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Growth and Division – not a one-way road

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Summary

Maintaining cell size homeostasis and regulating cell size in response to changing conditions is a fundamental property of organisms. Here we examine the recent advances in our understanding of the interplay between accumulation of mass (growth) and the progression through the cell cycle (proliferation), the coordination of which determines the size of cells. It is well established that growth affects cell division (reviewed in [1]). This review will focus on the reverse, less well-defined relationship – how cell cycle progression affects growth. We will summarize findings that indicate that growth is not constant during the cell cycle and discuss the surprising possibility that cyclin-dependent kinases (CDKs) inhibit growth.

Introduction

All organisms, from single celled bacteria and yeast, to multi-cellular organisms can vary and adjust the size of their cells, to optimize growth, storage, regenerative capacity, or production capacity [2]. It is well established that cells need to reach a critical size in order to initiate a new cell cycle, although there are specific exceptions in multicellular organisms (reviewed in [1,3]. If growth is inhibited by starvation or by chemical inhibitors of macromolecular synthesis, cells stop proliferating. In the presence of nutrients or appropriate intracellular cues, cell growth is stimulated by the activity of the Tor and RAS pathways, and cells division can occur (reviewed in [4–6]. The regulation of proliferation by growth has been extensively covered recently and we wish to direct the readers to the following excellent reviews and books on this topic [1,2,4,7–9]. This review will focus on recent advances in understanding how cell cycle transitions affect growth in eukaryotes and discuss the importance of this regulation.

Growth rate changes at multiple points during the cell cycle of *Schizosaccharomyces pombe*

The rod-shaped yeast *Schizosaccharomyces pombe* grows by elongation at the cell poles (Figure 1A). Microscopic size measurements of *S. pombe* cells showed that the growth rate changes during the cell cycle. These points of change are called the Rate Change Points (RCPs) [10,11]. After cell division each daughter cell is half the size of the mother and should therefore grow at half the rate of the mother cell. This is not the case. The newly born daughter cells grow faster than half the rate of the mother cell. This change in growth rate that coincides with cell division is called RCP1 (Figure 1B) [12]. In the newborn cells,

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growth occurs only from the old pole of the cell (Figure 1A). This early growth rate depends on nutrient conditions and strain background [11]. During mid-G2, growth rate increases again by approximately 30% (RCP2; Figure 1B). This change in growth rate coincides with the switch from mono-polar growth (growth only at the old pole) to bi-polar growth (growth at both poles) [10,13], a transition that has been termed NETO (New-End-Take-Off). Curiously however, RCP2 does not depend on NETO. *wee1* and *cdc11* conditional mutants, in which NETO does not take place, show a growth rate increase at RCP2 [10,11]. Instead, RCP2 depends on the completion of DNA replication. When DNA replication is inhibited with hydroxyurea, RCP2 is not detected [14**]. The degree of increase in growth at RCP2 is sensitive to growth conditions and genotype. Furthermore, RCP2 is under size control [11]. The timing of RCP2 is inversely correlated to the birth size of the cell [11]. During mitosis, most likely during early anaphase, growth rate changes again. This growth rate change does not have a name (shown as an asterisk in Figure 1B) but is the starting point of what is known as the constant size period [10,12].

Measurement of protein and RNA synthesis in synchronously growing *S. pombe* cells confirmed growth rate changes during the cell cycle [15,16]. At 25°C, the amount of S^{35} labeled protein increases during the first 75% of the cell cycle, but then remains constant during the last 25% of the cell cycle [15] (Figure 1B). Protein synthesis then increased again at the “acceleration point”, which coincides with or slightly precedes RCP1 at the beginning of the next cell cycle (reviewed in [12]). At 17°C, protein synthesis markedly decreases during the constant length period, more closely mimicking the growth pattern of cells [17].

