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Metabolism: The clock of the eukaryotic cell?

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The eukaryotic cell division is thought to be controlled by periodic activity of the cyclin dependent kinase (CDK) machinery. However, the fact that CDKs came late in the evolution of eukaryotes, and the fact that oscillations in global transcription and the anaphase promoting complex activity were also found in during cell cycle arrest, suggest that cell cycle regulators external to the cyclin/CDK machinery could exist. We hypothesized that an autonomous metabolic oscillator could represent such global cell cycle regulator. Using microfluidics technology, in combination with single cell metabolite and cell cycle reporters, we found that yeast metabolism is a CDK-independent oscillator, which orbits across nutrients and at different metabolic modes, in synchrony with the cell cycle, but also in non-dividing cells. Using environmental perturbations and conditional protein depletion experiments, we found that the metabolic oscillator and the cyclin/CDK machinery form a system of coupled oscillators. Through analysis of our experimental data with a Kuramoto model, we unraveled the high-level topology of this coupled oscillator system. In this system, the metabolic oscillator robustly gates the phase of the early and the late cell cycle, whereas a minimal metabolic frequency threshold must be reached for the cell cycle to START. This work suggests that cell cycle control is not just the result of the cyclin/CDK machinery, but emerges as a higher order function from coupled and mutually entrained oscillators, including the oscillating metabolism. Given the evolutionary conservation of metabolic pathways across life kingdoms, the metabolic oscillator may constitute an ancestral regulator of cell division.

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