lifespan of long-lived mitochondrial mutants (*64*).

Another plausible mechanism involved is signaling and the activation of alternative metabolic routes that will counter the mitochondrial defect and energy deficit. Long-lived yeast mitochondrial mutants activate a retrograde signaling pathway that results in the activation of specific transcription factors that will shift metabolism away from the Krebs cycle toward the glyoxylate cycle. This metabolic shift has also been observed in dauer larvae and long-lived *daf-2* mutants (*65, 66*). It is possible that a metabolic shift also contributes to the extended lifespan of *C. elegans* mitochondrial mutants. Reduced AMP/ATP ratios activate the AMPK. The *C. elegans* aak-2/AMPK is partially required for the life extension of *daf-2* and mitochondrial mutants (*30, 67*). In addition, recent investigations suggest that cell cycle checkpoint control plays an important role in specifying longevity of mitochondrial mutants (*63*).

It is generally believed that mitochondrial dysfunctions exert their effect on lifespan independently of the IIS pathway, because according to some reports, they extend lifespan independently of DAF-16 and show a synergistic effect with *daf-2* mutations (*50–52, 58*). However, some mitochondrial mutations require DAF-16 for lifespan extension and influence its nuclear localization (*52, 57*). IIS is coupled to mechanisms that regulate metabolism and oxidative stress. For example, mitochondrial defects are associated with insulin resistance and diabetes. Therefore, it is possible that alteration of mitochondrial function affects longevity, in part, through components of the IIS pathway. To date, there is no clear mechanistic explanation for the observed increased longevity of mitochondrial mutants. Mitochondrial mutations result in pleiotrophic effects, and possibly, different mutations will affect the aging rate differently and in a tissue specific manner. Certainly, mitochondrial dysfunction results in more intricate physiological responses than merely increasing or reducing oxidative damage, and unveiling the mechanisms implicated in mitochondrial-mediated life extension is crucial to understand how lifespan is regulated.

PROTEIN SYNTHESIS

Protein synthesis is critical for all biological process and is influenced by aging. The activity of key mRNA translation factors declines with age in many organisms, resulting in reduction of protein synthesis rates (*68, 69*). For example, old mice tend to show an increase in small polysomes and a decrease in large polysomes, compared with young individuals, which is consistent with a reduction in the rate of translation (*70*). Supporting evidence from *Drosophila melanogaster* shows that polyribosome levels exhibit a marked, age-related decrease (*71*). Global mRNA translation is reduced in response to most, if not all types of cellular stress. Studies on mRNA translation regulation under conditions of stress have focused on the formation and regeneration of the translation initiation factor 2 (eIF2)-methionyl-initiator tRNA-GTP ternary complex, and the recruitment of ribosomes on the mRNA (*72*). However, the significance of this decline in senescence remains unclear. Is it a beneficial adaptation to reduced mitochondrial function and energy production, as a consequence of aging, or does it directly contribute to the aging process? Because protein synthesis is essential for growth and development, it is not straightforward to dissect its specific role in aging. Manipulation of general mRNA translation is likely to have pleiotropic effects, thus obscuring any explicit contribution to aging. Nevertheless, several recent studies capitalize on the genetic malleability of invertebrate models such as *C. elegans* and *Drosophila* to investigate the link between protein synthesis and aging. These studies provide an entry point into what might turn out to be an important aspect of the biology of aging.

The process of protein synthesis involves three major, tightly regulated, events; initiation of mRNA translation, elongation of the polypeptide chain, and termination of mRNA translation. Initiation is the rate-limiting step in mRNA translation and is the most common target of translational control (*73*). Several cellular signaling mechanisms converge to influence the rate of mRNA translation, in response to a variety of stimuli, by modulating the activity or the availability of important translational regulators (*74*). Alterations in protein synthesis occur during embryonic development, cell growth, cell differentiation, and aging. Signal transduction cascades, such as the insulin/IGF-1, the kinase *target of rapamycin* (TOR), and p38 mitogen-activated protein kinase pathways, play a key role in the global control of protein synthesis by targeting several components of the translation machinery (*74, 75*). For example, a variety of agents that promote cell growth and proliferation, including hormones, growth factors, and nutrients, have stimulatory effects on the initiation of protein synthesis (*76*). Global control of protein synthesis is generally achieved by changes in the phosphorylation state of initiation factors or their regulators. The rate of protein synthesis is mainly determined by regulation of two discrete steps during mRNA translation initiation: recruitment of the 40S ribosomal subunit at the 5′ end of mRNA and loading of the 40S ribosomal subunit with the initiator methionyl-tRNA. These events are coordinated by initiation factors eIF4E and eIF2/eIF2B, respectively. Phosphorylation of the eIF2 α-subunit regulates dissociation of the eIF2B/eIF2 complex and eIF2 recycling (*77*). Similarly, the availability of active eIF4E is controlled by phosphorylation of eIF4E binding proteins [4E-BPs (*78*)].

