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Review

The Biosynthetic Basis of Cell Size Control

Kurt M. Schmoller[1] and Jan M. Skotheim[1,*]

Cell size is an important physiological trait that sets the scale of all biosynthetic processes. Although physiological studies have revealed that cells actively regulate their size, the molecular mechanisms underlying this regulation have remained unclear. Here we review recent progress in identifying the molecular mechanisms of cell size control. We focus on budding yeast, where cell growth dilutes a cell cycle inhibitor to couple growth and division. We discuss a new model for size control based on the titration of activator and inhibitor molecules whose synthesis rates are differentially dependent on cell size.

Introduction

Cell size determines the geometry of all intracellular compartments and sets the scale of biosynthetic processes [1,2] (Figure 1). Biosynthesis increases in larger cells, which have proportionally more protein [3–6], total RNA [3,7], total mRNA [8], and mRNA for specific investigated genes [7,9,10]. The proportionate increase in building blocks in larger cells is likely to govern the size of organelles such as the nucleus [11,12], mitochondria [13], centrosome [14], vacuole [15], nucleolus [16], and mitotic spindle [17–21]. Due to its important role in cellular processes, many organisms actively control cell size by coupling growth and division [22–24] and target cell size is often modulated by environmental conditions [23]. Yet, despite the fundamental importance of cell size control, the molecular mechanisms underpinning this regulation have remained elusive.

Actively controlling cell size requires the generation of a size-dependent biochemical signal. However, biochemical reaction rates are typically determined by the concentrations of the reacting molecules and most protein amounts are proportional to cell size, such that their concentrations are unaffected by cell growth. This raises the question of how a cell can generate size-dependent biochemical signals using constant-concentration proteins. One proposed general mechanism to generate a size-dependent signal from proteins whose concentration is size independent is to localize those proteins in gradients with characteristic length scales [25–27]. The size of the cell can then be measured using the gradient length as a ruler. Specifically, in fission yeast cell size control was proposed to rely on a spatial gradient of Pom1, an inhibitor of mitotic entry localized in a gradient from the cell poles. As cells grow, the concentration of Pom1 at the middle of the cell decreases so that division is triggered [25,26]. However, recent work has cast doubt on this model because Pom1 is not essential for size control [28] and a new model based on increasing local concentration of Cdr2, a kinase activating mitotic entry, has been proposed [29]. Importantly, geometry-based size control mechanisms require a consistent geometry and therefore are unlikely to be employed by animal cells, which are more irregularly shaped. Moreover, geometric mechanisms are unlikely to work well in near-spherical budding yeast where characteristic lengths scale as the volume to the one-third power. A second general mechanism to create a size-dependent signal relies on the

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Whereas most macromolecules accumulate in proportion to cell size, some do not. The resulting differential size dependencies of molecular concentrations can be used to create size-dependent signals.

In budding yeast, the differential size dependence of the synthesis of the cell cycle activator Cln3 and the cell cycle inhibitor Whi5 results in cell size control.

In frog embryos, the differential size dependence of DNA and histone concentrations controls the mid-blastula transition of early development.

[1]Department of Biology, Stanford University, Stanford, CA 94305, USA

*Correspondence:
skotheim@stanford.edu
(J.M. Skotheim).

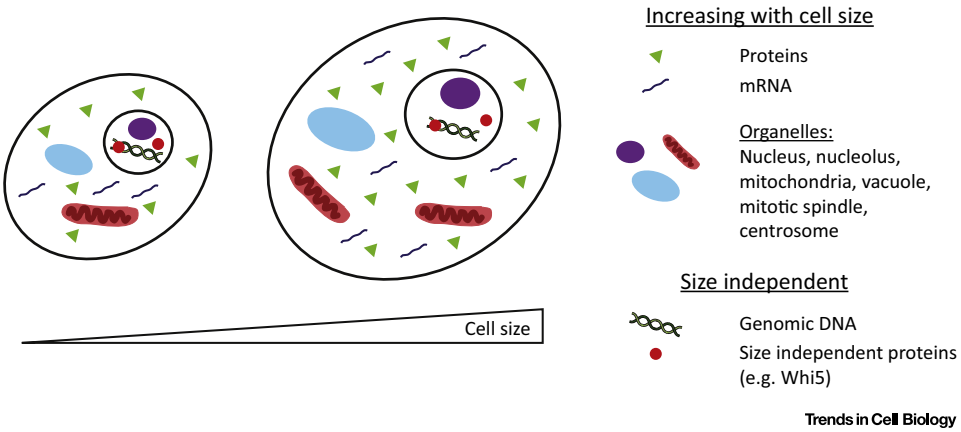

Figure 1. The Size or Number of Many Cellular Components Increases with Cell Size. Most proteins and mRNAs increase in direct proportion to cell size so that molecular concentrations are constant in growing cells. Moreover, organelle size often scales with cell size. By contrast, cells of different size often have the same amount of genomic DNA. Recently, it was shown that some proteins, including the cell cycle inhibitor Whi5, are not synthesized in proportion to cell size, to generate size-dependent concentrations and couple growth to division.

localization of proteins, whose amount is proportional to cell size, into compartments whose volume is not proportional to cell size. This gives rise to a size-dependent local concentration that can be used to trigger a cellular transition.

Here we discuss a new general alternative. While most macromolecules accumulate in proportion to cell size, some do not. This differential size dependency of synthesis can be used to generate size-dependent changes in the relative concentrations of activator and inhibitor molecules to couple cell size with specific cellular transitions.

Differential Cell Size Dependence of Protein Synthesis Controls Budding Yeast Size

While geometric gradient-based mechanisms are unlikely to apply to budding yeast, compartmentalization-based mechanisms are a viable alternative. In general, such mechanisms rely on generating a local size-dependent protein concentration by concentrating a protein whose amount is proportional to cell size in a compartment whose volume increases more slowly than the cell volume. We note here that we generally use the words cell size, volume, and total protein content interchangeably because of the small density differences associated with cell cycle progression in budding yeast [30].

In budding yeast, the duration of the G1 phase, between cell division and DNA replication, is strongly affected by cell size, while the duration of S/G2/M depends only weakly on cell size [23,31–35]. An analysis of cell-to-cell variability in G1 duration showed that differences in cell size at birth account for approximately half of the G1 variability, while molecular noise accounts for the other half [34]. The G1/S transition is promoted by the G1 cyclin Cln3 in complex with the cyclin-dependent kinase Cdk1 and by Bck2 through a currently unknown mechanism (*cln3Δbck2Δ* cells are unviable) [36–38]. Here we focus on the mechanism through which the Cln3 cell cycle pathway promotes division.

Although average cell size in a population is sensitive to *CLN3* dose, the concentration of Cln3 protein in G1 does not change appreciably as cells grow [35,39]. This has raised the question of how this putative trigger protein could initiate the cell cycle in a size-dependent manner. It was first proposed that Cln3's nuclear localization could generate a size-dependent signal. If the ratio