Sexual Conflict: Male Control of Female Longevity

Males and females have different evolutionary interests resulting in sexual conflict over optimal life histories. A new study in *Caenorhabditis elegans* shows that males hijack female physiology after mating to cause body shrinking and, ultimately, death. But how do males benefit from female demise?

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The evolutionary interests of individual males and females commonly differ [1,2]. These differences are rooted in anisogamy — males produce smaller gametes than females [3] — and extend to all types of reproductive decisions often resulting in conflict over timing and frequency of mating, number of mating partners and rate of reproduction [1,2,4]. While there is broad empirical support for the key role of sexual conflict in the evolution of life histories in general [4,5], and male effects on female longevity and ageing in particular [6,7], we still know relatively little about the mechanisms by which one sex affects reproduction and longevity in the other sex. Moreover, despite the fact that the idea of a male deliberately harming its mate may be counterintuitive, there are several non-mutually-exclusive reasons as to why males could evolve to reduce female longevity. First, males can manipulate female reproduction by causing females to start reproducing earlier or at a higher rate, thereby increasing the cost of reproduction by diverting female resources away from somatic maintenance. Second, males can evolve traits that aid in sperm competition with females’ potential future partners but are harmful to females thus indirectly reducing female longevity [6,8]. Both of these explanations fall within the broadly defined ‘pleiotropic harm hypothesis’ [9]. Third, males may deliberately harm females in order to prevent females from re-mating and/or reduce female residual reproductive value and thereby cause females to invest relatively more into current reproduction [9].

A recent study in *Science* explores sexual conflict in *Caenorhabditis elegans*, where the sexes are male and hermaphrodite. Shi and Murphy [10] present a remarkable account of how both sperm and seminal fluids of male *C. elegans* tinker with at least two different molecular pathways that control aging and longevity in hermaphrodites to cause death after the hermaphrodite has completed laying all of its eggs. Importantly, the authors present several findings in support of the hypothesis that hermaphrodites do not simply because of an increased rate of reproduction. The authors suggest that males deliberately cause hermaphrodites/females to shrink and die in order to prevent them from mating with other males.

Costing Reproduction

Although an inverse relationship between reproduction and lifespan lies at the heart of life-history evolution, a complete understanding of its nature is constrained by the lack of knowledge of proximate mechanisms. The traditional view, as exemplified by the Y model of resource allocation, assumes that limited resources are allocated to competing functions, such as reproduction and somatic maintenance [11]. Recent advances in our understanding of endocrine regulation of life-history traits have led to the integration of the insulin/IGF-1 signaling pathway into the Y model [12]. Crucially, some costs of reproduction may result directly from the costs of mating, rather than from differential resource allocation, and male-induced harm to females could potentially play a key role in generating such costs. Yet distinguishing between costs associated with the classic trade-off between somatic maintenance and reproduction on one hand, and costs related to endocrine signalling that do not rely on differential resource allocation on the other, is notoriously difficult [12,13].

Shi and Murphy [10] document that mating decreases lifespan of *C. elegans* hermaphrodites by about 40% and describe two molecular pathways underlying these effects. The authors show that mating triggers two main physiological responses in *C. elegans* hermaphrodites — fat loss and shrinking — both of which contribute to premature death. Shrinking results from increased hypertonic stress susceptibility and is tightly coupled with germline proliferation induced by male sperm. The signal causing shrinking acts through the steroid hormone receptor DAF-12, which is in turn affected by the steroid-processing enzyme DAF-9 (cytochrome P450) and by a signal from the proliferating germline [10]. The fat loss induced by seminal fluid involves the inactivation of DAF-16, a transcription factor known for promoting lifespan extension in insulin-signaling mutants. Shrinking and longevity decreases are abolished in daf-12;daf-16 double mutants, suggesting that these pathways are sufficient to mediate the longevity costs of mating in *C. elegans* hermaphrodites. Furthermore, mating reduces the attractiveness of hermaphrodites to males.

Recent years have witnessed enormous progress in our understanding of how environmental adaptations may result in increased body shrinking and lifespan decreases.
cues and internal signals guide life-history decisions: reproductive schedules and longevity proved to be plastic traits regulated by, among others, smell of food, presence or smell of conspecifics, reproductive opportunities, and signals from reproductive organs and the nervous system [14,15]. Conserved endocrine pathways that integrate these signals involve steroid hormones, insulin/IGF-1 and target-of-rapamycin (TOR). Together these pathways control developmental timing, larval diapause, reproductive maturation, stress resistance, metabolism and lifespan [16]. Since all these pathways converge on fat metabolism, the idea emerged that fat mediates the trade-off between lifespan and reproduction [16]. Indeed, fat loss (up to 50%) was observed by Shi and Murphy [10], and contributed to the early death of hermaphrodites. However, shrinking induced by osmotic stress susceptibility represented an independent life-shortening mechanism. This agrees with studies reporting that reproduction renders organisms more vulnerable to different stresses [12]. Furthermore, Shi and Murphy [10] did not find longevity costs of egg production, in agreement with previous studies in C. elegans [17]. Thus, in Caenorhabditis nematodes endocrine signaling pathways control resource allocation, stress susceptibility and longevity and these very pathways are hijacked by males, causing death of hermaphrodites or females. But does the absence of correlation between fecundity and longevity rule out the classic life-history trade-off between reproduction and somatic maintenance? First, trade-offs between reproduction and survival are often seen only under conditions when resources are limited. Second, it has been emphasized previously that endocrine signalling can cause damage to soma in different ways — for example, by altering somatic anabolism — and ablation of egg production does not necessarily remove this cost [12,13]. The germine signal can cause resources to be diverted to reproduction away from the soma and this would result in somatic damage even if the resources are not subsequently utilized in egg production because gonads are ablated or because eggs cannot be synthesized. This is the so-called ‘tap’ analogy — if the bucket is being filled from the tap, removing the bucket will not save water [13,18]. Similarly, if the tap to the ‘soma bucket’ is closed, somatic maintenance will suffer even if freed resources are not used for reproduction.

