Spatial complexity of mechanisms controlling a bacterial cell cycle
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Cell cycle progression in Caulobacter is governed by a multilayered regulatory network linking chromosome replication with polar morphogenesis and cell division. Temporal and spatial regulation have emerged as the central themes, with the abundance, activity and subcellular location of key structural and regulatory proteins changing over the course of the cell cycle. An additional layer of complexity was recently uncovered, showing that each segment of the chromosome is located at a specific cellular position both during and after the completion of DNA replication, raising the possibility that this positioning contributes to temporal and spatial control of gene expression.

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Current Opinion in Microbiology 2004, 7:572–578
This review comes from a themed issue on Growth and development
Edited by Mike Tyers and Mark Buttner
Available online 27th October 2004
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DOI 10.1016/j.mib.2004.10.005

Abstract

Introduction

The crescent-shaped α-proteobacterium Caulobacter crescentus has proven to be a valuable model system for studying the bacterial cell cycle. The technical advantage provided by Caulobacter’s distinctive physiology is that synchronized cultures can be obtained by means of a simple density gradient centrifugation that yields a homogeneous population of swarmer cells [1–3]. Swarmer cells have a single flagellum and several pili, with both structures positioned at the same cell pole (Figure 1). The swarmer cell is the bacterial functional equivalent of the eukaryotic G1 cell in that chromosome replication is silenced. After a defined period, the motile swarmer cell differentiates into a sessile stalked cell. During this transition, the late swarmer pole is remodeled: the flagellum is shed, pili are lost, the receptors for the chemotaxis sensory apparatus are degraded, and growth of the envelope is redirected to give rise to a cylindrical polar structure (the stalk) that is capped with an adhesive polysaccharide (the holdfast). Coincident with these morphological changes, the stalked cell acquires the ability to initiate chromosome replication. As the stalked cell grows into a pre-divisional cell, a new polar flagellum, a chemosensory apparatus and the pili secretion machinery are assembled at the pole opposite the stalk. Shortly after the completion of DNA replication, but before cell separation, the cytoplasm of the pre-divisional cell partitions, with each half inheriting a sister chromosome [4∗]. Because the cytoplasm is now discontinuous, the two compartments of the pre-divisional cell diverge and accumulate different cell fate determinants [4∗]. Finally, asymmetric cell division yields the distinct swarmer cell and stalked cell progeny.

Here, we review mechanisms that control the cell cycle and are spatially confined in a bacterial cell.

Chromosome structure and replication

The circular Caulobacter chromosome — with a contour length around 1000-fold longer than that of the long axis of the cell — exists in a highly compact and reproducibly organized state in the non-replicative swarmer cell, with the origin of replication (ori) positioned near the flagellated pole (Figure 2a,c) [5,6∗∗]. The terminus of replication (ter) is situated at maximal distance from ori, near the opposite pole. Intervening chromosomal loci are located at positions inside the cell that correlate linearly with their relative genetic distance from ori on the chromosome, suggesting that compaction of the chromosome extends uniformly across the long axis of the cell (Figure 2b,c) [6∗∗].

In the swarmer cell, the components of the DNA replication machinery (replisome), such as the HolB and HolC clamp loader proteins, the DnaB helicase and the ParC subunit of the decatenating enzyme topoisomerase IV are dispersed in the cytoplasm [7,8]. The formation of the replisome, visualized as a tight focus by epifluorescence microscopy, occurs at or near ori in the stalked cell, and marks the onset of DNA replication (Figure 2a). As the cell cycle progresses, the replisome sequentially copies each locus and disassembles upon termination of chromosome replication [8].

The newly synthesized segments of sister DNA that continuously emerge from the replisome are transported...
The Caulobacter cell cycle and the oscillatory pair of master regulators, CtrA and GcrA. The motile swarmer cell harbors several pili (thin lines) and a rotating flagellum (thick wavy line). (a) After a defined period, the swarmer cell differentiates into a sessile stalked cell. (b) At this time, the flagellum (thick line) is shed, the pili are lost and stalk and holdfast biogenesis is initiated. (c) The stalked cell matures into a pre-divisional cell that assembles a flagellum opposite the stalk. (d) Shortly before cell division the flagellum begins to rotate. (e) The pre-divisional cell divides asymmetrically into a swarmer cell and a stalked cell. The presence of active CtrA (CtrA–P) and GcrA and the biological functions they control are shown in green and pink, respectively. CtrA–P is present in the swarmer cell and the incipient swarmer cell compartment of the pre-divisional cell. During the swarmer-to-stalked cell transition and in the stalked cell half of the compartmentalized pre-divisional cell, CtrA–P first localizes to the stalked pole (blue dot) and is subsequently degraded by the ClpXP protease. GcrA levels peak in the stalked cell, drop transiently in the pre-divisional cell, and rise again in the daughter stalked cell.

