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Connecting chromosome replication with cell growth in bacteria

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Abstract

For bacteria to proliferate they must duplicate their genetic material so that it can be passed to their progeny. This requires that DNA replication is coordinated with cell growth and division. In the natural environment bacterial growth is dynamic and strongly influenced by changes in nutrient availability. Recent studies have found that bacteria utilize a range of regulatory systems, many of them species-specific, to coordinate DNA replication with cell growth. This variability likely reflects the diverse lifestyles of different bacterial types.

Introduction to bacterial cell growth and chromosome replication

During batch culture in the laboratory bacterial growth displays distinct phases: lag phase, the adaptive delay before the start of exponential growth; exponential phase, where all major biosynthetic activities proceed at a constant rate; and stationary phase, when nutrients become limited and growth slows (see Graphical Abstract). DNA replication must be carefully coordinated with cell growth and division to ensure production of viable progeny.

In the archetypical bacterial genome bidirectional DNA replication is initiated from a single defined origin termed *oriC* [1]. Straight after the start of DNA replication the newly duplicated origin regions are rapidly partitioned away from one another; subsequently the remainder of the genome is replicated and progressively organized to promote chromosome segregation [2]. Cell growth increases cell size and creates space between the two daughter chromosomes where the cell division machinery can be established to drive cytokinesis [3,4]. This mini-review will highlight new findings regarding the coordination of bacterial DNA replication with cell growth, focusing on regulation occurring within the different growth phases.

DNA synthesis in Cyanobacteria during the lag phase

Cyanobacteria have the ability to convert solar energy into biomass, thus they have attracted strong attention because of their potential application in biotechnology. Importantly however, synthetic manipulation of cyanobacterial photosynthesis requires a clear understanding of

the organisms' cell cycle and growth properties, which in many cases appear to be distinct from well-characterized model systems such as *Escherichia coli*, *Bacillus subtilis*, and *Caulobacter crescentus*. For example, many cyanobacteria are polyploid with some species containing more than 100 genome copies per cell, DNA synthesis is light-dependent, and DNA replication is initiated asynchronously [5-7]. These intriguing findings suggest the presence of unique regulatory mechanisms to control chromosome replication. Recent studies using the freshwater species *Synechococcus elongatus* PCC 7942 (*S. elongatus*) have started to elucidate connections between DNA replication and cell growth in cyanobacteria.

Measurements of *S. elongatus* DNA synthesis and chromosome content following a transition between light and dark indicates that both DNA replication initiation and elongation require light irradiation [8]. These connections were investigated using two photosynthesis inhibitors: 3-(3,4-dichlorophenyl)-1,1-dimethylurea (DCMU) which inhibits electron transport between the photosystem II complex and the plastoquinone pool, and 2,5-dibromo-3-methyl-6-isopropyl-p-benzoquinone (DBMIB) which inhibits electron transport between plastoquinone and the cytochrome *b₆f* complex [9]. When the inhibitors were added to cultures prior to exposure to light, both DCMU and DBMIB strongly inhibited DNA synthesis. In contrast, when the inhibitors were added several hours after transfer to light, only DBMIB repressed DNA synthesis. This indicates that DCMU specifically blocks DNA replication initiation while DBMIB inhibits DNA replication elongation, and it suggests that DNA replication initiation depends on proper photosynthetic electron transport whereas DNA replication elongation requires integrity of the electron transport pathway downstream of the cytochrome *b₆f* complex. Future work will be aimed at identifying the specific regulatory effectors and determining how these signals are transduced to DNA replication proteins of the initiation and elongation complexes.

Classical studies indicated that bacterial growth upshifts result in increased rates of both DNA synthesis and cell division to achieve a synchronous cell cycle [10,11]. Unexpectedly, it has been found that *S. elongatus* undergoes rapid DNA synthesis during

the lag phase before the onset of cytokinesis, such that DNA replication and cell division in *S. elongatus* are not coordinated in parallel as they are in *E. coli* and *B. subtilis* (Figure 1)[12]. The initiation of DNA replication before cell growth and division results in a substantial increase in the chromosome copy number per cell. During the exponential growth phase the rate of DNA replication slows as cell divisions begin, decreasing the number of chromosomes per cell. Later as the culture begins to enter stationary phase, which corresponds to the beginning of light (i.e. - cell shadowing) and nutrient limitation, DNA replication is markedly reduced while cell division continues, producing newborn cells containing fully replicated chromosomes. It will be highly informative to produce *S. elongatus* strains that continue DNA synthesis during the exponential phase and then observe cell growth and chromosome replication in order to understand why this cyanobacterial species has disconnected these cell cycle activities.

