

Title: Pathogen type and host genotype shape mitochondrial responses to infection**Authors:**

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Abstract

Mitochondria are essential organelles not only for cellular energy metabolism and thermogenesis, but also for immune responses. Variation in mitochondrial function can influence immunity, and various pathogens are also known to exploit mitochondrial functions for their own benefit. In this study, we utilized the genetic model species fruit fly *Drosophila melanogaster*. We combined comparative RNA sequencing and metabolomic analyses to investigate how genetic variation influences host immunity and mitochondria-related transcriptional and metabolic responses to various infections. We included two nuclear genotypes (commonly used *Drosophila* strains *w¹¹¹⁸* and Oregon-R (OR)), three mitochondrial genotypes and five pathogen models in our analysis. We show that the mitochondrial responses at the transcriptional level are both pathogen specific and modulated by genetic variation originating from both the nuclear and the mitochondrial genomes. Metabolomic profiling showed that the genotype had more pronounced effects on the metabolite levels than bacterial infection. *w¹¹¹⁸* flies are known to have defects in the kynurenine pathway leading to NAD⁺ biosynthesis, which was evident also in our analysis. These flies were the most susceptible to pathogenic bacterial infection, potentially due to low NAD⁺ levels. Supplementing with NAD⁺ precursor nicotinamide partially rescued the *w¹¹¹⁸* phenotype. Overall, our data show that mitochondrial responses to infection are highly pathogen specific and further shaped by the host's genetic background. This should be considered when implementing personalized medicine in infectious diseases.