Mitochondrial content determines lifespan through metabolic reprogramming

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ABSTRACT

Mitochondria are critical regulators of the aging process. Their impairment leads to leakage of toxic metabolic by-products causing cellular and organismal demise. However, mild mitochondrial impairment can induce lifespan extension in several model organisms. The actual mechanism of this beneficial effect is poorly understood. The protein quality control of the organelle governed by the mitochondrial unfolded protein response (UPR^{mt}) pathway has been proposed to mediate the beneficial effects on lifespan, although this notion has recently been challenged. Here, we show that reducing mitochondrial content by blocking the mitochondrial protein import machinery, induces UPR^{mt} and positively regulates lifespan of the nematode *C. elegans*. Moreover, reduction in mitochondrial content, leads to a metabolic shift towards glycolysis, *de novo* serine biosynthesis and fat storage. Body wall muscles and intestine, the nematode's energy-storing tissues, mediate the lifespan prolonging effects. Both glycolysis and *de novo* serine biosynthesis are required for the observed longevity. Intriguingly, metabolic rewiring induced by reduced mitochondrial content reverses glucose toxicity, further implicating carbohydrate metabolism in the longevity phenotype. Part of this metabolic shift is mediated by ATFS-1, the transcription factor governing mitochondrial unfolded protein response. Our data uncouple UPR^{mt} to longevity while placing ATFS-1 at the center of the longevity-driving pathway as an essential regulator of the concurrent metabolic shift. We support the notion that reduction of mitochondrial content activates ATFS-1 to orchestrate the channeling of carbon sources to alternative metabolic pathways leading to reversal of glucose toxicity and lifespan extension.