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α-Ketoglutarate-A New Currency of Longevity

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"Less is more" aptly applies to the effect of diet on longevity. Emerging evidence implicates several metabolites as influencing longevity, but the mechanism of this phenomenon has hitherto remained elusive. Leveraging *Caenorhabditis elegans* as a model system, Chin *et al*. have uncovered a critical role of α-ketoglutarate (α-KG), a product of tricarboxylic acid metabolism, in prolonging life span.

Among several metabolites tested, supplementation of α-KG to the growth medium specifically prolonged the life span of worms by 50% and delayed their age-related phenotype. The growth medium also contained bacteria, raising a possibility of an indirect effect of α-KG. However, the effect of α-KG persisted even with growth-arrested bacteria, providing evidence for a direct effect on the worms. Inhibition of α-KG catabolism by silencing its degrading enzyme, α-KG dehydrogenase, mimicked its effect on longevity, supporting a critical role of α-KG in prolonging life span. To discern the molecular target of α-KG, the authors used an unbiased approach called drug affinity responsive target stability (DARTS), which takes advantage of the fact that proteins bound to α-KG are protected from digestion and can be identified with mass spectrometry. ATPSB, a subunit of adenosine triphosphate (ATP) synthase and part of mitochondrial electron complex *V*. was protected in α-KG-treated samples, suggesting ATP synthase as a potential target. Further studies confirmed the interaction of α-KG and ATP-2 (*C. elegans* ortholog of ATP5B) and revealed α-KG as a noncompetitive inhibitor of ATP synthase, resulting in decreased ATP and oxygen consumption.

The authors examined several additional modulators of worm longevity, such as target of rapamycin (TOR), 5′ adenosine monophosphate-activated prote1in kinase (AMPK), and FoxO. Silencing experiments revealed that TOR was downstream of α-KG and that α-KG-treated cells showed lower TOR activity. The authors also observed an increase in autophagy in α-KG-treated animals, corresponding with the inhibition of TOR, a known mediator of autophagy. α-KG's physical interaction with ATP synthase appeared to inhibit its activity and that of TOR, thus increasing autophagy. Autophagy is known to support maintenance rather than growth, which delays aging and extends life span, helping explain the effect of α-KG on longevity.

Although the present study raises several questions, including the mechanism of inhibition of TOR by α-KG and the relationship of ATP58 inhibition to TOR, it uncovers a new function of α-KG. This represents an important advance in the field of aging and underscores the balance of growth and maintenance as a seminal determinant of longevity.

References

1. Chin RM, et al. The metabolite α-ketoglutarate extends lifespan by inhibiting ATP synthase and TOR. Nature. 2014; 510:397–401. [PubMed: 24828042]