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Invertebrates as model organisms for research on aging biology

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Invertebrate model systems, such as nematodes and fruit flies, have provided valuable information about the genetics and cellular biology involved in aging. However, limitations of these simple, genetically tractable organisms suggest the need for other model systems, some of them invertebrate, to facilitate further advances in the understanding of mechanisms of aging and longevity in mammals, including humans. This paper introduces 10 review articles about the use of invertebrate model systems for the study of aging by authors who participated in an ‘NIA-NIH symposium on aging in invertebrate model systems’ at the 2013 International Congress for Invertebrate Reproduction and Development. In contrast to the highly derived characteristics of nematodes and fruit flies as members of the superphylum Ecdysozoa, cnidarians, such as *Hydra*, are more ‘basal’ organisms that have a greater number of genetic orthologs in common with humans. Moreover, some other new model systems, such as the urochordate *Botryllus schlosseri*, the tunicate *Ciona*, and the sea urchins (Echinodermata) are members of the Deuterostomia, the same superphylum that includes all vertebrates, and thus have mechanisms that are likely to be more closely related to those occurring in humans. Additional characteristics of these new model systems, such as the recent development of new molecular and genetic tools and a more similar pattern to humans of regeneration and stem cell function suggest that these new model systems may have unique advantages for the study of mechanisms of aging and longevity.

Aging and longevity studies in invertebrate model systems, especially the round worm (*Caenorhabditis elegans*) and the fruit fly (*Drosophila melanogaster*), have yielded many insights into the understanding of the genetics and biology of lifespan and healthspan. These two short-lived invertebrate organisms, the fruit fly *D. melanogaster* and the nematode *C. elegans*, along with studies in single-celled organisms like the yeast, *Saccharomyces cerevisiae*, demonstrated the usefulness of genetically tractable model systems for uncovering the complexities of the aging process. Since the discovery of *age-1*, the first gene that was identified to increase the lifespan of *C. elegans* when mutated (Friedman & Johnson 1988), considerable progress has been realized in the understanding of factors and processes that contribute to aging (Gems & Partridge 2013; Lepez-Otin et al. 2013). However, much remains to be learned about the mechanisms of aging and longevity, and the new model invertebrate systems may provide the necessary tools and paradigms for advancing our knowledge in this area.

Biological Aging is characterized by a progressive loss of physiological integrity, leading to impaired function and increased vulnerability to death, which happens in most living organisms. This disruption is often associated with slow and gradual build-up of metabolic products from physiological processes leading to a decrease

in fitness and greater susceptibility to diseases (Finch & Morgan 1990). Although the mechanisms that accompany ‘biological aging’ and its variability in humans are complex, we have begun to understand this biological, potentially modifiable aging phenotype at the molecular and cellular level from an ever-expanding set of available models, including simple invertebrate organisms, new technologies, and many high throughput tools (Klass 1983). Understanding aging and how to slow or prevent it has attracted the curiosity and imagination of people, ranging from philosophers to scientists, throughout history. Recent scientific discoveries have now set this field on the path of potential new knowledge of life and disease at the cellular and molecular level, particularly with the discovery that the rate of aging is controlled, at least to some extent, by genetic pathways and biochemical processes conserved in evolution.

A recent review enumerates ‘nine tentative hallmarks’ that represent common denominators of aging in different organisms, with special emphasis on mammalian aging (Lepez-Otin et al. 2013). They include: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. However, a major challenge still remains in being able to dissect the

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interrelationships between these and other potentially new candidate hallmarks and their relative contributions to aging and age-related susceptibility to disease.

