Impaired insulin/IGF1 signaling extends life span by promoting mitochondrial L-proline catabolism to induce a transient ROS signal.

Zarse K, Schmeisser S, Groth M, Priebe S, Beuster G, Kuhlow D, Guthke R, Platzer M, Kahn CR, Ristow M (2012) Impaired insulin/IGF1 signaling extends life span by promoting mitochondrial L-proline catabolism to induce a transient ROS signal. *Cell Metab* 15(4), 451-465.

Abstract

Impaired insulin and IGF-1 signaling (iIIS) in C. elegans daf-2 mutants extends life span more than 2-fold. Constitutively, iIIS increases mitochondrial activity and reduces reactive oxygen species (ROS) levels. By contrast, acute impairment of daf-2 in adult C. elegans reduces glucose uptake and transiently increases ROS. Consistent with the concept of mitohormesis, this ROS signal causes an adaptive response by inducing ROS defense enzymes (SOD, catalase), culminating in ultimately reduced ROS levels despite increased mitochondrial activity. Inhibition of this ROS signal by antioxidants reduces iIIS-mediated longevity by up to 60%. Induction of the ROS signal requires AAK-2 (AMPK), while PMK-1 (p38) and SKN-1 (NRF-2) are needed for the retrograde response. IIIS upregulates mitochondrial L-proline catabolism, and impairment of the latter impairs the life span-extending capacity of iIIS while L-proline supplementation extends C. elegans life span. Taken together, iIIS promotes L-proline metabolism to generate a ROS signal for the adaptive induction of endogenous stress defense to extend life span.

Beteiligte Forschungseinheiten

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