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To divide or not to divide: control of the bacterial cell cycle by environmental cues

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Whether to divide or not is an important decision that nearly all cells have to make, especially bacteria that are exposed to drastic environmental changes. Under adverse conditions proliferation and growth could compromise cellular integrity and hence must be downregulated. To this end, bacteria have evolved sophisticated mechanisms to transduce environmental information into the cell cycle engine. Recent studies in *Escherichia coli*, *Bacillus subtilis* and *Caulobacter crescentus* indicate that these mechanisms often involve small molecule-based signaling, regulated proteolysis, as well as protein–protein interactions. Most of them delay replication initiation or septum formation by targeting the key regulators DnaA or FtsZ, respectively. Remarkably, while the targets are conserved, the precise mechanisms show a considerable degree of diversity among different species.

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Introduction

All bacteria must rapidly adapt to environmental changes. Drastic stress conditions, including rapid temperature shifts, nutrient depletion, changes in pH or osmolarity, or the presence of toxic agents can lead to cellular damage that can have lethal consequences if not repaired. Over the past decades numerous mechanisms have been uncovered in diverse bacteria that trigger adaptive responses that alleviate cellular stress. Many of them involve complex signal transduction and gene regulation networks that gear gene expression programs toward damage repair and prevention [1,2]. Importantly, cells also have to reprogram their reproductive activities in response to environmental cues. Under favorable conditions they strive to proliferate and grow to produce progeny. However, during periods of nutrient limitation or environmental stress, proliferation and growth could compromise cellular or genome integrity and hence should be downregulated. Cells have evolved a variety of mechanisms that allow them to modulate their division cycle according to the needs of the environment. This review discusses recent progress in understanding these mechanisms in the model bacteria *Escherichia coli*, *Bacillus subtilis* and *Caulobacter crescentus*.

The bacterial cell cycle

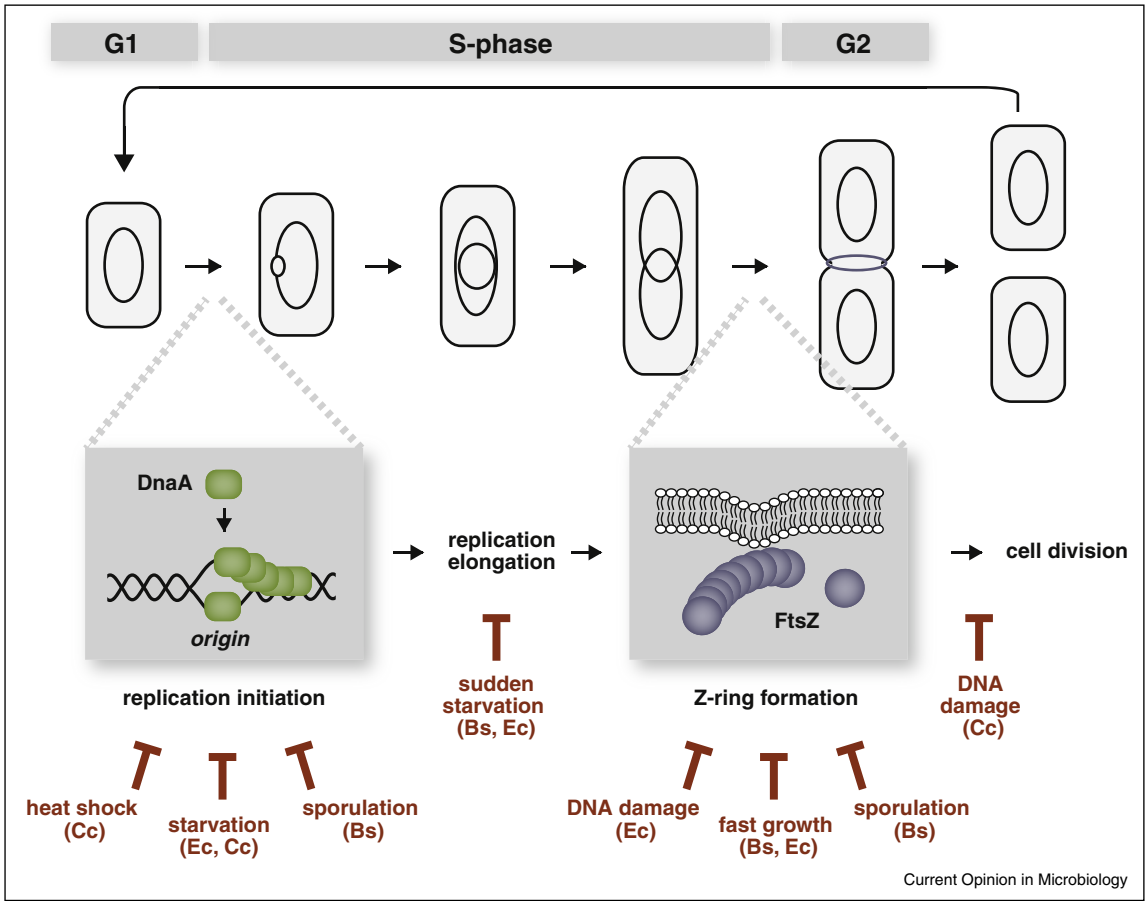
Successful progression through the cell cycle relies on the completion of a series of events that ultimately lead to the generation of daughter cells, each endowed with a complete copy of the genome (Figure 1). It starts with the initiation of DNA replication, which depends in nearly all bacteria on the conserved replication initiator DnaA, an AAA+ ATPase that binds the origin of replication, unwinds the DNA and recruits the replication machinery [3]. Following initiation, replication proceeds bidirectionally toward the terminus producing two complete copies of the genomic material. The termination of DNA replication is accompanied by the segregation of chromosomes and the establishment of a site for cell division. The GTP-binding tubulin homolog FtsZ polymerizes at this site into a ring-like structure and drives assembly of the divisome, a multicomponent complex that mediates constriction of the division ring and subsequent cytokinesis [4]. In many bacteria, including *C. crescentus* [5], DNA replication initiates exactly once per cell cycle, whereas fast-growing bacteria like *E. coli* and *B. subtilis* can, in nutrient-rich conditions, initiate new rounds of DNA replication before previous replication rounds have completed, a phenomenon called multifork replication [6].

