The Yeast Metabolic Cycle Triggers the Cell Division Cycle Through Control of Start

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The yeast metabolic cycle is a synchronous rhythm observed in *Saccharomyces cerevisiae* grown under slow-growth aerobic chemostat conditions, known to couple to the cell division cycle. It has been hypothesized that this coupling could be driven either by metabolic shifts triggering cell cycle Start, or by Start triggering changes in metabolism. By measuring cell cycle Start at single-cell resolution in a cycling population, we show that the metabolic cycle drives synchronization of cell cycle Start in this coupled system. Our data support a model in which this synchronization is due to modulation of the cell size threshold for cell cycle Start due to increased metabolic carbon flux.

***Keywords* — Saccharomyces cerevisiae, yeast metabolic cycle, cell cycle, coupled oscillations, systems biology**

I. Introduction

The yeast metabolic cycle (YMC) is a synchronous population oscillation in which yeasts growing aerobically under chemostat conditions alternate between building storage carbohydrates during a low-oxygen-consumption phase (LOC) and their rapid consumption in a high-oxygen-consumption phase (HOC), with large oscillations in the transcriptome content [1]. The cell division cycle (CDC) couples to this oscillation, with a subpopulation of cells passing through cell cycle Start once per YMC.

Our previous work on the coupling between the YMC and CDC has revealed that during the YMC, DNA replication is triggered at a characteristic time after entry into HOC phase [2]. This suggested that cell cycle Start was closely associated with entry into HOC phase. Two models of YMC/CDC coupling present themselves. It has been suggested that rapid carbon metabolism during HOC causes production of acetyl-coenzyme A and chromatin acetylation, triggering the production of Cln3 pushing cells through Start [3]. The phosphorylation of carbohydrate-degrading enzymes by the cyclin-dependent kinase has alternately been shown to trigger carbon metabolism during cell division, providing a mechanism for the CDC to control the YMC [4]. To distinguish between these models, we measured the timing of cell cycle Start relative to the phases of the YMC.

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II. Methods & Results

Yeast bearing a fluorescent fusion of the "Start" network protein Whi5 were grown under oscillating chemostat conditions. Samples were fixed over the course of multiple oscillations and examined via fluorescence microscopy. The fraction of cells with nuclear localized (G1) and delocalized (S/G2/M) Whi5 were recorded at each time point, as well as cell volume and replicative age. We found that cells only pass cell cycle Start ~15 minutes *after* entry into HOC phase. This supports a model of coupling in which the YMC drives the CDC after HOC entry via production of acetyl-coenzyme A and Cln3 during HOC. The behavior of yeast of different replicative ages and volumes was compared. Larger cells commit to division at a higher rate during HOC phase, suggesting that size control is influenced by the YMC.

HOC phase was then artificially induced by addition of ethanol to the growth medium, which is metabolized to acetyl-coenzyme A. Similar to natural oscillations, cells commit to division shortly after this induction. The largest cells again commit to division most frequently, and also commit earlier than smaller cells, supporting the role of size control in YMC/CDC coupling.

III. Conclusions

Cell cycle Start occurs *after* the switch from low oxygen consumption to high oxygen consumption. This supports the model in which the YMC drives cell cycle Start during natural oscillation, due to shifts in chromatin acetylation. The relationship between cell size and the rate of cells passing Start is consistent with a model in which the production of Cln3 in response to metabolic shifts modulates the size threshold for division, with a low size threshold during HOC and a high size threshold during LOC.

References

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