Growth rate regulation of DNA synthesis during the exponential phase

In many bacteria, particularly those utilized by biotechnology industries (e.g. - *Bacillus*, *Corynebacterium*, *Escherichia*, *Lactococcus*), cell growth rate during the exponential phase is dictated by the abundance and quality of nutrients in the environment, and accordingly can vary from less than 20 minutes up to several hours. To ensure inheritance of genetic material over this wide range of potential doubling times, the rates of DNA synthesis and cell division in these organisms are tightly linked with the rate of cell growth [13]. Importantly, these key cell cycle activities of chromosome replication, cytokinesis, and growth are not organized into dependent sequential steps as they are in eukaryotes. Rather, these operations run in parallel to one another and it is this flexible circuitry that provides the means to proliferate at such great speed because it allows essential cell cycle events to overlap in time.

It has been shown that both *E. coli* and *B. subtilis* coordinate their DNA synthesis rate with their steady-state growth rate by regulating the frequency of DNA replication initiation [13-16]. Although this phenomenon was originally documented over forty years ago,

the molecular mechanisms that connect bacterial metabolism with DNA replication initiation remain a mystery.

DnaA is the master bacterial DNA replication initiator protein and is a candidate factor linking cell growth with DNA synthesis. DnaA directly stimulates DNA replication initiation from *oriC* once per cell cycle [17]. It has been observed that the concentration of DnaA is positively correlated with cell growth rate and size, suggesting that the amount of DnaA could dictate the frequency of DNA replication initiation [18-20]. Recently, this long-standing model for growth rate control of DNA replication initiation was rigorously evaluated in *E. coli* and *B. subtilis* [21,22]. In both organisms the amount of DnaA within cells was artificially increased and in neither situation was the frequency of DNA replication initiation significantly affected. These results indicate that the accumulation of DnaA alone does not control the time of initiation. However, in *B. subtilis* it was shown that nutrient-mediated growth rate regulation of DNA replication initiation requires DnaA and *oriC*, indicating that the target of this control system is DnaA activity localized at the endogenous replication origin (Figure 2)[22]. Thus, the key questions are (i) how does a bacterial cell detect its growth rate and (ii) how does it transmit this information to the DNA replication initiation complex.

Historically it was suggested that there is a constant cell mass at the time of bacterial DNA replication initiation and it was proposed that a positive regulator would accumulate in a growth-dependent manner to trigger a new round of chromosome replication when cells attained a critical size [23]. This model was attractive because it provided a mechanism which functioned independently of the specific nutrient sources in the environment that dictate growth rate. However, subsequent studies of single bacterial cells within steady-state populations of both wild-type and mutant strains showed that the relationship between cell size and DNA replication initiation is, in fact, variable, indicating that the control for timing of DNA replication initiation is not governed by a direct connection with cell mass accumulation [20,24].

To investigate the connections between cell growth and chromosome replication in *B. subtilis*, molecular and chemical genetic approaches were used to limit essential cellular activities (e.g. carbon metabolism, respiration, fatty acid synthesis, protein synthesis, phospholipid synthesis and cell wall synthesis), followed by analysis of both growth rate and DNA replication initiation frequency [22]. In all cases examined the decrease in growth rate was matched by a decrease in DNA replication initiation. Surprisingly however, for several perturbations it was found that inhibition of DNA replication occurred independently of DnaA (i.e. – in a $\Delta dnaA$ mutant strain, which initiates chromosome replication using an integrated plasmid origin, regulation of DNA replication was retained when cell growth slowed). This unanticipated result suggests that multiple regulatory pathways are involved in coordinating DNA replication initiation with the rate of bacterial cell growth, with different regulators responding to distinct physiological and chemical changes. Notably, this model deviates from the long-standing concept of a single universal cellular property utilized to link bacterial DNA replication with cell growth. The aim now is to determine the molecular mechanisms underlying each regulatory system.

Regulation of DNA synthesis during starvation and stationary phase

When bacteria become starved for essential cellular building blocks such as amino acids and fatty acids they induce a stress protocol termed the stringent response [25]. Under these conditions the small molecule alarmone (p)ppGpp is synthesized and acts by altering cellular physiology from catabolism to anabolism. One of the main targets for (p)ppGpp in many organisms is RNA polymerase, where ligand binding leads to differential transcription of hundreds of genes [25]. In addition (p)ppGpp inhibits DNA synthesis, and interestingly it appears to affect distinct steps of the replication cycle in different organisms.

In *B. subtilis* (p)ppGpp targets DNA replication elongation by directly inhibiting primase, which is responsible for synthesizing short oligoribonucleotides required for replication of the lagging-strand [26-28]. Crucially, although (p)ppGpp can arrest DNA replication fork progression it does not lead to fork collapse, thereby allowing DNA synthesis

to rapidly resume when starvation is alleviated [26]. It is interesting to note that (p)ppGpp acts through separate mechanisms to regulate different RNA polymerases; it allosterically regulates transcription initiation of RNA polymerase in *E. coli*, whereas it appears to competitively bind within the active site of primase in *B. subtilis* [29,30].

