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Guest Editorial

There Are Worms in My Aging Research!

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Caenorhabditis elegans (the worm) has long been a key model organism for understanding the biological mechanisms that underlie life span, health span, and aging. The first mutations that modulate life span were identified in worms (1–4). Subsequent cloning of *daf-2*, an insulin-like receptor (5), and its downstream target *daf-16*, a FOXO transcription factor (6,7), opened up the field of aging research to genetic analysis. Since this time, there has been an explosion of aging research, much using worms, that has revealed many fundamental aspects of metabolism and cellular signaling that impinge on life span and health span. Today, the worm is still teaching us about fundamental aspects of aging, as highlighted by several recent publications in JGBS.

Tissue Aging

Tissue degeneration is a common feature of aging, but not all tissues "age" the same. Because the worm is transparent, individual tissues are easily observed over the course of aging. Indeed, early observations of aging worms suggested that different tissues have different morphologically observable, age-associated deterioration (8,9). Three recent studies in JGBS have focused on understanding the functional decline of specific tissues during worm aging; two of these focus on the pharynx and the third on the intestine. Together, these studies provide detailed measurements of aging phenotypes in individual organs.

The pharynx is the eating organ of the worm. The pharynx is a bilobed tubular structure composed of 8 muscle cells, 20 neurons, and an assortment of epithelial, support, and gland cells. Rhythmic contraction, or pumping, of pharyngeal muscles sucks bacteria into the mouth of the worm, mechanically disrupts the bacteria with the cuticular grinder, and then pushes the food into the lumen of the gut. As worms age the pumping rate of the pharynx declines, and pumping rate can predict life span (10). In a recent study, Russell and colleagues (11) have used electrophysiological measurements of pharynx muscle contraction to characterize changes in pharynx function with age. In addition to a decline in the frequency of pumping with age, they observe that the duration of contraction is extended in older worms. This study also suggests that the variation in pumping rate for an individual worm decreases with age. These trends are maintained, but delayed, in long-lived mutants. In another study, Eckley and colleagues (12) used a machine learning approach to define aging "states." In these studies, they used machine learning to classify states of chronologically aged worms based on 2,919 measurements of pharynx images from 3,523 worms. This approach revealed five morphological aging states that all worms traverse. They isolated worms in each state for transcriptome analysis by microarray. Their analysis suggests that changes in the production of small heat-shock proteins are associated with transitions between aging states. Although the molecular features that define these changes in pharyngeal morphology and function remain to be determined, these two studies provide a new, high-resolution view of aging in this tissue.

The intestine of the worm is the digestive system, where nutrients are absorbed, and it also serves as a central metabolic tissue. Many genes that modulate life span act in the intestine. The intestine atrophies with age, losing both microvilli and some nuclei (13). One critical function of the intestine is to produce yolk, a lipoprotein complex similar to LDL that is packaged into oocytes. Yolk accumulates in postreproductive worms (8,9). Production of yolk is associated with intestinal atrophy, as autophagy is used to convert intestine biomass into yolk (14). Sornda and colleagues (15) show that yolk accumulates because the synthesis of vitellogenins (yolk proteins) continues even after egg production has ceased. Moreover, they show that accumulation of vitellogenins is associated with decreased production of other intestinal proteins. The authors suggest that this is an example of a genetic program that is useful during early life (reproduction), but then contributes to tissue dysfunction later when it is not turned off.

Pharmacology and Toxicology

As is famously attributed to Paracelsus, "the dose makes the poison." As such, the difference between pharmacology and toxicology is quantitative, not qualitative, as both approaches aim to understand the biological effects of exogenous compounds. The worm is an excellent system in which to understand the basic biological effects of small molecules, and to identify functionally relevant targets of biologically active compounds. Two recent studies published in JGBS

highlight the use of the worm for these studies. It seems likely that the worm will continue to have an important role in understanding the pharmacology and toxicology of compounds that modulate aging and disease.

