Letter

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Even more functions of sperm RNA: a response to Hosken and Hodgson

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As recently outlined in *TREE* [1], many animals and plants are thought to load their male gametes with multiple types of RNA, some of which enters the oocyte upon fertilization. Four classes of ultimate hypotheses for sperm RNA were proposed [1], adding to existing mechanistic hypotheses [2]. We suggest two more ultimate hypotheses to be considered when investigating sperm RNA. Throughout, we only consider sperm RNA deriving from the diploid male genome.

First, sperm RNA could mediate an anticipatory paternal effect [3] that encodes information about the environment. Males might vary the RNA content of their sperm under different conditions to prime the embryo to develop appropriately for the environment. Additionally, in external fertilizers, sperm RNA might be modified (or simply differentially degraded) based on the environment of the sperm *en route* to the egg. Anticipatory maternal effects are widely studied, but this is less true of paternal effects, perhaps because males are assumed to have negligible power to influence offspring phenotype in species where males only provide sperm [3]. However, sperm RNA offers a potentially widespread mechanism by which fathers could alter the development of their offspring.

There are multiple reports of fathers nongenetically influencing offspring despite only providing sperm [3], although it is unclear whether parental effects are frequently adaptive, or whether sperm RNA is involved. For example, stressed male rats fathered offspring with modified behavior and rates of DNA methylation in the hippocampus and frontal cortex [4], and sperm contain RNAs putatively capable of mediating epigenetic changes, including DNA methylation and histone modification [2]; however, decisive experiments linking sperm RNA to offspring methylation and fitness consequences are lacking. Experiments have suggested that offspring survive comparatively well in environments matching those experienced by their fathers [5] or the sperm of their fathers [6]. Spermatogenesis typically occurs closer to fertilization than oogenesis does, especially in species in which ova are sequestered early in life. Therefore, sperm RNA might sometimes provide more current information on the environment compared with nongenetic signals in eggs.

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Second, sperm RNA could derive from selfish genetic elements (SGEs), which promote their own transmission in ways that harm the fitness of the rest of the genome [7]. Sperm RNA might also represent a defense against SGEs.

Retrotransposons, which occur in most organisms and spread by copying themselves throughout the genome, might produce or select for sperm RNA. Some retrotransposons might act within sperm, or load sperm with RNA in the hope of transposing inside the embryo; indeed, intragenomic conflict is probably one reason why sperm are stripped of their cytoplasm and the potentially selfish genetic material that it contains [7]. Sperm contain transposon-associated RNA as well as Piwi-interacting (pi)RNA, suggesting transposition and evolutionary countermeasures acting in the sperm or early embryo [2]. Sperm are also exposed to viruses that cause damage or hitch a ride to the egg [8]; therefore, some sperm RNA could be antiviral.

Sperm RNA might also derive from segregation distorters that kill sperm or zygotes carrying a different allele. Several sperm-killing segregation distorters exist [7] and, although their mode of action is incompletely understood, sperm RNAs may be involved [9]. Using a poison-and-antidote system [7], an SGE in the host genome could load sperm with RNA that incapacitates sperm that do not contain it. Under this hypothesis, certain sperm RNAs should predict infertility, which is the case [2].

Sperm RNA might also underlie a male equivalent of *Medea* in *Tribolium* beetles. *Medea* is a maternal effect killer that poisons all offspring except those that inherit it and, therefore, have the antidote [7]. If males heterozygous for this hypothetical 'male *Medea*' (we suggest *Hercules*, another infanticidal mythic figure) loaded all their sperm with RNA that killed fertilized eggs lacking the *Hercules* element, competition on the remaining offspring would be reduced, increasing the fitness of *Hercules* (Figure 1). Thus, *Hercules* is similar to the *peel-1/zeel-1* system of *Caenorhabditis elegans*, although *peel-1/zeel-1* is based on sperm proteins rather than on RNA [10].

Hercules could only have a selective advantage if new eggs replace dead zygotes (assuming these eggs are preferentially available to *Hercules* males), or if surviving offspring have higher fitness, for example because of decreased competition (Figure 1). In polyandrous species, zygote-killing segregation distorters might even have a larger fitness advantage than those that kill sperm, because they should not reduce the sperm competitive ability

