A Novel Caloric Restriction-Like Mimetic Affects Longevity in Yeast by Reprogramming Core Metabolic Pathways

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Abstract
Glucose limitation is a simple intervention that extends yeast replicative lifespan (RLS) via the same pathway(s) thought to mediate the benefits of caloric restriction (CR) in mammals. Here we report on “C1”, a small molecule that mimics key aspects of CR. C1 was identified in a high throughput screen for drug-like molecules that reverse the RLS shortening effect of the sirtuin inhibitor and NAD+ precursor nicotinamide. C1 reduces the cellular dependence on glycolysis and the pentose phosphate pathway, even in the presence of glucose, and compensates by elevating fatty acid -oxidation to maintain acetyl-CoA levels. C1 acts either downstream of Sir2 or in an independent CR pathway. In this regard, chemical-genetic interactions indicate that C1 influences Tor2 signaling via effects on phosphoinositide pools. Key activities of C1 extend to mammals. C1 stimulates β-oxidation in mammalian cells, and in mice, reduces levels of triacylglycerides and cholesterol in livers of lean and obese mice. C1 confers oxidative resistance to diamide in both yeast and mammalian cells. In conclusion, C1 induces global changes in metabolism in yeast and mammalian cells that mimic aspects of CR. Future work will be aimed at identifying the cellular target of C1.

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ABSTRACT:
Glucose limitation is a simple intervention that extends yeast replicative lifespan (RSL) via the same pathways thought to mediate the benefits of caloric restriction (CR) in mammals. Here we report on ‘C1’, a small molecule that mimics key aspects of CR. C1 was identified in a high throughput screen for drug-like molecules that reverse the RLS shortening effect of the insulin-inhibitor and NAD+ precursor nicotinamide. C1 reduces the cellular dependence on glycolysis and the pentose phosphate pathway, even in the presence of glucose, and compensates by elevating fatty acid β-oxidation to maintain acetyl-CoA levels. C1 acts either downstream of Sir2 or in an independent CR pathway. In this regard, chemical genetic interactions indicate that C1 influences Tor2 signaling via effects on phosphoinositide pools. Key activities of C1 extend to mammalian cells. C1 stimulates β-oxidation in mammalian cells, and in mice, reduces levels of triglycerides and cholesterol in lean and obese mice. C1 confers mitotic and replicative resistance to diabetics in both yeast and mammalian cells. In conclusion, C1 induces global changes in metabolism in yeast and mammalian cells that mimic aspects of CR. Future work will be aimed at identifying the cellular target of C1.

Small molecule probes reverse the lifespan shortening effects of nicotinamide

Lifespan assay using the standard life span assay and extra-ribosomal rDNA circles (ERCs)

C1 provides resistance to oxidative stress (CR mimicry)

Fig 1. Chemical genetic screening of C1 with the temperature sensitive collection reveal that C1 provides a growth rescue for the ts mutants of PIP and the TORC2 complex (Sirt2/Bach). Interestingly C1 also increased the resistance of yeast to the phosphoinositide pool, the PIP2 and the PIP3 pools. All these results suggest that C1 is bypassing the acetyl-CoA-producing enzyme, as well as the downstream effects of CR mimetics.

Fig 2. Metabolic change due to C1 supports a shift away from glycolysis and the pentose phosphate pathway

Fig 3. Pro-oxidant treated with C1 creates a vulnerability to reduced Co-enzyme A and a decrease in flux which could account for these data.

Fig 4. A novel bioactive small molecule that presents multiple phenotypes in both yeast and mammalian cells (whole animal and tissue culture). The shared phenotypes of oxidative stress resistance, metabolic shift, and a resistance to reduced glucose metabolism suggest a conserved pathway by which C1 is effective.

Conclusion: C1s is a novel bioactive small molecule that presents multiple phenotypes in both yeast and mammalian cells, whole animal and tissue culture. The shared phenotypes of oxidative stress resistance, metabolic shift, and a resistance to reduced glucose metabolism by which C1 is effective could provide great medical benefits in the treatment of age related diseases such as diabetes and atherosclerosis.