January 9, 2024

Review of the doctoral dissertation entitled ""Mechanisms and developmental roles of XRN-2 mediated RNA regulation in Caenorhabditis elegans" by Ilkin Aygun Soyalp

This review is prepared by Prof. Dr. H. Gunes Ozhan.

The dissertation being the subject of the review fulfills the conditions laid down in the Act of July 20, 2018, The Law on Higher Education and Science (Journal of Laws 2018, item 1668 as amended), the Act of July 3, 2018, Provisions Introducing the Act – The Law on Higher Education and Science (Journal of Laws 2018, item 1669 as amended), and The Rules of Proceeding in the Matter of Awarding the Doctoral Degree in the Institute of Bioorganic Chemistry PAS (Resolution of the Scientific Board of IBCH PAS No. 59/2023/Internet of March 29, 2023) and I recommend that the Scientific Board of the Institute of Bioorganic Chemistry PAS allows it to further steps in PhD defense process.

XRN-2 is a nucleus-localized 5'-to-3' exoribonuclease prominent in the nematode *Caenorhabditis elegans* (*C. elegans*). XRN-2 exerts diverse effects on gene expression and development by participating in the degradation and trimming of various RNA classes, controlling transcription termination and ribosome biogenesis. XRN-2's target selectivity *in vivo* is critical for its role in *C. elegans* development. However, the intricate molecular pathways underlying XRN-2's actions remain elusive, partly due to its widespread expression pattern throughout development. This study provides a thorough investigation of the developmental functions and RNA regulatory mechanisms of XRN-2 by following two approaches. The first one aims to identify the specific developmental role of XRN-2 during development by identifying its genetic suppressors. The second one aims at unraveling the functional interplay between XRN-2 and its synthetic lethality partners. Through these strategies, the research seeks a more comprehensive understanding of XRN-2's developmental roles within specific molecular pathways, shedding light on its intricate contributions to *C. elegans* development.

This is a well-written doctoral dissertation that reflects the author's meticulous research and contributions to the field. The clarity of thought, coherence of arguments, and systematic presentation of findings display a profound understanding of the subject matter. The thesis not only adds valuable insights to the existing literature but also demonstrates the author's intellectual rigor and commitment to advancing knowledge. Overall, it is a creditable work making a significant contribution to the academic landscape.

Below are some questions that I would like to ask to Ilkin Aygun Soyalp:

1. What insights does the research provide into the intricate interplay between xrn-2 and the genetic modifiers, and how does this contribute to our understanding of germline development?
2. In what ways do the findings suggest potential molecular mechanisms underlying the interactions between xrn-2 and the genetic suppressors, and how might these mechanisms be crucial for germline development?
3. How do the results of this study open avenues for further investigations into the regulatory pathways associated with germline development, and what potential applications or implications could arise from a deeper understanding of these pathways?

4. Can you discuss any challenges encountered during the research process and how they were addressed, particularly in the context of characterizing genetic suppressors in the xrn-2tsgerm strain?
5. Can you provide more details on the potential therapeutic interventions that could arise from the insights gained in this study, specifically in targeting fertility restoration? In what ways could the strategies developed from this research be applied to diverse biological systems to overcome fertility-related challenges?
6. Regarding the observed downregulation of gene expression due to RNAPII collisions, can you discuss the specific consequences of these collisions on the transcriptional process and how they interfere with normal gene expression? Additionally, are there specific genes or classes of genes that are more susceptible to downregulation as a result of RNAPII collisions?
7. Regarding the recognition and regulation of ceh-99 by XRN-2, how does this finding contribute to our understanding of the regulatory mechanisms involved in gene expression control?
8. In your opinion, what are the key takeaways from this research, and how do they contribute to the broader field of genetics and developmental biology?

Prof. Dr. Gunes Ozhan