Isolation of Novel Epigenetic Insights in Heritable Fertility Trends via NGS-Driven Analysis of DNA Damage Response and piRNA Biogenesis Pathways

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The global rate of infertility stands at an all-time high and nutrition has been discussed as an impactful factor in such concerning trends. Stable oogenesis is continually threatened by genotoxic stress stemming from DNA damage, much of which is inflicted by transposition at the germline. Using Drosophila melanogaster as a biological model, this study successfully identified multiple heritable mechanisms that govern nutritionally malleable responses to DNA damage and infertility at the molecular level, including piRNA and, downstream, checkpoint kinases such as ATR, CHK1, and CHK2. Flies were fed a control, non-, low-, and high-fat dairy supplement. The image analysis applications ImageJ and Icy were used to quantify increased intermediate stage development and pole plasm area in the high-fat fly germarium. Next-generation sequencing (NGS) was used to holistically profile the cellular transcriptome of wild-type and mutant D. melanogaster. This uniquely elucidated the role of kinase-mediated DNA damage response pathways in the context of genotoxic insults and further identified the PIWI-interacting RNA (piRNA) pathway, a mammalian homologue, as a safeguard against genomic instability in response to variable dietary intake. This study also identified MT-ND3, MT-ND4, and MT-ND5 as potentially implicated genes in piRNA localization. Presented herein is a previously nonexistent model for further experimental analysis of the heritable properties of DNA damage repression that could be used in the development of methods to address underlying intrinsic mutations fueling the burgeoning fertility crisis.

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