

Branched-Chain Amino Acid Catabolism is a Conserved Genetic Regulator of Physiological Aging

Mansfeld J, Urban N, Priebe S, Groth M, Frahm C, Hartmann N, Gebauer J, Ravichandran M, Dommaschk A, Schmeisser S, Kuhlow D, Monajembashi S, Bremer-Streck S, Hemmerich P, Kiehntopf M, Zamboni N, Englert C, Guthke R, Kaleta C, Platzer M, Sühnel J, Witte O, Zarse K, Ristow M (2015) Branched-Chain Amino Acid Catabolism is a Conserved Genetic Regulator of Physiological Aging *Nature Communications* 6, 10043.

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Abstract

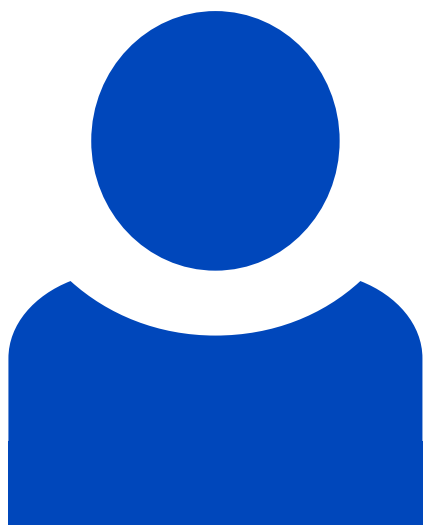
Ageing has been defined as a global decline in physiological function depending on both environmental and genetic factors. Here we identify gene transcripts that are similarly regulated during physiological ageing in nematodes, zebrafish and mice. We observe the strongest extension of lifespan when impairing expression of the branched-chain amino acid transferase-1 (bcat-1) gene in *C. elegans*, which leads to excessive levels of branched-chain amino acids (BCAAs). We further show that BCAAs reduce a LET-363/mTOR-dependent neuro-endocrine signal, which we identify as DAF-7/TGF β , and that impacts lifespan depending on its related receptors, DAF-1 and DAF-4, as well as ultimately on DAF-16/FoxO and HSF-1 in a cell-non-autonomous manner. The transcription factor HLH-15 controls and epistatically synergizes with BCAT-1 to modulate physiological ageing. Lastly and consistent with previous findings in rodents,

nutritional supplementation of BCAAs extends nematodal lifespan. Taken together, BCAAs act as periphery-derived metabokines that induce a central neuro-endocrine response, culminating in extended healthspan.

Involved units

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Identifier

doi: 10.1038/ncomms10043

PMID: 26620638