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Bacterial Cell Division: Non-models Poised to Take the Spotlight

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Abstract

The last three decades have witnessed an explosion in mechanistic details on how model bacterial organisms such as *Escherichia coli*, *Bacillus subtilis*, and *Caulobacter crescentus* undergo binary fission. These advances were possible by not only advances in microscopy that allowed cell biological questions to be answered, but also by the clever use of genetic manipulations in these systems in which specific hypothesis could be directly and easily tested. More recently, research using traditionally understudied organisms, or "non-model" systems, has revealed several alternate mechanistic strategies that bacteria use to divide and propagate. In this review, we will highlight these new findings and compare these strategies to cell division mechanisms elucidated in well-established model organisms.

Keywords

Min system; FtsZ; DivIVA; nucleoid occlusion; Noc

INTRODUCTION

The field of bacterial cell division has relied heavily on model organisms such as the Gram-negative *Escherichia coli* and Gram-positive *Bacillus subtilis*, largely because of the abundance of available genetic tools in these organisms. Since *E. coli* and *B. subtilis* are both rod-shaped cells that divide symmetrically along the short axis of the cell, it has been relatively straightforward to compare and contrast the mechanisms involved in regulating cell division in these two species, leading to tremendous progress over the last three decades in understanding the fundamentals of bacterial cell division. To gain a deeper appreciation of how bacterial cells divide, several labs have begun to examine differently shaped organisms that may undergo more complex cell cycles and occupy a variety of ecological niches, where many of the lessons learned from studying model organisms appear not to apply. Certainly, our understanding of molecular details in these systems is still in its infancy compared to what is known in model systems, but a wide array of interesting cell division mechanisms is already being reported (Fig. 1). Therefore, this review will highlight new research in

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traditionally understudied systems and compare these systems to cell division mechanisms elucidated in well-studied model organisms.

The bacterial tubulin homolog, FtsZ, is *almost* universally conserved in different bacterial species. FtsZ assembles as a ring (termed the "Z-ring") and marks the site for division by subsequently recruiting components of the divisome to initiate cytokinesis (58). A central question has been to understand how the correct placement of the Z-ring initially occurs. In *E. coli* two negative regulatory systems influence Z-ring assembly and localization: nucleoid occlusion (NO), mediated by the SlmA protein which prevents cell division atop the nucleoid, and the Min system, composed of three proteins in *E. coli*, which prevents cell division near the polar regions of the cell (131) (Fig. 2A). *B. subtilis* also harbors a NO system, mediated by the Noc protein which is not homologous to the *E. coli* SlmA protein and also functions in a different fashion (131). In *E. coli*, the Min system oscillates from one cell pole to another thereby creating a low time-averaged concentration at mid-cell, permitting Z-ring assembly to take place only near mid-cell (89) (Fig. 2A). Although *B. subtilis* harbors components of the Min system, it functions more to mediate the fidelity of cell division via the cell division protein DivIVA, rather than the actual placement of the Z-ring (45, 56, 136) (Fig. 2B). Curiously, both well-studied systems are somewhat dispensable for correct Z-ring placement, suggesting the presence of other, heretofore undiscovered, division factors that is the major focus of current research (7, 116). The notion that negative regulation can determine Z-ring positioning was also observed in another model organism, *C. crescentus*, that lacks both Min and NO systems, but instead employs a protein termed MipZ to prevent Z-ring assembly near the cell poles (discussed in detail below; Fig. 2C) (53, 129).

The model systems set up a central notion that placement of the division septum is largely the result of negative regulation, but recent results have also indicated that Z-ring placement in multiple species may be positively influenced, thereby setting up an entirely new paradigm for bacterial cell division. We will also highlight studies in several systems that are less well established but point to other novel mechanisms for cell division regulation, including those found in pathogens and symbionts. Finally, we will also review cell division behaviors of bacteria that break fundamental "rules" learned from model systems more dramatically: dividing along alternate axes of the cell and not utilizing the nearly universally conserved FtsZ protein at all.