Negi and colleagues (16) have investigated the effects of ursolic acid, a triterpene in fruit skins, stem bark, and leaves. In a previous study, this group showed that ursolic acid increases life span of worms by activating the JNK-1 kinase, independently of daf-16, the FOXO transcription factor. Protein modeling suggested that ursolic acid could bind directly to JNK-1. In this new study, the authors find that ursolic acid, acting through JNK signaling, also delays the onset of polyglutamine protein aggregation. These studies also show that ursolic acid does not increase the life span of animals with mutations in *skn-1*/Nrf or *eat-2* (a genetic approximation of dietary restriction).

Haghani and colleagues (17) uses the worm to investigate the effects of exposure to nano-sized particulate matter from traffic-related air pollution. Epidemiological studies have suggested an association between air pollution and increased risk for chronic diseases of aging (18). In this work, Haghani and colleagues show that air pollution nano-particulates can impact development and have a small effect on life span. This work provides a new model to integrate environmental toxicology and gerontology, and open a possibility to more fully understand the molecular basis of the effects of environmental exposures across life span.

Stress and Aging

When Klass first published his observation of life span in worms, he noted that decreasing food consumption increased life span. Since that time, there have been several approaches to study the effects of decreased food on aging and longevity, including the complete removal of all food after development (19), dilution of bacterial food either on plates or in liquid culture (20,21), genetic mutations that disrupt feeding (22), and growth in axenic culture (23). Not unexpectedly, the genetic requirements for increased life span vary (21). A study by Cai and colleagues (24) uses tissue-specific RNAi to show that *cbp-1*, the orthologue of p300/CBP, is required in GABAergic neurons for increased life span in axenic culture; however, GABA itself is not required. Depleting *cpb-1* in GABAergic neurons also disrupted the worm's ability to chemotax toward food, raising the possibility that some GABAeric neurons could mediate both the perception of food and increased life span associated with decreased food availability. It is not clear whether this is specific to dietary restriction from axenic culture, or if this is a more general role for GABAergic neurons.

One of the earliest insights from worm research was that life span is often associated with stress resistance. Indeed, selecting for mutations that confer thermal stress tolerance identified several long-lived mutants (25). The fact that many long-lived worms are resistant to environmental stress suggests the possibility that aging is just another form of stress, and that engaging stress responses enhance survival and therefore extend life span. Perhaps the best-known articulation of this idea is the "oxidative stress" hypothesis of aging, which posits that oxidative damage accumulates with age as a result of normal metabolic function.

Dues and colleagues (26) used RNAi to deplete stress–response factors in long-lived *daf-2* mutant animals. These animals have a mutation in the insulin/IGF-like receptor DAF-2 that confers increased life span and resistance to heat stress, osmotic stress, oxidative stress, anoxia, and pathogenic bacteria. This study shows that, in *daf-2* mutant animals, the increased life span is not directly associated with stress resistance. For example, mutation of all five superoxide dismutase enzymes severely reduce oxidative stress resistance of *daf-2* mutant animals, but has little effect on life span. Together, these experiments shown that stress resistance and longevity, while often associated, do not have a causal relationship. This is in line with previous observations that there was little correlation between life span and resistance to heat stress in animals with different mutant alleles of *daf-2* (27). Moreover, there are many mutations that increase stress resistance but do not increase life span. This study expands these previous observations, and suggests that no specific aspect of stress response is absolutely correlated with longevity even in this long-lived mutant. Together, these studies add evidence to the hypothesis that increased stress resistance is not a cause of enhanced longevity, though these phenotypes are closely related.

Conclusion

Many of the fundamental processes identified in worms, and other "simple" model systems have been conserved in mammals by evolution. These observations suggest that there are some similarities in the biological processes that influence cellular and organismal aging and survival, and there is great effort to leverage this evolutionary conservation to modulate the effects of aging in human populations. This is a laudable goal—age is the single greatest risk factor for a variety of devastating diseases in humans, including cardiovascular dysfunction, cancer, and neurodegenerative disease. However, the power of the worm—or any model organism—is not simply the recapitulation of an aspect of human disease. These models give us the power to explore the different ways that nature and evolution have solved common problems—such as those associated with aging.

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Conflict of Interest

None reported.

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