How Do Males Benefit?
Shi and Murphy [10] provide an exceptionally detailed account of how males take control over hermaphrodite/female ageing and longevity. But how do males benefit from female demise? Since traits related to sperm competition easily evolve in C. elegans [19], and males reduce female longevity in multiple ways [10,15,17], it is logical to suggest a male benefit. However, if the male-induced shrinking and reduction of hermaphrodite lifespan are manifestations of sexual conflict, it must also reduce the fitness of hermaphrodites. Evidence from gonochoristic C. remanei (where the sexes are male and female) has led to the suggestion that premature death following a single mating can indeed be costly. While the C. elegans hermaphrodites were allowed to mate for only one day in the study by Shi and Murphy [10], the reproductive output of C. remanei females increases with increased access to males over their reproductive lifespan, up to a point when the cost of mating apparently counteracts the reproductive benefit, suggesting that female C. remanei are sperm limited even after mating [20]. If this is true also for C. elegans, then male-induced shrinking and death may indeed be detrimental for hermaphrodites because it reduces their potential reproductive output.

The study by Shi and Murphy [10] provides an exciting new insight into how males can control female longevity. Further studies should continue to investigate the evolutionary consequences of this manipulation. One intriguing aspect of this study is that daf-12 mutants, which do not shrink, still have higher fecundity when mated. Future studies will likely continue investigating the effects of male manipulation on male and female/hermaphrodite fitness. This could be achieved by varying male manipulative ability or female response — mutants, RNAi knockdown, and experimental evolution all can come in handy — and then comparing fitness of manipulated and control worms under the conditions that allow for multiple mating and sperm competition. Ideally, this should be done while comparing the hermaphroditic species, where males are present in small numbers, with gonochoristic species, where a 50:50 sex ratio is the norm. The economics of sexual conflict has been at the forefront of evolutionary research for quite some time, but arguably the progress has been hindered by the lack of mechanistic understanding of the physiological and molecular processes behind the evolutionary patterns of sexual antagonism that we commonly observe. Findings like Shi and Murphy’s [10] will allow us to use advances in molecular biology to increase our understanding of male–female co-evolution.

References
Axon Guidance: FLRTing Promotes Attraction

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One of the most remarkable feats of early neural development occurs when neurons send out an axon to navigate through the embryo, eventually forming intricate networks of connections that are essential for all subsequent neural function. At the tip of each axon sits the growth cone (Figure 1), the dynamic hand-like structure that steers through the complicated, ever-changing embryonic landscape and interprets guidance cues in order to find and connect with its final target [1]. Many decades of axon guidance research have defined key extracellular cues, receptors and signaling pathways that are essential for guiding growth cones to their destinations [2,3]. Yet, we still do not understand the logic of how simultaneous inputs of numerous axon guidance cues are interpreted to steer the growth cone in the right direction (Figure 1). A new study in this issue of Current Biology by Leyva-Diaz et al. [4] provides insights into this important question by demonstrating a mechanism through which crosstalk between multiple cues is integrated during the guidance of thalamocortical axons.

The thalamocortical projection (neurons sending axons from the thalamus to the neocortex) is responsible for a significant component of higher-level processing in the mammalian brain, including the sensory pathways of vision, hearing, and touch. It represents a powerful and complex model system for examining the mechanisms that regulate the precise positioning of axonal tracts [5,6]. Neuronal cell bodies are spatially organized within the thalamus, with axons extending and then spreading out to acquire a precise rostrocaudal position before arriving at the neocortex (Figure 2A). Rostral nuclei project to the rostral motor cortex, while caudal nuclei project to the caudal visual cortex [6,7]. How this topographic positioning is achieved has been an area of intense investigation in the axon guidance field. While the repertoire of axon guidance factors known to be involved in steering thalamocortical axons includes the expected cast of chemotropic factors — Netrins and Slits, as well as Ephrins and Semaphorins [5,6] — the recent work from the lab of Lopez-Bendito [4] adds a new player to the team, the fibronectin and leucine-rich transmembrane protein FLRT3.

The study by Leyva-Diaz et al. [4] builds on previous work from Bielle et al. [8], which identified interesting interactions between Netrin and Slit that occur specifically in the rostral thalamocortical axons (rTCAs) [8]. For this particular axonal subset, when the guidance cue Slit1 is presented alone, it leads to a repulsive response, while the guidance factor Netrin-1 alone has no chemotactic effect. Yet, the two factors in combination attract rTCAs (Figure 2B). This finding was intriguing as the neighboring intermediate TCAs (iTCAs) are not attracted to Netrin-1 with or without Slit1. Despite the fact that both rTCAs and iTCAs express the same Netrin receptors, including DCC