Cell division in polar flagellates

Cell division in the monotrichous (one polar flagellum per cell) dimorphic prosthecate alphaproteobacterium *C. crescentus*, has been extensively studied. This bacterium lacks both MinCD and NO systems to regulate the placement of the FtsZ ring. Instead it employs a ParA-like ATPase MipZ (Midcell positioning of FtsZ) to regulate the assembly site of the Z-ring (34, 111, 129). MipZ forms a gradient by interacting directly with origin-proximal DNA-bound ParB-*parS* complexes at the flagellated (stalked) pole prior to cell division and translocating with the newly replicated origin to the non-flagellated pole (Fig. 2C). At both poles, the presence of the MipZ gradient displaces polar-localized FtsZ through direct interaction, thereby creating an FtsZ polymerization-permissive zone near mid-cell where

FtsZ is allowed to assemble into a Z-ring and form the division septum (72, 129). The formation of minicells has been observed in this bacterium dating back to 1978 (107) and, not surprisingly, cells in which MipZ is depleted produce minicells, due to the mis-regulated assembly of FtsZ at non-permissive subcellular regions (129). Similarly, the multi-functional polar-localized protein PopZ (Pole-Organizing Protein that affects FtsZ) undergoes transition from being unipolar to bipolar and captures the ParB-*parS* complex at the non-flagellated pole. Cells lacking *popZ* were unable to produce stalks, formed minicells and appeared elongated due to erroneous cell division (14, 38). These phenotypes were due to a malfunction of chromosome segregation and subsequent incorrect MipZ localization, linking stalk formation with cell division. TipN (Tip of New pole) is another protein involved in marking the new pole (the site of flagellar assembly) after cell division. Interestingly, overproduction of TipN resulted in the formation of both minicells and elongated cells(64, 79, 81). Absence of TipN together with TipF, a protein essential for flagellar assembly, results in cell elongation and filamentation (64). In this manner, a mechanism that coordinates cell division with flagellar assembly in this fresh water organism may provide a dispersal mechanism for progeny cells.

Campylobacter species exploit the formation of amphitrichous flagella (one flagellum per pole on both poles) to regulate FtsZ placement. These organisms require the correct number of flagella on each pole to be present to exhibit a behavior termed darting motility and for successful host colonization (119, 126). *Campylobacter* species lack a MinCD system and instead utilize a MinD/ParA-like ATPase protein FlhG (FleN), a known regulator of flagellar number (Fig. 3A). In *Campylobacter jejuni*, cells lacking *flhG* often produce more than one flagellum per pole, but intriguingly also forms minicells, suggesting a role in cell division for FlhG (8). Consistent with a MinD-like role for FlhG in cell division regulation, cells of an FlhG mutant lacking ATPase activity exhibit cell length elongation – a phenotype that was suppressed by increasing the levels of FtsZ (8, 70). By making use of the amphitrichous flagellation as a mechanism to regulate cell division, *Campylobacter* species ensure that cell division occurs away from the pole to increase the chances of daughter cell survival by confirming the formation of a flagellum and preventing minicell formation. Interestingly, *flhG* of *Helicobacter pylori*, which is a lophotrichous organism containing several flagella at one pole is able to complement the defect of a *flhG* null mutant of *C. jejuni* indicating that the usage of flagellar assembly to regulate cell division may not be unique to *Campylobacter* species (8).

In contrast, in a monotrichous magnetotactic bacterium of the *Gammaproteobacteria* class, the site of the cell division septum appears to dictate the site for the construction of the new flagellum: specifically, at the side of the septum facing the daughter cell that has no flagellum (83) (Fig. 3B). It is hypothesized that this mechanism permits offspring to align their cells along the same polarity of magnetic dipole as the parental cell and position the flagellated pole accordingly (83).