A need for additional model systems for aging studies

Although the nematode, the fruit fly models, and yeast have led to major advances in aging research, the gaps that exist in these models make a compelling case for additional, potentially invertebrate, model systems to identify longevity genes, whose roles have yet to be studied, and to investigate the role of additional cellular pathways in aging. Both the nematode and the fruit fly models have critical shortcomings (Austad 2009) including the following: (a) both nematode and fruit fly belong to Ecdysozoa, a superphylum, which has undergone extensive gene loss since their divergence from their common ancestor with humans and thus a large fraction of human orthologs are missing. These missing human orthologs are present in Cnidaria (Kortschak et al. 2003; Wenger & Galliot 2013); (b) larvae from these two species can enter a non-aging stage in response to stress, which suggests that modulation of lifespan observed in corresponding adult organisms may be mediated by stress response mechanisms that have no equivalent in humans; (c) except for the *Drosophila* gut, the somatic adult tissues of these two organisms have limited regenerative capabilities with scarce to null cell proliferation; finally, (d) nematodes and fruit flies poorly mimic the processes involving stem cell renewal and tissue repair mechanisms that maintain tissue homeostasis in mammals. Thus, new invertebrate models with proliferating cells in the adult, as well as in those with extensive regenerative capacity, have the potential to be informative on the perils of life-long cell division and mechanisms of tissue regeneration and homeostasis. In addition, unique life histories of new invertebrate models may offer opportunities to study the effects of reproductive mode (asexual vs. sexual) on longevity.

Given this background, researchers have begun to make new inroads in the study of aging and longevity in several new model systems, several of which are reviewed by leading scientists in this review issue. The papers presented here are the outcome of a symposium, entitled 'NIA-NIH symposium on aging in invertebrate model systems,' which was held on 15 July and 16 July 2013, at Wayne State University in Detroit, Michigan, USA. We provide here a brief outline of the advantages of several of the newest invertebrate model systems for the study of aging. In addition, the symposium included papers on recent advances in aging research in the more traditional invertebrate models, *C. elegans* and *D. melanogaster*, which are reviewed in this volume by Tissenbaum (*C. elegans*), Jasper (*D. melanogaster*), and Arking (*D. melanogaster*).

Botryllus schlosseri

Urochordates are considered to be the closest living invertebrate relatives of vertebrates, *B. schlosseri* is a colonial urochordate that invokes a stem cell-mediated budding program during subsequent rounds of asexual reproduction although it follows the chordate plan of development following sexual reproduction. Papers in this volume by Voskobonik et al. and by Munday et al. (laboratory of De Tomaso) describe how research on *B. schlosseri* can advance the study of aging and regeneration. Voskobonik et al. have sequenced and assembled 580 Mbp of the *B. schlosseri* genome, which is comprised of nearly 14,000 intron-containing predicted genes, and 13,500 intron-less predicted genes, 40% of which could be confidently parceled into 13 (of 16 haploid) chromosomes. A comparison of homologous genes between *B. schlosseri* and other diverse taxonomic groups revealed genomic events underlying the evolution of vertebrates and lymphoid-mediated immunity (Voskobonik et al. 2013). The draft genome has revealed a large number of genes, both with and without vertebrate homologs, but the spatial and temporal expression of these genes *in situ* has remained a challenge. In any event, the characteristics of this colonial ascidian make it an attractive model for studying immunology, stem cell biology, evolutionary biology, and regeneration. The ability to reproduce asexually renders colonial tunicates robust survivors, capable of rapid proliferation and whole body regeneration, both of which could prove to be highly valuable for studying alternative modes of reproduction, natural transplantation reactions, and stem cell-mediated regeneration (Friedman & Johnson 1988; Harada 2013; Rinkevich et al. 2013; Rosner et al. 2013; Voskobonik et al. 2013; Braden et al. 2014; Griggio et al. 2014; Manni et al. 2014; Matozzo et al. 2014; Taketa & De Tomaso 2014). Recent progress described in this volume may further help to identify and understand the roles of new markers for both developing and mature structures in *B. schlosseri*, permitting analysis of phenotypes induced in loss-of-function experiments (Langenbacher et al. 2014). Thus, the colonial urochordate, *B. schlosseri*, seems to be a valuable new model for studies on aging.

The tunicate Ciona

Ciona is known to be a powerful model for studying regeneration. Similar to what is observed in humans, its regeneration capacities seem to decline with age (Jeffery 2012, 2014). Furthermore, the close phylogenetic relationship of *Ciona* to vertebrates and its short life-span facilitate its use as a highly amenable model for studying the relationship between aging and regeneration (reviewed in this volume by William R. Jeffery). Indeed,

studies of regeneration of the neural complex of *Ciona* (Jeffery et al. 2008) show that this organism may be a highly valuable model for understanding age-related neurodegenerative diseases at the molecular level.