In *E.coli* DNA synthesis is also controlled by (p)ppGpp [31], but here the regulatory mechanism is less clear. On the one hand (p)ppGpp has been shown to inhibit *E. coli* primase *in vitro* and to slow the replication elongation rate *in vivo* [32,33]. However, stimulation of (p)ppGpp synthesis *in vivo* does not lead to rapid arrest of DNA synthesis as would be expected if primase activity was significantly inhibited [34]. Furthermore, it has been shown that induction of the stringent response blocks DNA replication initiation [27]. Thus, if (p)ppGpp is capable of strongly inhibiting primase activity in *E. coli* it may target an intermediate complex specific to the initiation stage of DNA replication. An alternative possibility is that (p)ppGpp inhibits DNA replication initiation indirectly [35,36]. There is precedent for this idea, as in *C. crescentus* where (p)ppGpp regulates the initiation of DNA replication when lipid biosynthesis is limited [37]. Under this stress condition (p)ppGpp is required to activate transcription of the cell cycle regulator CtrA, which in turn represses DNA replication initiation by binding *oriC*.

Although (p)ppGpp plays a role coordinating DNA synthesis with cell growth in *C. crescentus* under some nutrient stress conditions, following both glucose exhaustion and entry into stationary phase *C. crescentus* regulates DNA replication initiation via another mechanism [38]. When glucose is plentiful the synthesis rate of the master initiator DnaA outpaces its rate of Lon-dependent proteolysis, thereby producing enough DnaA to promote DNA replication. However, when glucose becomes limiting DnaA translation is downregulated and proteolysis of DnaA overtakes synthesis, leading to the elimination of DnaA and the arrest of DNA replication initiation (Figure 3). The mechanism of translational regulation is unknown, although it has been shown to require the 5' untranslated leader region of the *dnaA* transcript. This regulatory system involving constitutive degradation of DnaA provides cells a means of rapidly limiting the concentration of this key replication

190 initiator protein, which is likely critical for an organism such as *C. crescentus* living in
191 freshwater environments where nutrients can rapidly become scarce.

193 **Conclusions**

194 Coordination of DNA replication with cell growth and division is universally essential for
195 proliferation. This mini-review highlights the plethora of distinct regulatory strategies bacteria
196 have developed to achieve this conserved goal. Because this coordination is critical for
197 maximal cellular fitness, it could be advantageous to manipulate this connection, either
198 positively with regards to engineering bacteria for biotechnology or negatively to fight
199 bacterial infections. Crucially, as emphasized through the examples provided above, this will
200 require that the specific control systems within a given bacterial species are identified and
201 characterized.

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Figure Legends

Figure 1. DNA Replication and Metabolism during the Lag Phase in Cyanobacteria.

Based on work in model organisms such as *B. subtilis* and *E. coli* it was thought that bacteria proceed through an adaptive lag phase that prepared them for exponential growth where DNA replication and cell division are tightly linked. A different connection between DNA replication and cell division has been observed in the cyanobacteria *S. elongatus* 7942 where DNA replication is greatest during the lag phase, followed by cell division during exponential growth when genome number per cell decreases. Coloring of arrows indicates highest rates for each cell cycle activity. Cells are outlined in red (cell division sites are indicated by dashed lines) and chromosomes are shown as black circles.

Figure 2. Nutrient-mediated growth rate regulation of DNA replication initiation in *B.*

subtilis requires *oriC*. (A) Wild-type chromosome. (B) $\Delta oriC$ mutant strain initiates DNA replication from an integrated plasmid origin *oriN* which utilizes its cognate initiator protein RepN. (C) Strains were grown in various media (slowest to fastest: succinate, glycerol, glycerol + amino acids, LB, PAB) to generate a range of steady-state growth rates (doublings per hour). Genomic DNA was harvested from mid-exponential phase cells and marker frequency analysis was determined using qPCR. The *ori:ter* ratios, which here reflect the frequency of DNA replication initiation, are plotted versus growth rate. Adapted from [22].

Figure 3. Nutritional control of DNA replication in *C. crescentus* through the

proteolysis and regulated translation of DnaA. In *C. crescentus* DnaA is targeted for degradation by the protease Lon [39]. When glucose is abundant DnaA synthesis outpaces the rate of proteolysis by Lon and permits DNA replication initiation. When glucose become limiting DnaA translation is inhibited and Lon-dependent proteolysis of DnaA overtakes synthesis, leading to the elimination of DnaA and the arrest of DNA replication.

Connecting chromosome replication with cell growth in bacteria

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Highlights

- *S. elongatus* synthesizes DNA during lag phase before growth and division
- Multiple regulatory systems coordinate DNA replication with cell growth in *B. subtilis*
- The alarmone (p)ppGpp can target DNA replication initiation and elongation
- Nutritional control of DnaA accumulation by regulated translation in *C. crescentus*

Graphical Abstract

Growth Curve

Figure 1

Figure 2

A

B

C

Figure 3

Glucose abundant

Glucose limiting