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Direct regulation of cupins by the metabolic network in C. elegans

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isruption of mitochondrial respiration in the nematode Caenorhabditiselegans can result in life extension or life shortening. We recently discovered that the excretome of several long-lived C. elegans respiratory mutants (Mit mutants) is enriched in α -hydroxyacids and α -ketoacids; a property not shared by short-lived respiratory mutants or by unrelated long-lived strains. These compounds are structurally related to α -ketoglutarate, an essential co-substrate for a diverse family of cupin-fold containing enzymes called the α -ketoglutarate-dependent hydroxylases, suggesting they may be biologically relevant. One potential target is the cupin and prolyl-hydroxylase EGL-9, which negatively regulates hypoxia factor-1 (HIF-1), a transcription factor essential for Mit mutant longevity. Other potential cupin targets include the jumonji domain-containing (JmjC) histone demethylases (JMJDs), several of which also regulate lifespan in C. elegans. Here we show that compounds found in the Mitexometabolome stabilize HIF-1 when added to wild-type worms, and can directly inhibit recombinant JMJD2A. Provision of these same compounds to mouse fibroblasts resulted in increased amounts of transcriptionally competent HIF-1. Furthermore, we show that 2,4-pyridinedicarboxylic acid, a competitive inhibitor of several α -ketoglutarate-dependent hydroxylases, is sufficient to increase the lifespan of wild-type worms - an effect blocked by removal of HIF-1. These data uncover a novel mode of cellular signaling that not only explains the paradoxical life extension of Mit mutants, but also reveals a hitherto unappreciated link between mitochondrial dysfunction and a large family of enzymes found throughout eukaryotes which control fundamental cellular processes spanning DNA damage repair, epigenetic reprogramming, RNA modification and metabolite processing.

Biography

Shane L Rea is an Assistant Professor at Barshop Institute & Dept. Physiology. He did his Post-doctoral from McGill University, University of Colorado. In 2006, he was awarded with Excellence in science for Post-Doctoral Research sponsored by AAAS & UC Boulder.

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