Hydra

Basal metazoans like sponges, jellyfish, corals, and hydras are good models because of their longevity and immortality characteristics. Pluripotent stem cells present in these animals maintain somatic cell lineages central to regeneration and rejuvenation. Stem cell clones represent a holdover from immortal cell clones of single-celled organisms. Early bilaterians such as flatworms appear to retain stem cell-based immortality. However, higher bilaterians, including humans seem to have traded immortality for greater complexity and safeguards against unregulated cell growth. Several recent papers review the utility of *Hydra* as a model for aging studies (Galliot 2012; Martinez & Bridge 2012; Boehm et al. 2013; Schaible & Sussman 2013), and reviews by Galliot and by Bellantuono et al. (laboratory of Martinez) in this volume highlight their recent work on these organisms.

Hydra has several important characteristics relevant to longevity research, including an interesting deviation from typical life histories. *Hydra* species have: (a) an extensive capacity to regenerate and self-renew, defying the aging process; (b) the ability to decouple the aging process from their life history, which presents with a unique opportunity to obtain further insights into the aging process; and (c) the ability to escape aging as a result of high levels of cell proliferation and regenerative capacity. Cellular processes required for stem cell maintenance, such as telomere dynamics, which prevent the accumulation of damage and protect against diseases and pathogens that mediate this condition, may also be studied in this model.

Monogonont rotifers

Although rotifers do not have the ability to regenerate, their small size, short generation time, ease of culture, and new genetic tools make them a suitable model for studies of aging (Snell 2014). In the accompanying paper, Snell et al. discusses the advantages of rotifer models in general, and describes recent experimental lifespan and healthspan studies in the rotifer *Brachionus manjavacas*. Bdelloid rotifers may be especially useful in characterizing the role of redox systems, including the function of TOR kinase and JNK pathways, in regulating lifespan and healthspan (Snell et al. 2014).

Sea urchins

Sea urchins present a unique model for the study of aging due to the existence of species with tremendously

different natural lifespans (Bodnar 2009). The red sea urchin (*Strongylocentrotus franciscanus*) is one of the earth's longest living animals, living in excess of 100 years with no age-related increase in mortality rate or decline in reproductive capacity or health. In contrast, *Lytechinus variegatus* has an estimated maximum life expectancy of about four years while that of *Strongylocentrotus purpuratus* is estimated to be over 50 years (Bodnar 2013). Although sea urchins have been used for developmental studies, they have not been considered for aging studies until recently because of the general lack of molecular and genetic tools, in comparison with other models for aging research. However, as described in this volume, Bodnar et al. have recently developed this model for studying the molecular, cellular, and physiological basis for differences in longevity between species and the mechanisms underlying the absence of aging.

Other model invertebrates for the study of aging

Research on other invertebrate models, not included in this volume, may also prove valuable. Among them is *Daphnia*, a planktonic crustacean that has been widely used as a model invertebrate for toxicological studies. Recently, *Daphnia* has also been used to study cellular stress and longevity (Schumpert et al. 2014). Recent studies on *Daphnia* and a broad range of other organisms have shown that variation in the response to dietary restriction might be more common than previously thought, based on responses to resveratrol (Kim et al. 2014). Age-dependent mortality of *Daphnia* is affected by an age-by-environment interaction during times of stress (Roach et al. 2009).

Future directions

Although we continue to witness remarkable progress in aging research using invertebrate models, major limitations and challenges remain in the use of these new models for research in aging biology. These limitations include: (a) technologies to mass culture cells from these models are still lacking; (b) progress has been slow in fine tuning genetic and molecular tools and methodologies, including RNAi and transgenic approaches, for use in these models; (c) very few age-related phenotypes that are functions of specific cellular and molecular pathways in these systems have been identified; and, (d) information on cellular, molecular, and physiological mechanisms in tissue aging and homeostasis, including the role of stem cells and senescence, is still very meager in these new model systems. The research reviewed by papers in this volume describes a start towards solving these problems in order to understand the mechanisms of aging and longevity.

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