A possible integrated model of hydroxycitric acid based on analyses in *Saccharomyces cerevisiae*

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Abstract:

The caloric restriction mimetics (CRMs) are promising molecules to prevent age-related diseases because they mime some of the beneficial effects of true caloric restriction. Hydroxycitric acid (HCA) is considered a bona fide CRM since it reduces nuclear and cytoplasmic pool of acetyl-CoA (AcCoA) by acting as a competitive inhibitor of ATP citrate lyase (ACLY). Since, HCA can also reduce tumor development, it is important to understand if there are other relevant cellular targets, in addition to ACLY. The yeast *Saccharomyces cerevisiae* is well suited for this purpose since it naturally lacks ACLY.
HCA is a molecule extremely similar to citrate (CA), an important endogenous metabolite and substrate of ACLY, which also acts as a crucial sensor of the cell's energy levels and controls the activity of different enzymes. In addition, HCA and CA similarly regulate the activity of some enzyme, *in vitro*. Based on this, we formulated this hypothesis: in addition to inhibiting ACLY, hydroxycitrate might acts in a very similar way to citrate on cellular metabolism.
The experiments conducted in our laboratory show that HCA or CA is able to extend the chronological lifespan (CLS) of yeast cells with a similar effect. Based on this important phenotype, we performed a CLS experiment in presence of several concentration of acetate, which can raise intracellular levels of AcCoA. Acetate showed a moderate protective effect on cell survival while, HCA/CA, as expected, extended cell longevity. Furthermore, we investigate the possible control of autophagy by HCA or CA using GFP-Atg8. Preliminary data show that the formation of pre-autophagosomal structures is much more frequent in the presence of these two molecules versus control without treatments, suggesting, at a first approximation, a positive control of autophagic processes by HCA or CA.
We propose a model for eukaryotic cells, in which HCA acts both as an inhibitor of ACLY and as a regulator of metabolism with an action similar to CA. HCA promotes autophagy by reducing AcCoA levels, by inhibiting glycolysis and TCA cycle, and stimulating the enzyme acetyl-CoA carboxylase that controls the lipid synthesis.