Longevity

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Deadly males accelerate aging with piRNAs

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Mating is known to accelerate the aging of the opposite sex in a variety of species. A transcriptomic analysis of extracted germlines from mated and unmated *Caenorhabditis elegans* by Shi and Murphy now identifies a Piwi-interacting RNA-to-Hedgehog signaling pathway that regulates the accelerated aging of hermaphrodites.

Although spouses will hyperbolically complain that their significant other is driving them into an early grave, work of the past several decades in *Caenorhabditis elegans*, *Drosophila melanogaster* and *Mus musculus* has demonstrated that — to a certain extent — this complaint might actually be true[1–3]. Phenotypic studies have revealed that both male and female lifespan can be shortened by exposure to members of the opposite sex, independently of reproduction. However, the mechanisms that drive accelerated aging in the presence of the opposite sex have remained largely enigmatic. The presence of specific components of seminal fluid, pheromones or secreted compounds have all been demonstrated to shorten the lifespan of the opposite sex[4–7]. In a recent report in *Nature Aging*, Cheng Shi and Coleen Murphy[8] performed a transcriptional analysis of germlines of mated and unmated *C. elegans* to identify a Piwi-interacting RNA (piRNA)-to-Hedgehog signaling pathway that regulates the accelerated aging of hermaphrodites in response to males.

Groundbreaking work in *C. elegans*, which live on average for 2–3 weeks, has demonstrated that aging is regulated by both environmental manipulations and genetics[9,10]. Work in *C. elegans* has also demonstrated that signaling between reproductive and somatic tissues can regulate lifespan, with removal of the germline leading to extended lifespan[11]. *Caenorhabditis elegans* are predominantly hermaphrodites; 0.01 to 0.1% of the population are males, which lack one of the X chromosomes. Mating with males shortens the lifespan of the hermaphrodites[2], and causes a shrinking of the germline and a loss of both fats and glycogen[6]. This process has previously been proposed to be regulated by copulation itself[2]; secreted pheromones known as ascarosides[7]; the dafachronic acid and insulin signaling pathways[6,12,13]; and fat metabolism of oleic acid[13,14] (Fig. 1). However, the downstream consequences of these proposed regulatory pathways, and what changes specifically occur in the female germline in response to mating, are still unclear.