Cell cycle control in response to nutrient availability

Free-living bacteria often undergo periods of nutrient deprivation and starvation. Under such conditions cells stop generating new mass and consequently must also arrest the cell cycle to maintain cellular integrity. It has long been suggested that DNA replication and entry into the cell cycle are triggered by a given cell-mass/origin ratio [7]. However, more recent work indicates that the situation is more complex, involving multiple layers of regulation and a considerable degree of diversity between different bacteria [8,9].

A common mechanism of control involves guanosine pentaphosphate or tetraphosphate ((p)ppGpp) which is produced in response to amino acid or carbon starvation [10] (Figure 2a). (p)ppGpp has a well-documented effect

Figure 1



Schematics of the bacterial cell cycle and its modulation by regulatory inputs. The bacterial cell cycle is illustrated as a series of events leading to two daughter cells. Chromosomes are indicated inside the cells. The events of replication initiation by DnaA and formation of the FtsZ-ring are highlighted in boxes. Regulatory inputs that delay or block cell cycle events in *E. coli* (Ec), *C. crescentus* (Cc) or *B. subtilis* (Bs) are shown in red. In fast growth conditions *E. coli* and *B. subtilis* delay division to ensure coordination of cell size with growth rate.

on global protein synthesis and growth rate, but also affects cell cycle processes. In both *E. coli* and *C. crescentus* it can prevent replication initiation following nutrient depletion, resulting in a G1-arrest [11–14]. Early work in *E. coli* showed that the molecule inhibits the transcription of *dnaA* and a gene adjacent to the origin whose expression promotes the process of initiation [15,16]. However, it is unclear whether these effects are direct or indirect and to what degree they contribute to the starvation-induced replication arrest. In *C. crescentus*, ppGpp seems to influence DNA replication by altering the abundance of replication factors. In contrast to *E. coli*, ppGpp was suggested to affect protein stability rather than synthesis [11,14]. Upon starvation of swarmer cells, DnaA is rapidly eliminated, while CtrA, a negative regulator of replication [17], is stabilized [11,14,18]. Although ppGpp and inorganic polyphosphate (polyP), another small signaling molecule that is produced in response to nutrient depletion [19], have been reported to be required for this reciprocal regulation of protein levels [11,14], the exact mechanisms remain to be elucidated. In contrast to *E. coli* and *C. crescentus*, in *B. subtilis* (p)ppGpp interferes primarily with replication elongation, rather than initiation. Accumulation of (p)ppGpp leads to an immediate arrest of replication forks irrespective of their location on the chromosome, which depends on a direct interaction of (p)ppGpp with DNA primase [20••]. The replication fork arrest was suggested to help cells maintain genomic integrity during sudden and transient periods of nutrient limitation. Indeed (p)ppGpp is also thought to influence replication fork progression in *E. coli*, although to a lesser extent [21].

Uridine-5′-diphosphoglucose (UDP-glucose) is yet another small molecule that transduces information about the nutritional status into the cell cycle (Figure 2b). In contrast to (p)ppGpp, UDP-glucose is produced in nutrient-rich conditions and targets cell division. In *E. coli* and *B. subtilis* two distinct enzymes, the glucosyltransferases OpgH and UgtP, respectively, bind UDP-glucose and then