Figure 1

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The Caulobacter cell cycle and the oscillatory pair of master regulators, CtrA and GcrA. The motile swarmer cell harbors several pili (thin lines) and a rotating flagellum (thick wavy line). (a) After a defined period, the swarmer cell differentiates into a sessile stalked cell. (b) At this time, the flagellum (thick line) is shed, the pili are lost and stalk and holdfast biogenesis is initiated. (c) The stalked cell matures into a pre-divisional cell that assembles a flagellum opposite the stalk. (d) Shortly before cell division the flagellum begins to rotate. (e) The pre-divisional cell divides asymmetrically into a swarmer cell and a stalked cell. The presence of active CtrA (CtrA–P) and GcrA and the biological functions they control are shown in green and pink, respectively. CtrA–P is present in the swarmer cell and the incipient swarmer cell compartment of the pre-divisional cell. During the swarmer-to-stalked cell transition and in the stalked cell half of the compartmentalized pre-divisional cell, CtrA–P first localizes to the stalked pole (blue dot) and is subsequently degraded by the ClpXP protease. GcrA levels peak in the stalked cell, drop transiently in the pre-divisional cell, and rise again in the daughter stalked cell.

Regulation of DNA replication initiation

Many gene products control the timing of replication initiation at the swarmer-to-stalked cell transition, including the oscillatory pair of global regulators, CtrA and GcrA, the SsrA tmRNA and the DnaA initiator protein.

The CtrA response regulator exerts transcriptional control over a large fraction of cell-cycle-regulated genes, including those affecting chromosome replication and polar morphogenesis [15**]. Active (phosphorylated) CtrA (CtrA–P) is present in the swarmer cell, where it silences ori and regulates the expression of genes, such as the ftsZ cell division gene and the pilA gene, which encodes the structural subunit of the pilus filament [16–21]. Repression of ori must be relieved by eliminating CtrA–P activity, either through proteolysis or by active (or
to the flagellated and opposite cell pole, respectively. The axis of the cell, with loci in the vicinity of chromosome is compacted in a uniform fashion across the long (b) is determined by their physical location on the chromosome. The intracellular position of the loci shown in position of 112 loci on the chromosome and their subcellular location within the swarmer cell. The intracellular position of the loci shown in (b) are shown in orange and yellow, respectively. The color gradient from orange to yellow indicates the origin of replication (ori) and ter subunit of topoisomerase IV are dispersed in the cytoplasm (green). Coincident with the initiation of chromosome replication, HolB, HolC, DnaB and ParC localize at or near ori. Once replicated, one copy of ori is rapidly moved to the incipient swarmer cell pole. As replication proceeds, the replisome complex gradually moves toward the plane of division. (b) Regions in proximity to ori and ter are shown in orange and yellow, respectively. The color gradient from orange to yellow indicates the proximity of any given chromosomal locus to ori and, conversely, its distance from ter. The black lines mark 112 distinct loci on the 4.01-Mbp circular Caulobacter chromosome. (c) Co-linearity of the position of 112 loci on the chromosome and their subcellular location within the swarmer cell. The intracellular position of the loci shown in (b) is determined by their physical location on the chromosome. The chromosome is compacted in a uniform fashion across the long axis of the cell, with loci in the vicinity of ori and ter being proximal to the flagellated and opposite cell pole, respectively.

Dynamic movement and co-linear organization of chromosomal loci within Caulobacter cells. (a) In the non-replicative swarmer cell, the chromosomal origin of replication (ori, orange dot) is located at the flagellated pole. The components of the DNA replication machinery (HolB, HolC and DnaB) and the ParC subunit of topoisomerase IV are dispersed in the cytoplasm (green). Coincident with the initiation of chromosome replication, HolB, HolC, DnaB and ParC localize at or near ori. Once replicated, one copy of ori is rapidly moved to the incipient swarmer cell pole. As replication proceeds, the replisome complex gradually moves toward the plane of division. (b) Regions in proximity to ori and ter are shown in orange and yellow, respectively. The color gradient from orange to yellow indicates the proximity of any given chromosomal locus to ori and, conversely, its distance from ter. The black lines mark 112 distinct loci on the 4.01-Mbp circular Caulobacter chromosome. (c) Co-linearity of the position of 112 loci on the chromosome and their subcellular location within the swarmer cell. The intracellular position of the loci shown in (b) is determined by their physical location on the chromosome. The chromosome is compacted in a uniform fashion across the long axis of the cell, with loci in the vicinity of ori and ter being proximal to the flagellated and opposite cell pole, respectively.

spontaneous) dephosphorylation for cells to exit the G1 phase [15**,17,18,22,23*,24].

