Role of sirtuins in lifespan regulation is linked to methylation of nicotinamide.

Schmeisser K, Mansfeld J, Kuhlow D, Weimer S, Priebe S, Heiland I, Birringer M, Groth M, Segref A, Kanfi Y, Price NL, Schmeisser S, Schuster S, Pfeiffer AF, Guthke R, Platzer M, Hoppe T, Cohen HY, Zarse K, Sinclair DA, Ristow M (2013) Role of sirtuins in lifespan regulation is linked to methylation of nicotinamide. *Nat Chem Biol* 9(11), 693-700.

Details

PubMed

Abstract

Sirtuins, a family of histone deacetylases, have a fiercely debated role in regulating lifespan. In contrast with recent observations, here we find that overexpression of sir-2.1, the ortholog of mammalian SirT1, does extend Caenorhabditis elegans lifespan. Sirtuins mandatorily convert NAD(+) into nicotinamide (NAM). We here find that NAM and its metabolite, 1-methylnicotinamide (MNA), extend C. elegans lifespan, even in the absence of sir-2.1. We identify a previously unknown C. elegans nicotinamide-N-methyltransferase, encoded by a gene now named anmt-1, to generate MNA from NAM. Disruption and overexpression of anmt-1 have opposing effects on lifespan independent of sirtuins, with loss of anmt-1 fully inhibiting sir-2.1-mediated lifespan extension. MNA serves as a substrate for a newly identified aldehyde oxidase, GAD-3, to generate hydrogen peroxide, which acts as a mitohormetic reactive oxygen species signal to promote C. elegans longevity. Taken together, sirtuin-mediated lifespan extension depends on methylation of NAM, providing an unexpected mechanistic role for sirtuins beyond histone deacetylation.

Beteiligte Forschungseinheiten

Microbiome Dynamics Gianni Panagiotou Mehr erfahren

Leibniz-HKI-Autor*innen



Reinhard Guthke

Details



Steffen Priebe

Details

Themenfelder

RNA-Seq Datenanalyse und Modellierung

Identifier

doi: 10.1038/nchembio.1352

PMID: 24077178