Although it is clear that growth rate is under cell cycle control in *S. pombe* the molecular mechanisms that modulate growth in response to cell cycle cues remain to be elucidated. Cyclin-dependent kinases (CDKs) appear to be required – directly or indirectly - for the slowing of growth rate during mitosis. Cells carrying temperature sensitive mutations in the sole fission yeast CDK, *cdc2+*, arrest in G2 and the drastic reduction in growth that occurs during mitosis, does not take place [10]. The regulation of RCP1 is likely related to the cell cycle events that occur at the end of mitosis. Septum formation, however does not appear to be one of these events, as *cdc11* mutants, which are incapable of forming a septum, still exhibit both RCP1 and RCP2 [10], at least during the first cell cycle after inhibition of *cdc11+* function.

Ploidy is a key determinant of growth rate. Cells with a higher DNA content grow faster than cells with a lower one (reviewed in [1]). It is tempting to speculate that RCP2 reflects, at least in part, the increase in ploidy that has occurred by G2. It is also worth noting that changes in growth rate during the cell cycle also implies that the growth pattern of *S. pombe* cells does not conform to either a simple exponential or single linear model [12,14**].

Actin polarization limits cell growth in budding yeast

Several studies of the growth of the budding yeast *Saccharomyces cerevisiae* indicate that growth is constant throughout the cell cycle. Protein synthesis does not appear to vary during the cell cycle [18]. Measurement of a protein synthesis reporter in single cells or measurement of growth by estimating cell volumes by microscopy of synchronized cultures supported this conclusion [19,20]. Other studies reported growth rate changes during the cell cycle [21,22]. By examining dry cell mass by interference microscopy, Murdock Mitchison reported a growth rate of 0.17pg/min during G1, followed by a double growth rate of 0.32pg/min after budding (Figure 2A, solid line). When measuring growth by volume using light microscopy for the same cells, Mitchison observed a slightly different pattern: cells grew at a given rate until before budding, then growth slowed down, then it increased at a faster rate (Figure 2A, dashed line). A recent examination of the growth rates of *S.*

cerevisiae cell division cycle (cdc) mutants that arrest at different points of the cell cycle cells using volume displacement (coulter counter) support this idea of varying growth rates during the cell cycle. Cells arrested at different cell cycle stages grow at different rates and the maximal cell size reached in the arrest varies greatly between cell cycle stages (Figure 2B). Cells arrested in G1 by the inactivation of the single CDK in budding yeast, Cdc28, grow the most [23**]. High growth rates were also observed in anaphase-arrested cells. Cells that arrest at the time of cell cycle entry or in metaphase exhibited lower growth rates. Microscopic measurements of wild type single cells also suggested a slowing of growth at the time of budding, indicating that at least some of the differences in growth rate observed in cell cycle arrests are not artifacts of the cell cycle arrests [23**].

One mechanism whereby cell cycle events affect growth is through changes in the actin cytoskeleton. In order to grow in size, cells must fuse new lipid vesicles with the cell membrane. The vesicles are transported to sites of fusion on actin cables by Myosin V [24–26]. The actin cytoskeleton undergoes dramatic changes during the cell cycle (Figure 2C). In G1 phase, actin cables are evenly distributed throughout the cytoplasm, resulting in uniform vesicle deposition, isotropic growth and spherical cell morphology (Figure 2Ci). As cells enter the cell cycle, the actin cytoskeleton becomes polarized through the action of the Cln cyclin G1 CDKs (Figure 2Cii) and vesicle deposition occurs apically at the site of bud emergence (Figure 2Ciii). After initial bud emergence, growth remains limited to the developing daughter cell, but becomes isotropic to create a spherical bud (Figure 2Civ) [24–26].

Studies of cdc mutants and of cells treated with the mating pheromone α-factor, which polarizes the actin cytoskeleton and causes mating projection formation, showed that polarization of the actin cytoskeleton decreases growth. Mutants that arrest with high G1-CDK activity (*cdc34* or *cdc53* mutants) or form mating projection showed decreased growth and protein synthesis rates compared to other cell cycle arrests. Preventing actin polarization after pheromone treatment suppressed the growth inhibitory effects of pheromone [23**]. Inactivation of actin organizers or inactivation of cyclin-CDK activity also improved the growth of cells that arrest with a hyper-polarized actin cytoskeleton such as *cdc34* mutants [23**].

