AGING

A new defense in the battle of the sexes

Young Caenorhabditis elegans hermaphrodites use their own sperm to protect against the negative consequences of mating.

GEORGE L SUTPHIN

Related research article Shi C, Booth LN, Murphy CT. 2019. Insulin-like peptides and the mTOR-TFEB pathway protect Caenorhabditis elegans hermaphrodites from mating-induced death. eLife 8:e46413. DOI: 10.7554/eLife.46413

Related research article Booth LN, Maures TJ, Yeo RW, Tantilert C, Brunet A. 2019. Self-sperm induce resistance to the detrimental effects of sexual encounters with males in hermaphroditic nematodes. eLife 8:e46418. DOI: 10.7554/eLife.46418

In popular culture, the phrase ‘the battle of the sexes’ conjures images of the complexities of dating, discussions about gender or, for some, a movie about the ultimate tennis grudge match. In the animal kingdom, the battle of the sexes can be much more visceral, and often deadly. Consider the roundworm Caenorhabditis elegans: hermaphrodite worms can reproduce through self-fertilization or by mating with male worms, but sexual interaction between males and hermaphrodites shortens the lifespan of both (Maures et al., 2014; Van Voorhies, 1992).

Self-fertilizing hermaphrodites enjoy a substantial post-reproductive lifespan, whereas those that mate with males typically only survive until they produce the last of their offspring (Shi and Murphy, 2014). The negative impact of sex on the lifespan of hermaphrodite worms is mediated by a number of molecular mechanisms including pheromones, the transfer of seminal fluid, and germline activation (Shi et al., 2017). Now, in two papers in eLife, researchers at Stanford University and Princeton University report that the ‘self-sperm’ produced by young hermaphrodites protects them from the dangers associated with mating. Each paper describes different signaling pathways involved in providing this protection.

In one paper Anne Brunet of Stanford University and co-workers – including Lauren Booth as first author with Travis Maures, Robin Yeo, and Cindy Tantilert – report that self-sperm protects C. elegans against aging by activating the ‘sperm-sensing’ pathway (Booth et al., 2019). Young hermaphrodite worms that mate have normal lifespans, while old worms die soon after mating. Booth et al. showed that, in young worms, normal lifespan after mating was the result of activating of the sperm-sensing pathway, which repressed the transcription factor CEH-18 and the ephrin receptor VAB-1 (Figure 1). In old worms, self-sperm was depleted and could no longer repress these proteins, leading to death. Booth et al. also investigated whether other species of roundworm were protected by self-sperm, discovering that Caenorhabditis briggsae shared this characteristic. However, this protection evolved relatively recently and independently from that of C. elegans, which suggests that roundworms continue to experience pressure from natural selection related to sexual interaction.

In the other paper Coleen Murphy of Princeton University and colleagues – including Cheng
Shi as first author and Lauren Booth – explore the influence of male seminal fluid on the insulin and the mTOR signaling pathways (Shi et al., 2019). In particular, they find that the insulin signaling pathway is activated by two peptides present in male seminal fluid (INS-7 and INS-8) and repressed by INS-37, a peptide found in self-sperm. As aging hermaphrodite worms deplete their supply of self-sperm, they lose the protective repression of insulin signaling and only experience the mating-induced activation. Shi et al. also find that unknown molecules in male seminal fluid activate the mTOR signaling pathway, driving the removal of the pro-longevity transcription factor HLH-30 from the nucleus, which leads to mating-related death (Figure 1).

The work at Stanford and Princeton has broader relevance to our understanding of the molecular mechanisms of aging. To take one example, the drug fluorodeoxyuridine (FUDR) is widely used to prevent C. elegans reproduction during aging studies because it inhibits the production of eggs and sperm in hermaphrodites. The drug affects lifespan differently depending on the age of the worms (Wang et al., 2019), while also enhancing some pro-longevity treatments (Anderson et al., 2016). Understanding the relationship between FUDR, self-sperm, and signaling pathways involved in aging may lead to the development of new methods to study aging in C. elegans.