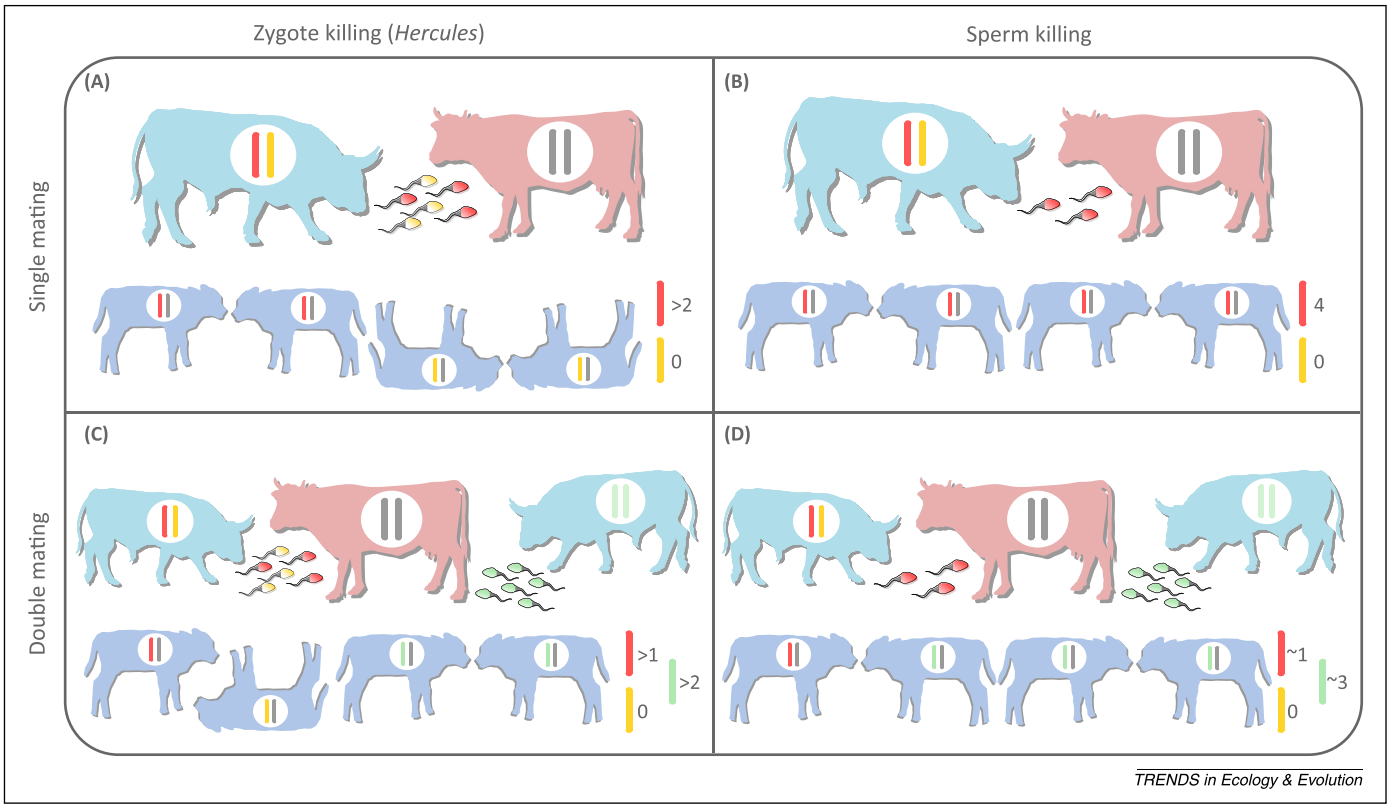

Figure 1. How selfish genetic elements that perform zygote killing (*Hercules* or *peel-1/zeel-1* [10]) and sperm killing (e.g., *t* or *Sd* [7]), both of which might involve sperm RNA, affect their own fitness under single and double mating. In short, sperm killing is equal or superior to zygote killing under single mating, while zygote killing can be superior under double mating, depending on the effect of sperm killing on sperm competitive ability. Note that, under double mating, the fitness of both zygote and sperm killers becomes positively frequency dependent, because matings involving two selfish males become increasingly frequent when the selfish genetic elements (SGE) are common, which helps the SGE under both scenarios (*cf.* [11]). **(A)** The male organism (blue) is heterozygous for the zygote killer *Hercules* (red; yellow is the wild type nonselfish allele). When females only mate with one male per reproductive event, offspring inheriting the wild type allele are killed (perhaps involving sperm RNA), and the surviving *Hercules*-bearing offspring have a degree of elevated fitness as a result of reduced competition with their siblings and/or replacement of the dead zygotes by the mother followed by fertilization with *Hercules*-bearing sperm (shown by the > sign). **(B)** A sperm-killing system in which the wild type sperm of the heterozygote male are killed (perhaps involving sperm RNA). Provided the male has enough sperm to fully fertilize the female, the sperm-killing SGE doubles its fitness. **(C)** When females mate with two males, one of which is heterozygous for *Hercules*, fertilizations might be shared between males equally but eggs fertilized by non*Hercules* sperm from the heterozygote male are killed. The fitness of the red and green chromosomes (where the latter represents the average genotype of a randomly chosen male, assumed here to have a nonselfish phenotype) is elevated and, thus, the *Hercules* allele (red) transmits at least as many copies as it would do if it lacked the zygote-killing phenotype. **(D)** For a sperm killer under double mating, the fitness of the selfish allele depends on how much it affects the sperm competitive ability of the bearer. If sperm killing more than halves the fertilization success of the male and all females mate twice, the sperm killer has lower fitness than the wild type allele; if fertilization success is reduced by less than half, the sperm killer will spread, although its fitness advantage might be lower than that of *Hercules*. Cattle images reproduced from phylopic.org.

of the bearer. Thus, *Hercules* would still be fitter than nonselfish competing alleles when sperm competition is common, which is not always true for sperm killers (Figure 1 [11]). Given that *Hercules* elements should spread to high frequencies after they evolve, observing zygote killing might require crossing genetically distant populations to generate *Hercules* heterozygotes, then mating them to females from both populations [12].

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