Caffeine extends yeast lifespan by targeting TORC1

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Summary

Dietary nutrient limitation (dietary restriction) is known to increase lifespan in a variety of organisms. Although the molecular events that couple dietary restriction to increased lifespan are not clear, studies of the model eukaryote Saccharomyces cerevisiae have implicated several nutrient-sensitive kinases, including the target of rapamycin complex 1 (TORC1), Sch9, protein kinase A (PKA) and Rim15. We have recently demonstrated that TORC1 activates Sch9 by direct phosphorylation. We now show that Sch9 inhibits Rim15 also by direct phosphorylation. Treatment of yeast cells with the specific TORC1 inhibitor rapamycin or caffeine releases Rim15 from TORC1-Sch9-mediated inhibition and consequently increases lifespan. This kinase cascade appears to have been evolutionarily conserved, suggesting that caffeine may extend lifespan in other eukaryotes, including man.
Introduction

• Dietary restriction slows ageing and extends lifespan.
• Reducing activity of TORC1 or its target Sch9, extends lifespan in yeast.
• When Rim15 is blocked, stress responsive genes, and others stationary phase genes are downregulated and lifespan is decreased.
Introduction (cont.)

• Rapamycin- immunosuppressant used to prevent rejection in organ transplantation (inhibits the response to IL-2).
  – first discovered as a product of the bacterium *Streptomyces hygroscopicus* in a soil sample from Easter Island.
• Rapamycin targets TORC1.
• TORC1 is a major target of caffeine.
Introduction (cont.)

Typical culture-density profile of a fermentative batch culture of *S. cerevisiae*
Main players
Caffeine inhibits TORC1
Rim15 is required for induction of stress response genes
Main players
Sch9 targets Rim15
Main players
TORC1-Sch9 effector branch antagonizes the G₀ program by nuclear exclusion of Rim15
Caffeine extends yeast lifespan by downregulating TORC1-Sch9-Rim15 pathway
Conclusions

• Caffeine seems to target TORC1 in the same fashion as Rapamycin does.
• It seems to downregulate the TORC1/Sch9/Rim15 pathway.
• It prevents Sch9 to phosphorylate Rim15, therefore Rim15 can go in the nucleus and activate stress response genes and other stationary phase genes.
Can Caffeine extend lifespan in humans?

• TORC1, Sch9 and Rim15 have analogs in humans.
• Decreased TOR increases lifespan in flies and worms.
• Moderate consumption of caffeine could extend lifespan of humans.
• Caffeine could also be used as anti-cancer agent.
Proposed nutrition pyramid

Coffee

Tea

Soda (Pop)

Food

Vivarin

Energy drinks

Chocolate
Questions?