Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Microbiology

How yeast coordinates metabolism, growth and division

Jennifer C Ewald

All cells, especially single cell organisms, need to adapt their metabolism, growth and division coordinately to the available nutrients. This coordination is mediated by extensive cross-talk between nutrient signaling, metabolism, growth, and the cell division cycle, which is only gradually being uncovered: Nutrient signaling not only controls entry into the cell cycle at the G1/S transition, but all phases of the cell cycle. Metabolites are even sensed directly by cell cycle regulators to prevent cell cycle progression in absence of sufficient metabolic fluxes. In turn, cell cycle regulators such as the cyclin-dependent kinase directly control metabolic fluxes during cell cycle progression. In this review, I highlight some recent advances in our understanding of how metabolism and the cell division cycle are coordinated in the model organism *Saccharomyces cerevisiae*.

Address
Eberhard Karls Universität Tübingen, Interfaculty Institute of Cell Biology, Auf der Morgenstelle 15, 72076 Tübingen, Germany

Corresponding author: Ewald, Jennifer C (jennifer.ewald@ifiz.uni-tuebingen.de)

Current Opinion in Microbiology 2018, **45**:1–7

This review comes from a themed issue on **Microbial systems biology**

Edited by **Terence Hwa** and **Uwe Sauer**

https://doi.org/10.1016/j.mib.2017.12.012

One of the most fundamental challenges in modern biology is to understand how cells process and integrate information from their environment into coordinated physiological responses. Importantly, cells must coordinate the regulation of growth and division, that is, the cell cycle, with the catabolic and anabolic pathways that provide the energy and raw materials necessary for all cellular activities. Determining the mechanisms responsible for this coordination of metabolism with the cell division cycle is fundamental for understanding disease states such as cancer, physiological processes including differentiation and aging, as well as ecology and evolution of single cell organisms in their environments. Despite this importance, the molecular mechanisms determining the cell cycle — metabolism interface remain poorly understood, even in 'simple' and extensively-studied organisms such as the yeast *Saccharomyces cerevisiae*. *S. cerevisiae* is an ideal model to investigate the cell-cycle-metabolism interface, since both the cell cycle and metabolism have been extensively studied, and are easily manipulated.

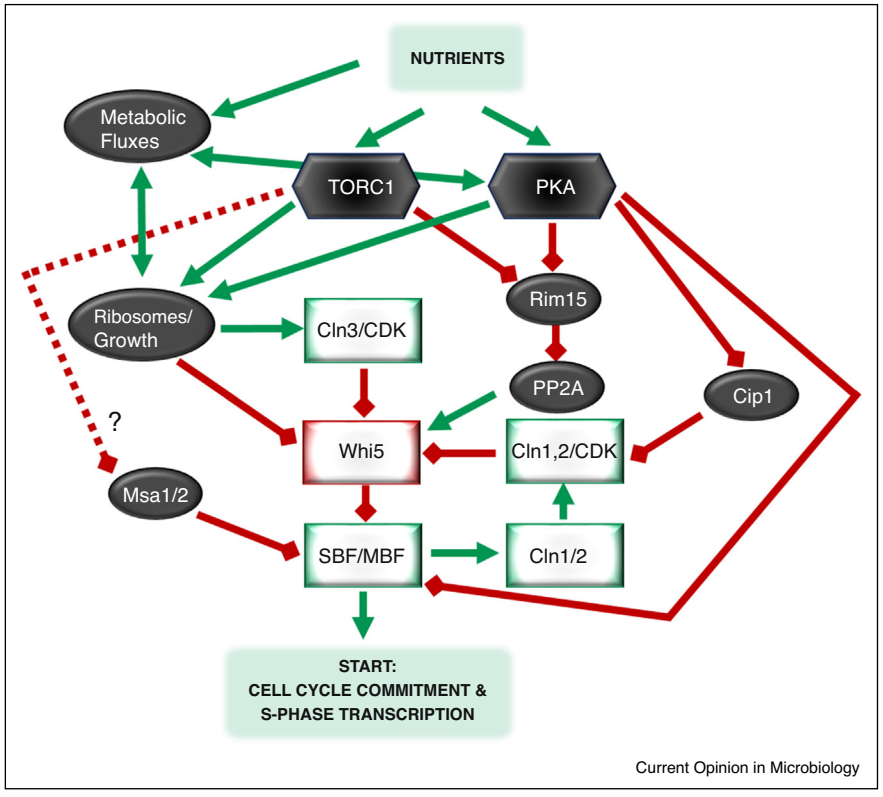
Pioneering cell cycle studies in *S. cerevisiae* in the 1970s showed that cell growth continues even if the cell cycle is arrested at various stages [1,2]. This led to the impression that the regulation of metabolism and growth on the one hand, and the cell division cycle on the other hand, are largely independent and are connected only through the cell size checkpoint at the G1/S transition. However, a large collection of evidence from 'omics' studies, biochemical studies, and single cell investigations now suggests that there is extensive cross-talk to coordinate metabolism and growth with the cell cycle. Here, I summarize some recent advances in unraveling this cross-talk. I will discuss our current understanding of how metabolic inputs control cell cycle progression, and in turn, how cell cycle progression shapes cellular metabolism.

