Longitudinal transcriptional analysis of vertebrate aging identifies mitochondrial complex I as a small molecule-sensitive modifier of lifespan.

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Abstract

Mutations and genetic variability affect gene expression and lifespan, but the impact of variations in gene expression within individuals on their aging-related mortality is poorly understood. We performed a longitudinal study in the short-lived killifish, Nothobranchius furzeri, and correlated quantitative variations in gene expression during early adult life with lifespan. Shorter- and longer-lived individuals differ in their gene expression before the onset of aging-related mortality; differences in gene expression are more pronounced early in life. We identified mitochondrial respiratory chain complex I as a hub in a module of genes whose expression is negatively correlated with lifespan. Accordingly, partial pharmacological inhibition of complex I by the small molecule rotenone reversed aging-related regulation of gene expression and extended lifespan in N. furzeri by 15%. These results support the use of N. furzeri as a vertebrate model for identifying the protein targets, pharmacological modulators, and individual-to-individual variability associated

with aging.

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