

Peer Review of “Roles of Progranulin and FRamides in Neural Versus Nonneural Tissues on Dietary Restriction–Related Longevity and Proteostasis in *C. elegans* (Preprint)”

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Related Article:

Preprint (BioRxiv) <https://www.biorxiv.org/content/10.1101/2024.02.06.579250v1>

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KEYWORDS

C. elegans; dietary restriction; lifespan; heat shock; proteostasis; neurodegeneration; motility

This is a peer-review report submitted for the preprint “Roles of Progranulin and FRamides in Neural Versus Nonneural Tissues on Dietary Restriction–Related Longevity and Proteostasis in *C. elegans*.”

Round 1 Review

General Comments

The manuscript titled “Roles of progranulin and FRamides in neural versus non-neural tissues on dietary restriction-related longevity and proteostasis in *C. elegans*” by Mir et al [1] examines the role of FMRamide-like neuropeptides in dietary restriction (DR)–mediated lifespan extension. To achieve this goal, the authors measured the survivability of animals under ad libitum (AL) and DR after knocking down these peptides specifically in the neuronal tissue or systemically (Figures 1 and 2). The authors did not obtain any significant results in these experiments and further performed other experiments to examine the impact of *pgrn-1* and *flp* knockdown in maintaining proteostasis in *eat-2* mutants (Figure 3) and influencing locomotion in the Alzheimer model of neurotoxicity (Figure 4). The data from all these experiments did not reveal any role for *pgrn-1* or *flp* genes in DR-dependent lifespan extension and proteostasis.

Specific Comments

Major Comments

1. The premise of this study was that the authors found that *pgrn-1* and *flp* genes exhibited increased recruitment to polysomes upon DR. These data imply that these genes are translated to higher levels upon DR. Hence, increasing the levels of these under AL should recapitulate a DR-like state. However, the authors decided to examine the phenotypes associated with the knockdown of these genes. However, their data did not show any significant changes in DR-dependent lifespan enhancement. Hence, the logic of performing the experiments in Figures 3 and 4 is unclear.

2. There is no data to indicate the level (-fold decrease) of the FRamides or progranulin after RNA interference.

3. The lifespan experiments corresponding to Figure 2 have been performed two times, and the data are noted in Supplementary Table 3. However, the data from the two repeats (for *flp-5*, *flp-14*) are not reproducible, with one experiment showing a significant difference in lifespan under AL and DR and the second repeat showing no significant difference. These data indicate nonreproducibility, and ideally, no inference should be drawn from them without repeating them.

4. Supplementary Figure 2 data and conclusions are drawn from a single experiment only.

5. The title of the paper reflects that progranulin and FRamides play a role in DR-mediated extension of lifespan; however, all the results noted indicate the opposite (lines 205 and 206, 213-217, 336-339, and 345-348). Hence, the rationale for continuing to assess the role of these genes in the DR pathway by performing experiments in Figures 3 and 4 is unclear. Moreover, the authors also concluded that knocking down the expression of *pgrn-1* or *flp* does not have any role in proteostasis, and their role in neural proteotoxicity is complex (lines 369-372). Based on the data from Figure 4, the authors conclude that downregulation of *pgrn-1* or *flp* has minimal or no effect on motility during adulthood under DR conditions. Overall, the findings indicate that though there is increased translation of *pgrn-1* or *flp* genes upon DR, these genes do not function as DR effectors.

Hence, a more appropriate title would be “Progranulin and FRamides do not play a role in DR-related longevity and proteostasis.” Moreover, a more detailed explanation of the results in Figures 3 and 4 might be helpful for the readers to understand the role of these genes in motility and why there are differences in young and late ages. Unfortunately, I cannot recommend this manuscript for publication in its current state.

Conflicts of Interest

None declared.

Editorial Notice

The authors of the preprint under review declined the opportunity to revise the preprint in response to the feedback in the peer reviews and publish it in the journal JMIRx Bio. The editors thank the peer reviewers for providing their feedback on this preprint.

Reference

1. Mir DA, Cox M, Horrocks J, Ma Z, Rogers A. Roles of progranulin and FRamides in neural versus non-neural tissues on dietary restriction-related longevity and proteostasis in *C. elegans*. bioRxiv. Preprint posted online on February 8, 2024. 2024. [[FREE Full text](#)]
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Abbreviations

AL: ad libitum

DR: dietary restriction

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