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Sex-specific lifespan and its evolution in nematodes

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ABSTRACT

Differences between sexes of the same species in lifespan and aging rate are widespread. While the proximal and evolutionary causes of aging are well researched, the factors that contribute to sex differences in these traits have been less studied. The striking diversity of nematodes provides ample opportunity to study variation in sex-specific lifespan patterns associated with shifts in life history and mating strategy. Although the plasticity of these sex differences will make it challenging to generalize from invertebrate to vertebrate systems, studies in nematodes have enabled empirical evaluation of predictions regarding the evolution of lifespan. These studies have highlighted how natural and sexual selection can generate divergent patterns of lifespan if the sexes are subject to different rates or sources of mortality, or if trade-offs between complex traits and longevity are resolved differently in each sex. Here, we integrate evidence derived mainly from nematodes that addresses the molecular and evolutionary basis of sex-specific aging and lifespan. Ultimately, we hope to generate a clearer picture of current knowledge in this area, and also highlight the limitations of our understanding.

Contents

1. Introduction

Improvements in healthcare and nutrition have led to a rapidly widening section of the population entering into old age. This is coupled with an increase in the burden of chronic diseases, including neuro-degeneration, cancer and heart disease. Cumulative physiological decline – or aging – is the predominant risk factor for death [1]. Aging therefore has clear biomedical implications [2], but also presents a fascinating evolutionary challenge [3]. In a variety of taxa, lifespan – a frequently measured proxy for aging defined as time from birth until death – varies according to sex [4–6]. In humans and other mammals, lifespan and aging also show sex-specific patterns, with a bias towards longer female lifespan [4]. Suggested explanations for sex-biased patterns range from male mal-adaptation driven by innate asymmetries in the transmission of genetic material, to differential selection arising from divergence of reproductive strategy [7]. Understanding the basis of sex dif-

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ferences in aging and longevity could reveal novel mechanisms underlying intraspecific variability in aging rate [4].

Nematode worms have been a fruitful system for uncovering the mechanistic and evolutionary causes of aging. Their popularity arises largely from lab tractability, manageable lifespans and – particularly for the androdioecious (hermaphrodite and male) species *Caenorhabditis elegans* – a fully sequenced and annotated genome with an abundance of genetic resources [8]. Crucially, aging in *C. elegans* recapitulates many aspects of mammalian senescence, including accumulation of macromolecular and cellular damage, progressive deterioration of physiological function, and increased mortality and morbidity [9]. Substantial modulation of aging has been achieved in *C. elegans* through mutation or down-regulation of widely conserved aging-associated pathways, such as insulin/insulin-like growth factor (IGF)-1 signalling and mitochondrial response networks, as well as restriction of food intake without starvation (dietary restriction) and the application of pharmacological agents [10]. The expression of over 800 genes have been shown to change in expression with age in the standard N2 (Bristol) strain [11], while many genes regulating *C. elegans* aging are deregulated in human age-associated diseases [9]. Although *C. elegans* primarily comprises self-fertilizing hermaphrodites with rare males, several studies have examined dioecious species in which lifespan is sexually dimorphic [12,13]. Broader insights have been gained from a range of free-living and parasitic nematodes, in which enormous diversity in lifespan – from a few days to decades – has been documented [14]. However, aging patterns are to date poorly characterised in nematodes, except for *Caenorhabditis* and, more recently, *Pristionchus* [13–16].

Investigation in nematode systems has been limited by factors including a poor understanding of nematode ecology, as well as the difficulty of characterizing aging itself. Physiological decline over time can be assessed in nematodes using parameters including motility and stress resistance [17], which are informative for understanding organismal health span (the period of unimpaired activity and function preceding age-related decline [18]). However, as studies focusing on sexual dimorphism in such traits are limited, comparisons of intrinsic lifespan comprise the majority of this review.

