

Neuronal ROS signaling rather than AMPK/sirtuin-mediated energy sensing links dietary restriction to lifespan extension.

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Abstract

Dietary restriction (DR) extends lifespan and promotes metabolic health in evolutionary distinct species. DR is widely believed to promote longevity by causing an energy deficit leading to increased mitochondrial respiration. We here show that inhibitors of mitochondrial complex I promote physical activity, stress resistance as well as lifespan of *Caenorhabditis elegans* despite normal food uptake, i.e. in the absence of DR. However, complex I inhibition does not further extend lifespan in dietarily restricted nematodes, indicating that impaired complex I activity mimics DR. Promotion of longevity due to complex I inhibition occurs independently of known energy sensors, including DAF-16/FoxO, as well as AAK-2/AMPK and SIR-2.1/sirtuins, or both. Consistent with the concept of mitohormesis, complex I inhibition transiently increases mitochondrial formation of reactive oxygen species (ROS) that activate PMK-1/p38 MAP kinase and SKN-1/NRF-2. Interference with this retrograde redox signal as well as ablation of two redox-sensitive neurons in the head of the worm similarly prevents extension of lifespan. These findings

unexpectedly indicate that DR extends organismal lifespan through transient neuronal ROS signaling rather than sensing of energy depletion, providing unexpected pharmacological options to promote exercise capacity and healthspan despite unaltered eating habits.

Beteiligte Forschungseinheiten

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