



Mating-induced Male Death and Pheromone Toxin-regulated Androstasis

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The manuscript titled “Mating-induced Male Death and Pheromone Toxin-regulated Androstasis” aims to explain the possible mechanism behind lifespan changes in males post-mating. Previously the lab has shown that female lifespan is impacted post-mating, but the effect of mating on males in the field is still conflicted. The authors in this paper, through a series of very interesting experiments, show that there is a decrease in male lifespan which is dependent upon two factors; the males own germ-line proliferation post-mating and male toxicity from pheromones of other males. The authors show that males that were mated die earlier and have a decrease in size compared to males that were kept solitary. Also in this paper, experiments where the germ-line proliferation was blocked resulted in rescue of the decreased lifespan in males post-mating indicating that germline proliferation may indeed be contributing to lifespan of mated males. The authors further validated the contribution of germline proliferation being a case effecting lifespan by generating germline-less mutants. They showed that the mutant males didn't appear to exhibit a decreased lifespan post-mating. The paper does a good job at trying to address the controversy that exists around male lifespan. The authors identified that the potential reason behind the reduced lifespan of grouped males (which were used as controls in previous studies) was pheromone toxicity. Experimentally, the pheromone deficient males fared better (lived longer) in solitary as well as in grouped conditions compared to their control counterparts. This study appears to give an insight into the reasons behind the decreased male lifespan, and also shows how evolutionary conserved the phenomena of decreased lifespan might for males post-mating.

In reading the manuscript, the clarity of the writing and the structural organization of the paper stood out positively. There were just a few questions that we had regarding some of the figures.

1) The claim made in figure 1 is that *C. elegans* males live shorter post-mating. It can be seen through this figure that indeed the duration of mating reduces lifespan while the number of mating partners and the days on which the males mated does not seem to make a difference. However, looking at figure 1E and supplementary 1A, it becomes a little confusing as both appear to be depicting the same thing but have different results. Could either one perhaps be mislabeled? Or does there exist such a variation when replicating the experiment?

The only difference we can see is that 1E say 13.8 ± 0.7 days while S1A says 10.5 ± 0.5 days. Could you possibly clarify why there exists such a differences between the two figures?

2) In 2C, it is very interesting that a germline specific inhibitor can potentially rescue the early male death phenotype. Looking at figures 2C and S1D however, it appears again that they are replicates of the same experiment? If such a variation exists, could you speculate on the mating behavior of the worms when treated with FUDR? Is FUDR toxic to the males? Do the worms still behave normally and practice normal mating behaviors?

In 2D could you possibly add the lifespan data for control solitary males and mated male for 6 days? It would allow for easy visual appreciation for their being no decrease between *glp-1* solitary and mutated worms compared to control solitary and mated. Further, the *glp-1* mutation model for the worm appears to have a very interesting phenotype of its own. The mutated solitary male appears to die earlier and be shorter in size compared to the normal solitary worm. Could you speculate on any off target effects that might be causing such a phenotype in the mutated worms? Could it be that the mutation of the worm is resulting in males that are so sick that they doesn't engage in mating or other behaviors characteristic of normal worms? Could you possibly expand on whether the mutated males behave similar to normal worms in terms of mating?

3) In figure 4, the claim is that "a component of mating specific and autonomous to the male, rather than transferred substance or pheromone, is responsible for male death in both species." Could you clarify how the transfer of substance is assessed between the mating groups? We feel that the claim for a male specific component could be strengthened if the 1. *C. r.* x 1 *C. e.* 6day mating group was treated with FUDR and that showed rescue of the decreased lifespan observed in *C. e.* males. This would validate that the germline proliferation component of the male was responsible for the decreased lifespan.

After reading the paper, we also started wondering about some further questions that could potentially be speculated upon in the discussion or addressed in future manuscripts.

1) Do other *vit* gene targets also affect lifespan? It would be interesting if the effect on lifespan could be attributed to either being specific to certain downstream genes or be acting a more general effect on the DAE dependent transcription factors.

2) For better understanding, could you speculate on why lifespan of *C. r.* is decreasing in 5C or why the FUDR treatment rescues the lifespan decrease in the mated males? The *C.r.* males don't mate when in a group so is early death all pheromone based (fig 5C)? But then in fig. 5D it appears like male death is also based on germline proliferation.

3) The body length of the males appears to reach a maximum at 2-1/2 to 3 days of adulthood and then decrease, could you speculate on what might be happening in this time window that might be regulating the size of the worms? The similar decrease in the *glp-1* mutants is not seen so they could potentially be used for comparison to identify differences that lead up to length of worms.

Another general comment that we had for the paper was regarding the discussion portion. We got a chance to hear your talk and it was very fascinating. The link you made with the lifespan of the Chinese emperors was not only entertaining but also memorable, and it helped the audience really connect with the results. However, the same reference in the text of the paper felt like it was an overselling that injected skepticism into the work where skepticism was otherwise minimal.