Recently, a complementary master regulator, GcrA, was identified that oscillates in time and space with CtrA (Figure 1) [15**]. Coincident with the proteolysis of CtrA–P, GcrA is synthesized in the stalked cell, where it regulates the expression of DNA replication factors such as DnaA, DnaB and DnaQ, along with the expression of proteins required for polar morphogenesis, including the PleC histidine kinase and the PodJ polar organelle determinant [15**]. CtrA and GcrA form an oscillatory genetic circuit controlling their own expression, with CtrA exerting negative control over GcrA expression and GcrA, in turn, activating the expression of CtrA. This regulatory loop results in a cyclical wave of CtrA and GcrA abundance during the cell cycle which, concomitantly, exerts precise spatial and temporal control overexpression of their target genes [15**].

SsrA abundance is regulated at the level of transcription and stability, peaking coincident with the onset of DNA replication [25*]. In cells lacking SsrA, entry into S phase is delayed while other stages of the cell cycle proceed normally [23*]. SsrA labels selected nascent polypeptides — primarily those translated from incomplete mRNAs — with a tag that targets them for degradation [26]. As a cellular quality control mechanism, lack of SsrA could prolong the swarmer-to-stalked cell transition indirectly, as a result of a physiological stress imposed by the elevated levels of truncated polypeptides that accumulate in the ssrA mutant. A regulatory role is also conceivable, however, with SsrA acting, directly or indirectly, on the abundance or activity of DNA initiation factors such as DnaA. The Caulobacter DnaA homolog is required for the initiation of DNA replication [24]. Thus, the ssrA mutant phenotype could be a consequence of the inefficient removal of CtrA activity or reduced DnaA activity. However, the kinetics of CtrA disappearance in wild-type and ssrA– cells are similar, implicating other factor(s), such as DnaA, as presumptive targets of SsrA in the control of replication initiation [23*].

Temporal and spatial control of CtrA proteolysis by a two-component signal transduction pathway

Cells harboring a mutation (divKcs) in the gene encoding the essential DivK single domain response regulator [27] arrest in the G1 phase of the cell cycle at the restrictive temperature [28*]. In these cells, CtrA is phosphorylated and stable [28*]. Thus, a DivK-controlled signaling pathway, activated by an unknown internal cue, is required for the proteolysis of active CtrA, a process known to require the ClpXP protease [29]. A temperature-sensitive suppressor mutation (soxA) in ctra was isolated that restores viability to divKcs cells at the restrictive temperature [30]. It is conceivable that ectopic activation of CtrA, rather than impaired CtrA activity, underlies the lethality of divKcs.

Proteolysis of CtrA also requires two cis determinants: a bipartite degradation signal (BDS) comprised of an amino-terminal component in the receiver domain and a stretch of 15 amino acids at the carboxyl terminus [31]. Unexpectedly, CtrA or the BDS fused to the carboxyl terminus of the yellow fluorescent protein were found to transiently localize to the nascent stalked pole during the swarmer-to-stalked cell transition and later in the cell cycle once the pre-divisional cell has compartmentalized
In both instances, condensation at the stalked pole preceded the disappearance of the proteins, suggesting a link between polar localization and proteolysis (Figure 1). Further support for this connection stems from the observation that divKcs mutant cells, which are unable to degrade CtrA, are also severely impaired in localizing the fluorescent reporter to the stalked cell pole [32*]. Moreover, a non-proteolyzable version of the BDS reporter was unable to coalesce at the stalked pole in wild-type cells [32*]. In vitro, ClpXP cannot degrade CtrA even if phosphorylated DivK (DivK–P) is present ([28*] and references therein), predicting an as-yet unidentified stimulatory factor that facilitates CtrA proteolysis by the ClpXP proteosome.

These observations support a model in which degradation of CtrA by ClpXP is spatially and temporally controlled by the DivK signaling pathway and occurs at or near the stalked cell pole [32*].

Subcellular localization of signal transduction proteins

DivK is not uniformly distributed within cells, but is localized to the stalked pole throughout the cell cycle and also to the incipient swarmer cell pole at the late predivisional cell stage (Figure 3a) [33]. A mutant form of DivK that cannot be phosphorylated is unable to support viability and unable to localize [34*], suggesting a link between activity and polar localization of response regulators. The difference in activity of the phosphorylated compared with the unphosphorylated form of DivK has not yet been established, but it seems plausible that the underlying mechanistic principle for the localization of phosphorylated response regulators, such as DivK and PleD [35**], is conserved. PleD, which controls morphogenetic events at the cell pole, was recently shown to possess di-guanulate cyclase activity (Figure 3b) [35**]. PleD localizes to the stalked cell pole in response to a phosphorylation-dependent conformational switch that thrusts PleD into the enzymatically active (cyclic-di-GMP-synthesizing) state [35**]. The cyclase activity is required to implement the morphogenetic changes but is dispensable for polar localization, suggesting that the conformational change that occurs upon phosphorylation not only results in cyclase activation but also exposes a surface within PleD that mediates polar targeting [35**]. The localized activity of PleD raises the possibility that the synthesis of cyclic-di-GMP and the subsequent downstream signaling by this secondary messenger take place at the stalked cell pole [36].