Sexual interactions also affect health in mammals, albeit in a less dramatic fashion. For
example, the presence of male mice is sufficient to increase female body weight and stress while accelerating the onset of puberty (Garratt et al., 2016; Flanagan et al., 2011). Conversely, male mice maintained in the presence of females remain fertile substantially longer than those who live alone (Schmidt et al., 2009). While the specific role of self-sperm is not directly relevant to mammals, this work places evolutionarily conserved longevity pathways squarely at the intersection of sexual interaction and long-living invertebrates. Will the same be true for mammals?

George L Sutphin is in the Department of Molecular and Cellular Biology and the BIO5 Institute at the University of Arizona, Tucson, United States sutphin@email.arizona.edu

https://orcid.org/0000-0002-3659-4678

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References

Anderson EN, Corkins ME, Li JC, Singh K, Parsons S, Tucey TM, Sorkac A, Huang H, Dimitriadi M, Sinclair DA, Hart AC. 2016. C. elegans lifespan extension by osmotic stress requires FUdR, base excision repair, FOXO, and sirtuins. Mechanisms of Ageing and Development 154:30–42. DOI: https://doi.org/10.1016/j.mad.2016.01.004, PMID: 26854551

Booth LN, Maures TJ, Yeo RW, Tantilert C, Brunet A. 2019. Self-sperm induce resistance to the detrimental effects of sexual encounters with males in hermaphroditic nematodes. eLife 8:e46418. DOI: https://doi.org/10.7554/eLife.46418, PMID: 3128263

Flanagan KA, Webb W, Stowers L. 2011. Analysis of male pheromones that accelerate female reproductive organ development. PLOS ONE 6:e16660. DOI: https://doi.org/10.1371/journal.pone.0016660, PMID: 21347429

Garratt M, Kee AJ, Palme R, Brooks RC. 2016. Male presence can increase body mass and induce a stress-response in female independent of costs of offspring production. Scientific Reports 6:e23538. DOI: https://doi.org/10.1038/srep23538

Maures TJ, Booth LN, Benayoun BA, Izrayelit Y, Schroeder FC, Brunet A. 2014. Males shorten the life span of C. elegans hermaphrodites via secreted compounds. Science 343:541–544. DOI: https://doi.org/10.1126/science.1244160, PMID: 24292626

Schmidt JA, Oatley JM, Brinster RL. 2009. Female mice delay reproductive aging in males. Biology of Reproduction 80:1009–1014. DOI: https://doi.org/10.1095/biolreprod.108.073619, PMID: 19164172

Shi C, Runnels AM, Murphy CT. 2017. Mating and male pheromone kill Caenorhabditis males through distinct mechanisms. eLife 6:e23493. DOI: https://doi.org/10.7554/eLife.23493, PMID: 28290982

Shi C, Booth LN, Murphy CT. 2019. Insulin-like peptides and the mTOR-TFEB pathway protect Caenorhabditis elegans hermaphrodites from mating-induced death. eLife 8:e46413. DOI: https://doi.org/10.7554/eLife.46413, PMID: 31282862

Shi C, Murphy CT. 2014. Mating induces shrinking and death in Caenorhabditis mothers. Science 343:536–540. DOI: https://doi.org/10.1126/science.1242958, PMID: 24356112

Van Voorhies WA. 1992. Production of sperm reduces nematode lifespan. Nature 360:456–458. DOI: https://doi.org/10.1038/360456a0, PMID: 1448167

Wang H, Zhao Y, Zhang Z. 2019. Age-dependent effects of fluorouridine (FUdR) on senescent pathology and mortality in the nematode Caenorhabditis elegans. Biochemical and Biophysical Research Communications 509:694–699. DOI: https://doi.org/10.1016/j.bbrc.2018.12.161, PMID: 30611569