Together, these set of data indicate that regulation of flagella or stalk formation may be tightly intertwined with cell division. Further research in these organisms will shed light on the precise molecular mechanisms by which cell division is regulated via flagellar assembly.

The monotrichous Gram-negative bacterium, *Bdellovibrio bacteriovorus*, belongs to the class of *deltaproteobacteria* that parasitize other Gram-negative bacteria. In this organism, the non-flagellated pole is utilized to recognize and penetrate the outer membrane of the prey (121). Once inside the periplasm of prey such as *E. coli*, *B. bacteriovorus* undergoes growth in the form of filamentation, by undergoing unipolar growth (40), and feeds off of the nutrients provided by the prey. Just prior to inducing host lysis, *B. bacteriovorus* produces multiple motile daughter cells (18, 46) (Fig. 3C). The manner in which this bacterium spatially and temporally regulates this remarkable cell division event and the identity of cell division factors required for this remains to be elucidated. Although this organism encodes FtsZ that is speculated to be involved in cell division (33, 114), the Min system is completely absent (114). Unlike most bacteria, *B. bacteriovorus* encodes two copies of MreB (111), a protein that regulates peptidoglycan synthesis, and at least one MreB homolog appears to play a role in regulating cell division and nucleoid organization (20, 47). In this organism, concurrent septation has been reported (Fig. 3C), which appears similar to the event that occurs during *Streptomyces* sporulation (see below), and it was also observed that flagellation occurs before daughter cell separation (18), similar to the magnetotactic bacterium describe above. At this time, there is no knowledge of any positive regulatory mechanism similar to the one present in *Streptomyces* (discussed under positive regulation) or if flagellation has a role in regulating cell division in *B. bacteriovorus.* Being a small bacterium (1 μm in length and 0.25 μm in width, which is about 1/3rd size of *E. coli* or *B. subtilis*), light and fluorescence microscopy studies have been limited (46), but perhaps the increased use of super-resolution microscopy techniques will help trigger a renewed interest in understanding the cell division process in *B. bacteriovorus*.

Cell division in bacteria that exhibit polar growth

Unlike *E. coli* and *B. subtilis* which grow by incorporating peptidoglycan near mid-cell, the rod-shaped, Gram-negative, alphaproteobacterium, *Agrobacterium tumefaciens* undergoes growth by adding peptidoglycan specifically at the new poles (22, 63) (Fig. 4A). The non-growing pole, usually the old pole, is reserved for the secretion of an adhesive molecule to facilitate attachment to various surfaces. This organism possesses three copies of *ftsZ.* One copy encodes FtsZ that is equivalent to that of *E. coli*, where the gene is present within an operon coding for *ftsQ* and *ftsA*. The other two *ftsZ* copies exhibit varying levels of truncation and are encoded elsewhere on the genome. A recent study has elegantly shown that after septation, which occurs near mid-cell in *A. tumefaciens*, FtsA and FtsZ stay at the newly formed growth pole and presumably facilitate polar growth. Subsequent to cell enlargement, FtsA and FtsZ relocate to mid-cell to form an FtsZ ring which, upon completion of septum formation, mark the new pole for polar growth (15, 55, 146) (Fig. 4A). Two proteins (PopZ and PodJ) were identified and reported to mark the growth pole and old pole, respectively (55). An interesting feature that is present in both *A. tumefaciens* and *C. crescentus,* also an alphaproteobacterium, is the pole-localized intermediate population of FtsZ (129, 146), although the significance of this in *C. crescentus* is not clear. How the division site is determined in *A. tumefaciens* and if there is a MipZ-like factor regulating FtsZ placement also remains to be determined.