Loss-of-function mutations in two membrane-anchored histidine kinases, DivJ and PleC, affect the subcellular distribution of DivK, primarily thought to be caused by altering the steady-state levels of phosphorylated DivK (Figure 3a) [33,37]. DivJ and PleC are pleiotropic regulators that coalesce at the stalked cell pole and the swarmer cell pole, respectively, where they might physically interact with DivK [38]. In the case of PleC, polar localization was postulated to be necessary for proper signaling [39*]. A model has been proposed in which the spatial information inherent in polarly localized PleC and DivJ is translated into temporal information [40*,41*]. DivJ and PleC are localized at opposite poles in the predivisional cell and are thought to act as a DivK kinase and phosphatase, respectively [37]. As soon as the diffusion barrier forms [4*], these activities may become compartmentalized, with the stalked compartment accumulating DivK–P, while the swarmer cell compartment is enriched with DivK [40*,41*] (see also Update).

This model prompts the question of how polar conglomerates of DivJ and PleC form. The kinase activities of DivJ and PleC are dispensable for polar localization [34*,42,43]. Intact cytoskeletal filaments polymerized from MreB subunits could, directly or indirectly, pave the way for the directed movement of PleC and DivJ to

![Figure 3](https://www.sciencedirect.com/content/pii/S1369598604000983)
the poles — depletion of MreB resulted in loss of polar positioning of these proteins (Figure 4) [10]. However, recent quantum fluorescence experiments (J Deich et al., personal communication) showed that single PleC molecules move within the cell membrane in an unbiased fashion, suggesting that localization of PleC at the cell pole may rely on a ‘diffusion and capture’-type mechanism [44]. If so, additional polar factors might account for the observed dependency of PleC on MreB. The pleiotropic PodJ protein could represent this missing link. PodJ is localized to the incipient swarmer cell pole in advance of PleC and is necessary for PleC localization (Figure 4) [38,45]. Therefore, PodJ might be actively transported to the incipient cell pole along MreB filaments that are thought to exhibit polarized growth [10] and subsequently might be capturing diffusing PleC molecules. Whether or not the localization of PodJ is dependent on such polar MreB filaments is currently unknown.

Conclusions
The interplay between oscillatory pairs of global transcriptional regulators, location-specific two-component signaling pathways and the remarkable dynamics imposed on chromosome configuration within the cell constitute an intricate web of regulatory systems that control the Caulobacter cell cycle and demonstrate the remarkable spatial complexity of prokaryotic cells.

Update
A recent study [46] has provided the first experimental evidence for the model proposed in reference [40,41]. It is shown that DivK rapidly shuttles from pole to pole. In elongated, division-inhibited cells, DivK is not properly released from the swarmer cell pole and shuttling of DivK is decelerated. Release of DivK at the swarmer cell pole requires the phosphatase, but not the kinase, activity of PleC.

Acknowledgements
We thank Zemer Gitai and Sean Murray for critical reading of the manuscript.

References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:

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    Caulobacter crescentus and Sinorhizobium meliloti.

    Cell cycle-dependent dynamic localization of a bacterial 
    response regulator with a novel di-guanylate cyclase output 
This is an exhaustive study using genetic, cell biological and biochemical experiments to demonstrate that polar localization of the PleD response regulator is triggered by a phosphorylation-dependent conformational change that activates its guanylate cyclase activity.


The identification of a new polarity factor is reported that is localized to the cell pole and is required for the polar localization of a histidine kinase and the pilus secretion channel. It is proposed that the localization of the histidine kinase is crucial for proper downstream signaling.


This communication postulates a simple model in which the localization of two antagonistic two-component histidine kinases to opposite cell poles acts as a molecular timer for the compartment-specific activation of a cytoplasmic response regulator in the dividing pre-divisional cell.


This is an excellent review on the Caulobacter cell cycle and its checkpoints. The authors postulate the same model that has been discussed in [40].


Three possible mechanisms by which the sporulation protein SpoIVFB could specifically localize to the outer forespore membrane in sporulating Bacillus subtilis cells were investigated. The authors eliminate the two alternative models and provide cell biological evidence for the remaining model that SpoIVFB localization occurs by a ‘diffusion and capture’-type mechanism.


It is shown that DivK rapidly shuttles from pole to pole. In elongated, division-inhibited cells, DivK is not properly released from the swarm cell pole and shuttling of DivK is decelerated. Release of DivK at the swarm cell pole requires the phosphatase, but not the kinase activity of PleC.