The gatekeeper: metabolic control of *Start*

In most circumstances, division requires growth, and growth requires sufficient supply of carbon and all other nutrients. Thus, it is crucial that nutrient supply and biosynthetic fluxes regulate cell cycle entry. This regulation is most important and apparent at *Start*, the point that determines cell cycle entry at the end of G1. *Start* is a molecular 'switch' leading to irreversible commitment to DNA replication and division [3]. At *Start*, the cyclin dependent kinase (CDK) with the upstream cyclin Cln3 inactivates the inhibitor Whi5, which leads to the activation of a positive feedback loop causing irreversible cell cycle commitment and activation of cell cycle related transcription [4].

Many components of this molecular switch are targets of metabolic signaling (Figure 1). The major global regulators of metabolism and growth in yeast — the PKA (protein kinase A), SNF (sucrose non fermenting), and TOR (target of rapamycin) pathways (see e.g. [5–7] for recent comprehensive reviews on these pathways) — play an important role in regulating *Start*. Different components and branches of these pathways are impinging on different cell cycle regulators to promote, slow down or prevent passage through *Start* according to the abundance of nutrients such as carbon, nitrogen and phosphate. One way metabolism contributes to modulating *Start* is through global growth and protein production rates,

Figure 1



Metabolic regulation of *Start*. Shown are some of the regulatory interactions between the nutrient signaling pathways PKA and TOR and the cell cycle regulators (rectangles) determining *Start*; green arrows indicate activation; red squares indicate inhibition. Msa1/2 was shown to be regulated by nutrient deprivation. The upstream nutrient signaling is so-far unknown, but it seems likely the starvation signal is transduced through well-known pathways such as TOR or PKA (dashed red line).

including the production of Cln3 and the dilution of Whi5 [8]. Many aspects of *Start* regulation have been extensively discussed in the context of cell size control mechanisms [9–12]. I will focus here on a few recent examples of direct regulation of the *Start* machinery by metabolic signaling pathways.

Several nutrient responsive inhibitors of *Start* were only recently identified. The inhibitor Cip1 was shown to delay *Start* in response to various environmental conditions, including carbon deprivation [13]. Cip1 expression is controlled by the PKA pathway transcription factors Msn2/4 and acts by directly binding the cyclin-CDK complex and blocking its activity.

The inhibitors Msa1/2 act on the transcription factor complexes SBF/MBF [14]. After nutrient depletion, Msa1/2 bind SBF and MBF to prevent passage through *Start* [15]. Interestingly, Msa1/2 seem to be regulated by both cell cycle and nutrient responsive regulators to ensure a strong inhibition of SBF/MBF only in G1: Msa1/2 transcription is cell cycle dependent and the proteins are localized to the nucleus only in G1. In unperturbed cycling cells they then have only a minor function in regulating G1/S transcription. If cells become nutrient deprived however, Msa1/2 become strong inhibitors of SBF and thereby prevent the G1/S transition. The upstream regulators for the nutrient response are still unknown, but it seems likely that these will also be downstream components of the TOR or PKA pathways.

A more and more prominent player in the metabolic regulation of the cell cycle, including *Start*, is the Greatwall-Kinase homolog Rim15. The kinase Rim15 integrates signals from both the TOR and the PKA pathways [7]. When these growth promoting pathways become downregulated due to nutrient depletion or other stresses, Rim15 is activated and can induce cell cycle arrest and quiescence [16,17]. Interestingly, Rim15 also has a role in *promoting Start*. Rim15 deactivates the phosphatase PP2A which is responsible for counteracting several kinases including the cell cycle kinase CDK1 [18]. Under nutrient-poor, but non-starvation conditions such as growth on non-fermentable carbon sources, inhibition of the phosphatase PP2A by Rim15 promotes Whi5 phosphorylation by CDK, and thus allows cells to transition *Start* earlier