Another group of bacteria that display polar growth is predominantly in the *Actinobacteria* phylum. Some examples include *Mycobacterium tuberculosis*, *Streptomyces coelicolor* (see positive regulation section below), and *Corynebacterium glutamicum*. The bacterium *C. glutamicum* is reported to undergo uneven polar growth in which the old poles appear to grow faster than the newly-formed poles (120) (Fig. 4B). This rod-shaped bacterium lacks both Min and NO systems and the mid-cell division site is not precisely chosen, unlike its well-studied rod-shaped counterparts *B. subtilis* and *E. coli*. As a result, cell division often results in grossly unequal-sized daughter cells (31). *C. glutamicum* contains two ParA proteins, one encoded by the *parAB* operon and the other ParA encoded elsewhere as a standalone gene (32). The orphan ParA-like protein, referred to as PldP, appears to play a role in regulating cell division. Deletion of *pldP* results in a minicell phenotype while overexpression of *pldP* results in increased cell length, consistent with its role in regulating cell division. In further support of this idea, PldP localizes to the nascent division sites (31).

In *M. tuberculosis*, which also undergoes polar growth, cell division produces two unequal-sized daughter cells and it appears that the old poles elongate faster than the new pole (73) (Fig. 4B). The well-studied FtsZ anchoring proteins such as FtsA are curiously absent in this organism (25). However, *M. tuberculosis* harbors other FtsZ anchoring proteins such as FhaB (also referred to as FipA), FtsW, and CrgA (26, 73, 106, 125). Mycobacteria lack both a Noc-like and complete Min system (60). However, a protein homologous to MinD, termed *s*eptum *s*ite *d*etermining protein Ssd (Rv3660c), plays a critical role in determining the site of FtsZ ring assembly and appears to link cell division with environmental adaptation (41). The AAA+ family chaperone ClpX that is known to regulate and repurpose FtsZ in *E. coli* (21, 50, 124) and *B. subtilis* (57, 139), also plays a role in negatively regulating cell division in *M. tuberculosis* (37). It was also observed that in this organism a cell wall hydrolase, ChiZ, helps regulate FtsZ localization (134). Additionally, it was noted that a Ser/Thr Phosphatase (PstP) is important for cell division regulation (118), and that the GTPase activity of FtsZ and interaction with other divisome partners of FtsZ are negatively affected via phosphorylation by a Ser/Thr kinase PknA (125, 128). Several studies reported that the transcription factor-like WhiB homologs may be involved in the non-transcriptional regulation of cell division in Mycobacteria by either directly interacting with FtsZ or acting as a chaperone, depending on the species (11, 54, 77). Furthermore, there is evidence that *ftsZ* levels could be up- or down-regulated for adapting to various extracellular environments (74). Regulation of cell division in non-pathogenic *Mycobacterium smegmatis* may harbor a largely similar cell division regulation system as *M. tuberculosis*, since *M. smegmatis ftsZ* can complement the deletion of *ftsZ* in *M. tuberculosis* (36). Taken together, it appears that for cell division in bacteria that undergo polar growth, the use of either the Min or NO systems may be eschewed and several other components are used to couple cell division to cell growth.

Examples of positive regulation

For many years, a common mechanistic theme in bacterial cell division was that, as exemplified by the Min and NO systems, placement of the cell division machinery may be primarily mediated by negative regulation, whereby the Z-ring would assemble at subcellular locations where negative regulators were largely absent. However, several recent

examples in *Streptomyces coelicolor*, *Myxococcus xanthus*, and *Streptococcus pneumoniae*, which all lack both Min- and NO-like systems (105, 117), suggest that positive regulatory elements in some species may pre-localize to the future site of cell division to position the cell division machinery (Fig. 5).