2. Sexual dimorphism of intrinsic lifespan and aging in the laboratory

The culture of nematodes in laboratory conditions facilitates the monitoring and control of food, interactions with other individuals, and extrinsic mortality [19]. Phenotypes associated with somatic aging in *C. elegans* hermaphrodites include deterioration of muscle integrity, leakage of yolk from the intestine into the body cavities, immunosenescence [18], and degradation of intestinal microvilli and nuclei [20]. The pathobiology of aging in *C. elegans* males is currently unknown. The majority of studies in *C. elegans* focus on hermaphrodites, which is largely attributable to the difficulties associated with studying males. This includes their rarity (0.1% of hermaphrodite self-progeny), their mate-searching behavior leading to desiccation on the plate walls, as well as their attempts to mate with themselves via the excretory pore, leading to mortality [21,22]. In this section, we review sex differences in nematode lifespan and reproductive aging, and consider how the physiological factors behind intrinsic senescence are heavily contingent on genetic and environmental interactions.

2.1. Sex differences in lifespan

How robust and generalizable are the sex-specific lifespan and aging patterns in nematodes? In *Caenorhabditis* nematodes, comprising both androdioecious (males and hermaphrodites) and dioecious (males and females) species, male longevity biases have been broadly observed, with the exception of the androdioecious nematode *C. briggsae* [12]. However, the pattern is complex. Male-biased longevity was found in nine out of twelve wild *C. elegans* isolates, but hermaphrodite lifespan bias (possibly owing to sickly males) was also identified, and certain isolates showed no clear bias [12]. Alongside genetic background, culture conditions and intra/intersexual interactions can greatly influence the sexually dimorphic patterns observed. It is particularly important to determine whether mortality arises as a consequence of aging itself, as opposed to non-optimal culture conditions or other sources of age-independent mortality. Nematode populations are generally maintained on lawns of *Escherichia coli* at 15–25 °C. When populations are cultured in isolation at 20 °C, N2 *C. elegans* males have a similar pattern of age-specific mortality but reduced aging rate compared to hermaphrodites [22]. Males live ∼20% longer than hermaphrodites under solitary conditions, as a result of reduced mortality rate acceleration. In single-sex groups, however, median hermaphrodite lifespan exceeds that of males by ∼60% because homosexual male-male interactions shorten their lifespan [22]. Harmful male interactions within grouped populations might explain why *C. remanei* females outlive males when nematodes are housed in same-sex groups of 20 individuals [23], whereas males of *C. remanei* spp. *vulgaris* live longer than females when housed under solitary conditions [12]. A further factor known to dramatically alter nematode longevity is mating, which reduces the lifespan of *C. elegans* hermaphrodites by around 40% [24]. The lifespan of *C. remanei* males exceeds that of females in grouped mated populations, reversing the pattern seen in grouped virgin populations [23], which highlights the substantial cost of intersexual encounters (Table 1).

Clearly, a variety of known and unknown variables modify the relationship between sex, aging and fitness in nematodes, which must be carefully considered when drawing conclusions about the evolution of sexually dimorphic aging. Equally, however, this plasticity and variability among different nematode groups presents great opportunity for comparative approaches. For example, the putative pattern of male-biased longevity in certain rhabditid nematodes is reversed in *Pristionchus,* with females generally outliving males [13], opening avenues for research into the influence of reproductive biology on sexual selection and sex-specific aging.

2.2. Sex differences in reproductive aging

There has been growing interest in understanding the underlying molecular causes of reproductive senescence in nematodes, which could shed light on female reproductive decline and degeneration of oocyte quality in humans [26–28]. Unsurprisingly, studies in *C. elegans* have focused almost exclusively on hermaphrodites, which produce progeny by self-fertilization for 7 days at 20 °C, after which point they can be crossed with males for up to 15 days [29]. The decline in hermaphrodite fertility with age has been attributed to TGF-β and Insulin/IGF-1 signaling-dependent deterioration of oocyte quality [27]. A recent analysis of genes influencing reproductive span has indicated that contact with males influences reproductive as well as somatic aging [28] (also see section 3.3.). Males of *C. elegans* lose the ability to cross-fertilize by day 7 of adulthood, around 1/3 of their average lifespan, and this seems to reflect a declining ability to execute mating behavior that can be modulated by insulin signaling, rather than deterioration of gamete function [29]. However, *C. elegans* males are dispensable for reproductive success, whereas in dioecious species the maintenance of male vigour has more bearing on fitness. Indeed, males of the dioecious nematode *C. remanei* maintain progeny production for longer and reach peak reproductive performance at a later age than females [25]. A study in another dioecious species, *P. exspectatus,* found that changes in