Five eIF4E isoforms (IFE-1 to IFE-5) are encoded in the *C. elegans* genome. IFE-1, IFE-3, and IFE-5 are expressed in germline, whereas IFE-2 and IFE-4 are expressed specifically in

somatic cells. IFE-3 and IFE-4 bind only 7-monomethyl guanosine caps, whereas IFE-1, IFE-2, and IFE-5 can bind both 7-monomethyl guanosine and 2,2,7-trimethyl guanosine caps (*79*). In *C. elegans*, the majority of mRNAs acquire a 2,2,7-trimethyl guanosine cap, through the process of trans-splicing (*80*). Interestingly, depletion of IFE-2 results in significant (~40%) lifespan extension, whereas depletion of other isoforms does not alter nematode lifespan. Loss of IFE-2 results in downregulation of protein synthesis in somatic cells; *ife-2* deletion mutants show lower protein synthesis rates, compared with wild-type. Elimination of germline specific eIF4E isoforms does not significantly alter animal lifespan (*81*). Because IFE-2 is the most abundant eIF4E isoform in somatic *C. elegans* tissues, these findings suggest that reduction of protein synthesis specifically in the soma extends lifespan (*82*).

Postdevelopmental elimination of other translation initiation factors or their regulators has analogous effects on the longevity of the nematode. Reducing the levels of the scaffold protein eIF4G or the eIF2 beta subunit, using RNAi during adulthood, leads to a ~30% increase in lifespan (*83–85*). Similarly, reducing the levels of several ribosomal proteins or the ribosomal-protein S6 kinase during adulthood extends nematode lifespan. In all cases the rate of protein synthesis in RNAi-treated animals are reduced compared with wild-type controls (*83, 84*). In addition, many genes encoding components of the eIF complex and components of the 40S and 60S subunit of the ribosome were recovered in an RNAi screen for essential genes that extend lifespan when inactivated postdevelopmentally (*57, 85*).

The unexpected finding that reduction of protein synthesis in the soma extends lifespan in worms provides new insights on the basic cellular processes that play a role in senescent decline. At the same time, several new questions now emerge. Why is eIF4E activity in somatic tissues, but not in the germline, important for normal aging? Aging is a soma-specific phenomenon; the germline is an immortal cell lineage (*86, 87*).

Protein synthesis is one of the most energy-consuming cellular processes, devouring an estimated 50% of the total cellular energy, depending on the organism and cell growth state (*88*). Both mRNA and ribosome biosynthesis are controlled by insulin/IGF-1 and TOR signaling. Under favorable conditions, yeast cells synthesize ~2,000 ribosomes per minute, to maintain robust growth (*89*). Therefore, reduction of protein synthesis rates under unfavorable, stress conditions would result in notable energy savings. This energy could then be diverted to cellular repair and maintenance processes, thus contributing to longevity. Failure to divert energy toward repairing stochastic damage that accumulates in the soma during life is responsible for the inexorable decline of somatic functions and senescence. Thus, while in metabolically active somatic tissues energy is mostly consumed in biosynthesis, the germline invests in repair, instead. It remains to be determined whether regulation of protein synthesis is part of this scenario.

In addition to moderating the large energy requirement of protein synthesis in the soma and facilitating cellular maintenance and repair, downregulation of mRNA translation, under appropriate conditions, may prevent the synthesis of unwanted proteins that could interfere with the cellular stress response. Remarkably, the stress-induced attenuation of global translation is often accompanied by a switch to the selective translation of proteins that are required for cell survival under stress. However, the mechanisms that govern preferential translation of specific mRNAs under stress are poorly understood. The significance of the protein synthesis decrease during aging is also still an open issue (*82*). The tools are now available to address these issues in simple model organisms such as yeast, worms, and flies. Given the remarkable conservation of the core protein synthesis machinery, its accessories, and regulatory pathways, the outcome of this endeavor is likely to be relevant to aging in mammals.

CONCLUDING REMARKS

Despite its apparent simplicity, *C. elegans* has a surprisingly sophisticated neuroendocrine system that regulates development, metabolism, and lifespan. 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, with large amounts of stored fat. Importantly, the regulation of lifespan by insulin/IGF-1 signaling is conserved across taxa and reduction of insulin signaling has been shown to extend lifespan 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 lifespan in mammals and dietary restriction has been shown to extend lifespan in a wide variety of organisms. Likewise, sensory perception could also regulate lifespan in higher organisms, because 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. Protein synthesis has emerged as one candidate target process for insulin signaling. Lifespan extension caused by decreasing mRNA translation establishes a direct link between protein synthesis and aging. The biological relevance of this relationship is underscored by the tight integration between the insulin/IGF-1 pathway and the CR response with mechanisms governing mRNA translation regulation (*90–92*). Thus, the effects of insulin/IGF-1 signaling and CR on aging could in part be mediated by appropriately modulating protein synthesis, among other processes, to promote longevity.

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 lifespan and its amenability for genetic and molecular analysis makes it an ideal organism to pursue these studies further aiming to ultimately understand why and how animals age.

ACKNOWLEDGEMENTS

We apologize to colleagues whose work could not be cited due to space limitations. We acknowledge support from EMBO, the EU Sixth Framework Program, the Marie Curie Actions Program, and IMBB.

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