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 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 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 ura3-52 and nad4Δ1 precancerous lesions. C1 reduces the cellular dependence on glycolysis and the pentose phosphate pathway, even in the presence of glucose, and compromises by elevating fatty acid β-oxidation to maintain acetyl-CoA levels. C1 acts either downstream of sir2 or in an independent CR pathway. In yeast, these cellular interactions indicate that C1 influences Tor2 signaling via effects on phosphoinositide pools. Key activities of C1 extend to mammals. C1 stimulates a Δ3 oxidase in mammalian cells, and in mice, reduces levels of triglycerides and cholesterol in liver of lean and obese mice. C1 confers oxidative resistance to diethylnitrosamine by inducing resistance to oxidative stress 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

![Image]

Fig 1. C1 rescues PPP mutants (CR mimicry)

Lifespan probe acts independent of the sirtuin, Sir2, and extraribosomal RNA circles (ERCs)

![Image]

Fig 2. Small molecule probes reverse the lifespan shortening effects of nicotinamide

C1 provides resistance to oxidative stress (CR mimicry)

![Image]

Fig 3. Metabolic pathways influenced by C1

C1 reduces the levels of fatty-acid oxidation intermediates. Yeast and mouse liver cells (HeLa2) treated with C1 display decreased levels of fatty acid-CoA and beta-hydroxybutyryl-CoA (BHB-CoA) in the presence of glucose. C1 increases fatty acid β-oxidation levels of fatty acid-CoA in yeast and mouse liver cells (HeLa2) treated with C1. A decrease in fatty acid-CoA level in the presence of glucose is not seen in the no C1 control. Results only suggest a change in glucose metabolism, either an increase or decrease in flux could account for these data.

C1 elevates fatty acid B-oxidation

![Image]

Fig 4. C1 elevates fatty acid B-oxidation

C1 reduces triglyceride, cholesterol, and fat lipid retention in mammalian cells

![Image]

Fig 5. C1 reduces triglyceride, cholesterol, and fat lipid retention in mammalian cells

C1 increases fatty acid oxidation. HeLa2 cells were cultured in heavy-labeled palmitate with increasing doses of C1 and the fraction of total acetyl-CoA derived from heavy palmitate was determined by LC/MS. C1 increased heavy-labeled CoA (B) whereas total acetyl-CoA (B) and CoA-SH (C) remained unchanged. These data indicate increased fatty-acid oxidation in the presence of C1 and heavy-labeled palmitate and are consistent with decreased TAG levels obtained in mice treated with C1.

Conclusions: 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, interaction, and a metabolic shift toward B-oxidation of fatty acids suggest a conserved pathway(s) is being affected by C1. The phenotypes displayed by C1 treated cells are also shared by cells undergoing caloric restriction (CR) or contain mutations that mimic CR. These results suggest that C1 is acting on a pathway that is also affected by caloric restriction and may very well be a true CR mimic. Internally the most interesting of all the C1 results is the reduction in triglycerides, cholesterol and lipid storage in mammalian cells. Such a compound could provide great medical benefits in the treatment of age-related diseases such as diabetes and atherosclerosis. The next critical stop for C1 is the identification of the proven target.

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