In *S. coelicolor*, *ftsZ* is a non-essential gene that is likely only required for sporulation (93). Although it does contain a negative FtsZ regulator, CrgA, that plays a poorly defined function (27), it harbors another system mediated by SsgAB that positively affects FtsZ assembly by actively recruiting FtsZ to the division sites (140) (Fig. 5A). SsgB, the protein that brings FtsZ to the division sites during sporulation, mislocalizes in the absence SepG, a transmembrane protein that may be involved in nucleoid compaction (144), suggesting that chromosome organization and cell division may be coordinately regulated during sporulation in *S. coelicolor*. Consistent with this notion, the chromosome segregation proteins ParAB in this organism is able to regulate cell tip elongation and FtsZ assembly (30, 76), and the broadly conserved multi-functional cell division protein DivIVA interacts with ParA at least indirectly via a cytoskeletal protein Scy (29, 62). Finally, it is worth noting that, although most of the cell division research in *S. coelicolor* has been focused on sporulation in this organism due to the dispensability of *ftsZ* during normal growth, new observations suggest that this naturally filamentous bacterium does indeed routinely separate its cytosol and achieve compartmentalization by formation of FtsZ-independent “cross-membranes” that represent a form of cell division whose molecular details of formation and regulation await further study (23, 143).

Another example of positive regulation is observed in the deltaproteobacterium *M. xanthus*. In this organism, the ParA-like protein PomZ localizes to mid-cell division sites, which immediately precedes localization of FtsZ, and does so in an FtsZ-independent manner (130) (Fig. 5B). However, cells lacking *pomZ* formed filamentous cells and nucleoid-less minicells, suggesting that PomZ plays a central, currently undefined, role in dictating where FtsZ localizes and polymerizes within the cell to form Z-rings.

A third case of positive regulation is reported in the ovoid bacterium *S. pneumoniae*, where a recently identified protein MapZ (LocZ) localizes to the site of cell division prior to FtsZ and the FtsZ-anchoring protein FtsA, and recruits downstream divisome proteins beginning with FtsZ (48, 61) (Fig. 5C). Deletion of *mapZ* resulted in suboptimal septum placement and production of nucleoid-less minicells. MapZ is conserved only within *Streptococcaceae* and *Enterococcaceae* families among Firmicutes (52). MapZ is capable of binding nascent peptidoglycan and due to cell elongation, which slightly precedes septation during cell division process, it has been proposed that a MapZ subpopulation splits from the mid-cell associated population to migrate and subsequently mark new cell division sites (52). MapZ is under post-translational regulation via phosphorylation by a Ser/Thr kinase StkP, which also localizes to the division site and acts as a critical switch coordinating peptidoglycan synthesis during elongation and septation (48, 49). Depending on the strain background, the Δ*mapZ* phenotype may be less dramatic, indicating that there could be other redundant factors that may perform a similar role to that of MapZ (12). Another report shows that, FtsA, an essential protein in *S. pneumoniae* (80), is required for proper localization of FtsZ

and may play a role in regulating peptidoglycan synthesis during both septation as well as lateral cell elongation (98).

Cell division in bacteria that contain multiple chromosomes

A gammaproteobacterial cousin of *E. coli*, *Vibrio cholerae*, contains two chromosomes. As there are many bacterial species with multiple chromosomes that are being discovered, there is an accumulating interest in understanding how the faithful segregation of chromosomes is coordinated with cell division, and *V. cholerae* has emerged as a model to address these questions (39, 66, 108). Chromosome 1, the larger chromosome, communicates with chromosome 2 and signals the proper time to initiate DNA replication while undergoing its own replication (6, 109, 135). A recent report has provided evidence that mutants that lack both Min and NO systems are viable (51). However, the Min system becomes critical in maintaining cell division fidelity when the chromosome organization is compromised. Similar to *C. crescentus*, this bacterium also displays pole-localized FtsZ. The absence of SlmA, which mediates NO in this organism, results in the untimely accumulation of FtsZ at midcell, suggesting that chromosome segregation in *V. cholerae* is linked to the proper timing of cell division. Specifically, it has been proposed that the SlmA binding sites, especially on chromosome 2, may act as a cell division timing device that allows FtsZ assembly based on the status of nucleoid segregation (51).

