Stress Resets Transgenerational Small RNA Inheritance

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A preLight by Miguel Vasconcelos Almeida

Tweetable summary

Houri-Ze'evi and colleagues demonstrate that exposure to stress disrupts inheritance of RNAi responses established in the previous generation.

Background

While the concept of non-genetic, or epigenetic, inheritance is not new, there is a lack of understanding of its mechanisms and universality. Beyond the DNA sequence, small RNAs, and DNA and histone modifications (commonly methylation) embody epigenetic inheritance. Such epigenetic information was shown to alter gene expression, sometimes across generations, a phenomenon which challenges Mendelian genetics, and is termed transgenerational epigenetic inheritance. Small RNA-driven transgenerational epigenetic inheritance is a particularly prolific field of study in the nematode *Caenorhabditis elegans*. These tiny worms have many complex endogenous RNA interference (RNAi) pathways that employ small RNAs in silencing non-self genetic elements over generations. Moreover, *C. elegans* can acquire double-stranded RNA from its environment, and process it into small RNAs, which can elicit gene silencing. Both endogenous and environmental small RNAs can be inherited transgenerationally and respond to stressful stimuli, for example starvation and temperature. How small RNA inheritance is regulated is largely unknown, but now a preprint from the Rechavi lab sheds more light on these aspects using *C. elegans*.

Key findings

- The authors performed RNAi targeting reporter transgenes, followed by exposure to three different types of stress (starvation, high temperature, and high osmolarity) in the next generation. They found that stressed worms have less reporter silencing than non-stressed worms, meaning that stress can reset ongoing environmental small RNA responses.
- Resetting of small RNA inheritance occurred both in the generation undergoing stress and in following generations.
- Stress also resets endogenous RNAi, but only in the generation undergoing stress.
- Taking advantage of the powerful *C. elegans* genetic toolkit, the authors determined whether RNAi resetting is altered in mutants defective for stress responses. With this approach, the authors implicated the MAPK pathway and the SKN-1 transcription factor in heritable RNAi resetting. This suggests that resetting of small RNA inheritance is downstream of conserved factors that integrate environmental stress into a physiological response.

What I like about this preprint

Previous studies have demonstrated that many *C. elegans* small RNA pathways cross-regulate each other, for example by competing for shared limiting factors. This work elegantly adds another dimension to this cross-regulation, and highlights the plasticity of RNAi responses to an ever-changing environment. *C. elegans* has a very short generation time, therefore, in the wild, RNAi resetting may enable rapid integration of new environmental signals into physiological responses. Moreover, the action of conserved stress responders upstream of RNAi resetting may be suggestive of a broadly conserved mechanism. I also like the experiments demonstrating that the resetting of RNAi is specific to stressful conditions: exposure to merely different or favorable conditions does not reset RNAi.

Open questions

I find it very intriguing that endogenous RNAi, contrary to environmental RNAi, is not reset transgenerationally, indicating distinct regulation for exogenous and endogenous RNAi responses. What differentiates an exogenous response from an endogenous response within the germline? While it may be useful to recurrently integrate environmental cues, recurrently disturbing endogenous gene regulatory controls may be detrimental. Moreover, it will be interesting to determine whether MAPK genes are influencing small RNA pathways in other organisms. Or is this a nematode quirk? Indeed, worms are a great model for small RNA inheritance, a feat undoubtedly facilitated by their maternally determined germline. In mammals, wherein the germline is determined by induction, small RNA inheritance is harder to tackle.

Want to know more?

Principles of Transgenerational Small RNA Inheritance in *Caenorhabditis elegans*, Rechavi & Lev, 2017. https://www.sciencedirect.com/science/article/pii/S0960982217305791

Intergenerational Transmission of Gene Regulatory Information in *Caenorhabditis elegans*, Minkina & Hunter, 2018. https://www.sciencedirect.com/science/article/abs/pii/S0168952517301725

Intergenerational and transgenerational epigenetic inheritance in animals, Marcos Francisco Perez & Ben Lehner, 2019. https://www.nature.com/articles/s41556-018-0242-9