

Impairing L-threonine catabolism promotes helthspan through proteotoxic methylglyoxal.

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Abstract

Whether and how regulation of genes and pathways contributes to physiological aging is topic of intense scientific debate. By performing an RNA expression-based screen for genes downregulated during aging of three different species, we identified glycine-C-acetyltransferase (GCAT, EC 2.3.1.29). Impairing gcat expression promotes the lifespan of *C. elegans* by interfering with threonine catabolism to promote methylglyoxal (MGO; CAS 78-98-8) formation in an amine oxidase-dependent manner. MGO is a reactive dicarbonyl inducing diabetic complications in mammals by causing oxidative stress and damaging cellular components, including proteins. While high concentrations of MGO consistently exert toxicity in nematodes, we unexpectedly find that low-dose MGO promotes lifespan, resembling key mediators of gcat impairment. These were executed by the ubiquitin-proteasome system, namely PBS-3 and RPN-6.1 subunits, regulated by

the stress-responsive transcriptional regulators SKN-1/NRF2 and HSF-1. Taken together, GCAT acts as an evolutionary conserved aging-related gene by orchestrating an unexpected nonlinear impact of proteotoxic MGO on longevity.

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