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

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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.

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Leibniz-HKI-Authors



Reinhard Guthke

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Steffen Priebe

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