The actin cytoskeleton not only affects growth but also appears to influence cellular density. Murdock Mitchison predicted that cell density peaks around the time of budding [21]. Several studies provided experimental proof for this prediction [21,27–29]. How do changes in the actin cytoskeleton affect cell growth and density and are these two events connected? A simple hypothesis is that at the time of budding, the cell surface increases at a lower rate but initially protein synthesis continues at the same rate. This results in a temporary (<30min) uncoupling of cell surface growth and protein synthesis and hence increased cell density. The basis for this observation could be the properties of apical growth: there is limited space at the bud tip and only few vesicles are incorporated into the membrane to contribute to cell surface growth (Figure 2C). Initially protein synthesis continues unabated causing a transient increase in cell density. Sometimes thereafter feedback mechanisms are activated that down-regulate protein synthesis in response to actin hyperpolarization.

How actin polarization leads to the down-regulation of protein synthesis is not understood, but the analysis of mutants defective in secretion could provide a framework for how to think about this signaling mechanism. In cells defective for secretion, unincorporated vesicles accumulate [30]. Secretion mutants also show decreased protein synthesis rates [31]. The cell wall integrity (Pkc1) pathway, which senses cell wall stress [32], down-regulates protein synthesis in these secretion mutants [33,34]. Polarized growth may create a similar situation as is observed in secretion mutants. The area of membrane where vesicles

can be deposited is limited (Figure 2Cii and iii), which may lead to the accumulation of unincorporated vesicles. This could cause activation of the Pkc1 pathway and hence a down-regulation of protein synthesis.

Other cell cycle events could also regulate growth in budding yeast. Cells arrested in metaphase, grow relatively little compared to G1 arrested cells, although the actin cytoskeleton is not highly polarized in this arrest. Regulators of anaphase entry, i.e. the ubiquitin ligase APC, could accelerate growth as cells exit from mitosis and resume rapid growth. Like in *S. pombe*, duplication of the DNA content could also accelerate growth. However, given the poorly defined nature of G2 in *S. cerevisiae*, detecting this growth rate change may be difficult.

Cell cycle regulated growth in mammalian cells

Growth properties during the cell cycle have also been examined in mammalian cells. These studies demonstrated that RNA and protein synthesis varies during the cell cycle, with a sharp decrease in both taking place during mitosis [35]. The transcriptional down-regulation is thought to be due to chromosome condensation [36], the decrease in translation is due to the switch from cap-dependent to cap independent translation [37]. This change is mediated by inhibiting components of cap dependent initiation of translation, eIF4E and eIF4B [37,38**]. Interestingly, if this translation switch is abolished, cells undergo an aberrant mitosis. Cytokinesis is impaired leading to the formation of bi-nucleate or incompletely separated cells, which is suppressed by reducing protein synthesis through treatment with the TOR inhibitor rapamycin [38**]. The regulation of the mitotic translation is often lost in tumor cells, indicating that the coordination of growth with cell cycle phase has important implications for disease development [38**].

Recent studies of single celled mouse lymphoblast revealed additional regulation of growth by the cell cycle. Attaching cells to a membrane and capturing the cells that bud of the captured ones can be used to synchronize the lymphoblasts. This “baby-machine” allows for the isolation of new-born G1 cells whose growth properties can be analyzed as they progress through the cell cycle in a synchronous manner [39**]. Although the growth characteristics of single lymphoblasts may be different from cells that exist in tissues, the studies revealed that the co-ordination of cell growth with division is remarkably similar in mammalian cells as in single-celled organisms. Growth is proportional to cell size and cells need to reach a critical size before they can divide. Most striking was the discovery that, as in budding yeast, cells increase their growth rates the fastest in G1 compared to other stages of the cell cycle [39**]. A decrease in growth rate at the end of the cell cycle was also observed (cells larger than 2000 fL), consistent with the observation that mammalian cells dramatically decrease protein synthesis during mitosis. The molecular mechanisms accelerating growth during G1 and whether CDKs are involved in this regulation remains to be determined.