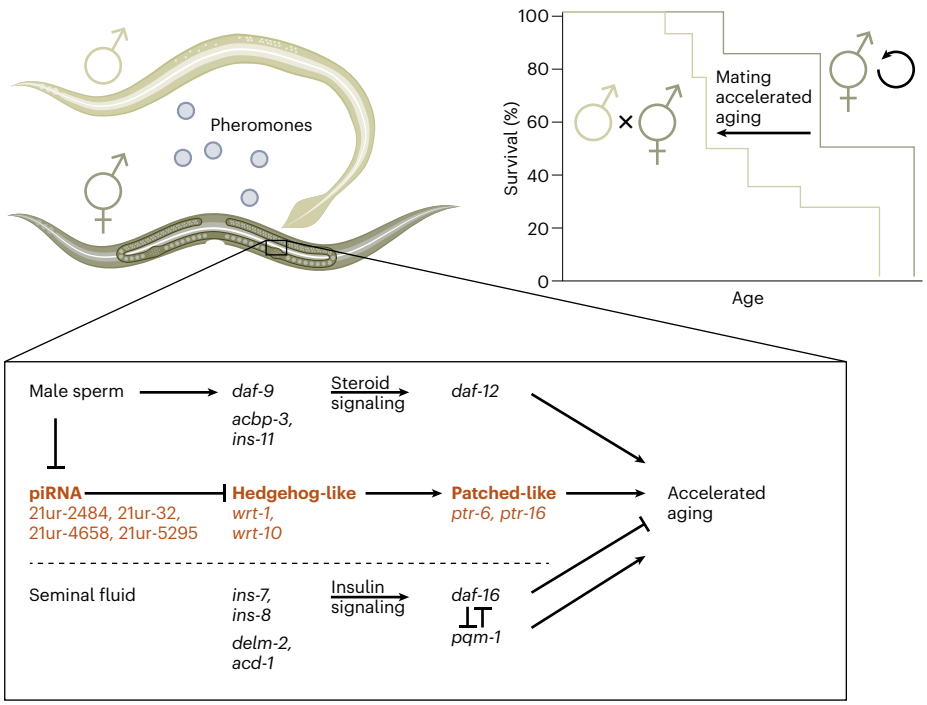

Fig. 1 | Males accelerate aging in hermaphrodite *C. elegans* through several signaling pathways. Previous work has demonstrated that secreted pheromones, male sperm and the seminal fluid all contribute to the accelerated aging of mated hermaphroditic *C. elegans*. Shi and Murphy[8] identify a global downregulation of piRNAs in the hermaphrodite germline in response to mating, as well as specific secreted targets of downregulated piRNAs — the Hedgehog-like ligands WRT-1 and WRT-10 (the pathway described in ref. 8 is highlighted in red). They further demonstrate that WRT-1 and WRT-10 function in the germline and signal to the Patched-like receptors PTR-6 and PTR-16 in the intestine and hypodermis.

Building upon these previous mechanistic findings, Shi and Murphy[8] performed mRNA and small RNA sequencing of dissected germlines from mated or unmated hermaphrodites to identify genes and noncoding RNAs that are differentially expressed in mated hermaphrodites. The authors observed a specific downregulation of piRNAs in the mated germlines, without obvious defects in the piRNA pathway. The piRNA pathway (but not other small RNA pathways) is required for mating-induced shrinkage, characterized by a 30% decrease in body length without apoptosis[6]. The authors use sequence homology to bioinformatically identify a set of putatively secreted proteins that are misregulated in the germline of mated hermaphrodites. Using a targeted screen of 13 of these molecules, the authors identify two Hedgehog-like ligands (WRT-1 and WRT-10) that are sufficient to cause germline shrinking and are partially required for the detrimental effect of mating on lifespan. They found that *wrt-1* knock down in particular eliminated about 50% of the lifespan-shortening effects of mating. From their resource of misregulated piRNAs in the germline of mated worms, the authors identify a subset of piRNAs that target and downregulate these Hedgehog-like ligands. They further demonstrate that overexpression of the specific piRNAs that target WRT-1 and WRT-10 are sufficient to regulate mating-induced shrinkage of the germline. Further fleshing out this signaling pathway, the authors identify putative Patched-like receptors (PTR-6 and PTR-16) for the Hedgehog-like ligands and demonstrate that these receptors have a role in regulating mating-induced accelerated aging (Fig. 1). Using tissue-specific RNA interference, the authors demonstrate that the Hedgehog-like ligands function in the germline and that the Patched-receptor homologs function in the intestine and the hypodermis.

Starting from unbiased sequencing, the authors methodically delineated a signaling pathway from piRNAs in the germline that regulate the expression of their secreted ligand targets to those ligands acting on their respective receptors in the soma. By providing comprehensive mechanistic insights on a new germline-to-soma pro-aging signal, this study represents an important advance in our understanding of how mating accelerates aging.

It remains to be determined how the disparate signaling pathways that have been implicated in mating-induced accelerated aging (including pheromones, dafachronic acid, insulin signaling and the piRNA–Hedgehog signaling pathway identified in this Article) communicate with each other: for example, whether the pheromones, dafachronic acid or insulin signaling pathways induce alterations specifically in piRNAs, or what the upstream signal is that triggers the dysregulation of piRNAs in general. In addition, it remains unknown how the Hedgehog signaling pathway (a critical pathway for development) is co-opted to respond to mating-induced accelerated aging, or whether the downregulation of piRNAs is an adaptation by the new mother to shift resources to the development of offspring. It will be critical to further explore how engaging Hedgehog signaling results in the marked cellular changes in the germline of mated hermaphrodites.

Although it is often exciting to extrapolate longevity findings in the nematode *C. elegans* to people, it remains to be seen whether these signaling pathways regulate longevity in mammals. Mating appears to decrease lifespan across a variety of species, and there is correlative evidence that this phenomenon might hold true in people. Although historical data on Korean eunuchs suggest that they lived 14–19 years longer than non-castrated men[15], it remains to be determined whether mating has any effect on human lifespan. It will be important to examine how well conserved the piRNA and other signaling pathways identified in *C. elegans* are in other species. As Hedgehog signaling has an essential role during development and its misregulation will lead to cancer, this pathway would probably not be a good candidate to manipulate in mammals. Regardless of whether the piRNAs and Hedgehog signaling pathway provide a viable drug target, this pathway delineated by Shi and Murphy[8] provides interesting insights into the antagonistic coevolution of the sexes.

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Competing interests

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