Conclusions and outlook

Maintaining the proper growth rate at the proper stage of the cell cycle (“balanced growth” [12]) is a fundamental property of cells that needs to be regulated in order to maintain a constant cell size. Observations from various model systems indicate that progression through the cell cycle affects growth rate. Furthermore it appears that growth is maximal during the major GAP phase of an organism - G1 in budding yeast and mammalian cells and G2 in *S. pombe*. Why would cells separate the maximal growth phase from the division phase? Cells may have evolved this mechanism in order to build up the necessary cellular resources prior to the increased energy demands of DNA replication and chromosome segregation. This notion of resource accumulation is consistent with the concept of cell

cycle commitment, called Start in yeast and the Restriction Point in mammalian cells [40,41]. Once cell cycle entry has occurred, CDK mediated events may help ensure that less energy is directed to protein synthesis and hence available for duplication and segregation of the genetic material. Furthermore, in terminally differentiated tissues a high G1 growth potential may aid in the regeneration of tissue in the absence of cell division [42]. The molecular mechanisms enhancing growth during G1 or that down-regulate it in the other cell cycle stages remain to be elucidated, but it would not be surprising if CDKs are central to this regulation. CDKs could regulate growth indirectly – by modulating actin cytoskeleton polarity – and/or affect macromolecule synthesis directly by modulating the activity of the biosynthetic machinery. Indeed, studies in several organisms indicate that, as in *S. cerevisiae* and *S. pombe*, cells lacking CDK function grow large [43,44], however a careful comparison of the growth rates of CDK deficient cell and other types of arrests has not yet been performed in these organisms.

The next five years will likely see great advances in understanding how growth and division interact and regulate each other. New powerful methods for measuring growth and mass at the single cell level such as the SMR (Suspended Microchannel Resonator) technique, will contribute to our understanding of the regulation of cell growth. SMR measures the buoyant mass of a particle (cells) and has already been used successfully to measure the mass and density of different cell types and growth rates of single eukaryotic and prokaryotic cells for short (<5min) or longer (>20min) times [27,45,46**]. The SMR will be the ideal tool to carefully dissect when growth rate changes occur during the cell cycle and to begin to describe the framework within which this regulation operates.

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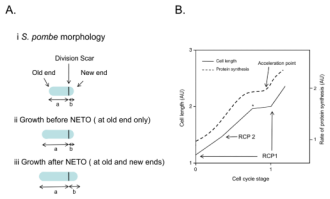

Figure 1. Growth during the cell cycle in *S. pombe*

A)

(i) The two cell poles of *S. pombe* have different characteristics. Morphologically they can be distinguished from each other by their distance from the division scar.

(ii) The growth characteristics of the two poles also differ. The old pole is further away from the division scar, which is shown as distance “a”. The new pole is closer to the division scar. The distance is “b”. Prior to G2 cells, only grow from the old pole and “a” increases.

(iii) In G2, after cells reach a critical size, NETO (new-end-take-off) occurs and cells begin to grow at both cell poles (“a” and “b” increase).

B) Growth rate changes during cell cycle in *S. pombe*. See text for details. The graph represents the growth pattern of a single cell. Cell length and rate of protein synthesis are shown as arbitrary units. Cell cycle length is shown on the x-axis with 0 representing the birth of the cell and “1” describing the end of the cell cycle. Adapted from [12].

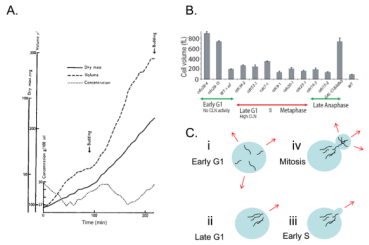

Figure 2. Growth during the cell cycle in *S. cerevisiae*

A) Cell volume (dashed lines) and cell mass (solid line) of single cells were measured by light and interference microscopy, respectively. Cell density was calculated based on the measured volume and mass (Reprinted with permission from [21]).

B) Growth potential varies during the yeast cell cycle. Various cell cycle mutants were arrested at the indicated cell cycle stage and their volume was measured using a coulter counter 10 hours after shift to the restrictive temperature (Reprinted with permission from [23]).

C) Changes in actin organization during the cell cycle of S. cerevisiae. Black wavy lines represent actin cables and red arrows indicate the locations of cell growth (vesicle deposition). Stages of the cell cycle are indicated under the Roman numeral. See text for detailed explanation.