Cell division in cocci

In the Gram-positive spherical bacterium, *Staphylococcus aureus*, new cell division planes arise orthogonal to the two previous division planes, which results in the formation of its signature grape-like clusters (78, 133) (Fig. 6A). In recent years this organism has become an increasingly-studied model for interrogating cell division in spherical bacteria, where the lack of distinctly symmetrical planes imposes an additional challenge in establishing the plane of cell division (105). *S. aureus* lacks a Min system and possess a NO system that may link nucleoid segregation and cell division (137). The gene coding for DivIVA, which spatially regulates the Min system in *B. subtilis* (45), is present in *S. aureus* but deletion of *divIVA* does not obviously affect cell division or chromosome segregation (104). The cell shape-determining protein MreB that is widely conserved in rod-shaped bacteria is absent in *S. aureus*. Interestingly, the shape-determining proteins MreC and MreD proteins are present in this organism and localize to division sites. However, deletion studies indicated that these proteins are not major factors in regulating septal or peripheral peptidoglycan synthesis (127). The homolog of a negative regulator of FtsZ, EzrA, which is conserved among several Gram-positive bacteria (86), directly interacts with FtsZ in *S. aureus* (122), and localizes to division sites and participates in regulating cell size in *S. aureus* by controlling peptidoglycan synthesis and cell division (68, 123). Recent reports have shown that, subsequent to cell division, daughter cell separation happens very quickly, within a span of two milliseconds, indicating a mechanism that uses physical forces rather than enzymes alone for cell separation (96, 145). A traditional view of *Staphylococcal* cell division was that the biosynthesis of peptidoglycan is restricted to division sites. This view also suggested a mechanism for the identification of sequential orthogonal mid-cell division plane selection that invoked the presence of peptidoglycan-based scar-like marks that appear after each round of divisions (132). In fact, DivIB, which was shown to bind peptidoglycan was

speculated to be a pointer for previously used sites for division, since depletion of DivIB resulted in incorrect placement of septa (13). However, newer measurements, generated with advanced microscopy and newly developed cell wall labeling techniques, indicated that septal cell wall material accounted for less than half of the cell wall material in a newly separated cell (96, 145) (Fig. 6), which contradicted the previously held model of restricted deposition of peptidoglycan (103, 132). The newer measurements also indicated that peptidoglycan synthesis occurs along the entire circumference of *S. aureus* cells, mediated by at least one of the four penicillin-binding proteins (96, 145). Thus, given new observations that revealed the non-restricted insertion of peptidoglycan, a model based on a peptidoglycan-based division marker appears less likely and the question of how cell division plane selection occurs in *S. aureus*, remains an open question.

Cell division in bacteria that lack FtsZ

Since FtsZ is apparently the central bacterial cell division factor, the discovery of a growing number of organisms that do not encode *ftsZ* posed the question of how cell division occurs in these FtsZ-less bacteria (10, 43, 67, 115). One such FtsZ-less organism is an obligate intracellular pathogen, *Chlamydia trachomatis*. Adding to this anomaly of the absence of FtsZ was the longstanding conundrum that, although these organisms possess the genes encoding peptidoglycan biosynthesis machinery, peptidoglycan production could not be measured directly. Nonetheless Chlamydial cells were sensitive to antibiotics that target peptidoglycan synthesis, indicating that cell wall material was likely present (97). With the aid of fluorescent D-amino acid labeling techniques that measure the nascent peptidoglycan incorporation, it was recently shown that peptidoglycan is indeed present in *C. trachomatis* and other related organisms (88, 100, 102). However, in *C. trachomatis*, what likely precluded earlier attempts at detecting peptidoglycan was the observation that peptidoglycan synthesis primarily occurred transiently during cell division and predominantly at the division site. This led to the model that peptidoglycan synthesis may drive cytokinesis in this organism (88). Indeed, in *C. trachomatis* and a related organism, MreB and RodZ (9), which are involved in spatially regulating peptidoglycan incorporation, localize to cell division sites (65, 71, 87). Interestingly, recent observations have suggested that, even in *E. coli*, FtsZ may not provide the force for membrane invagination and constriction during cell division and that peptidoglycan assembly may instead be the rate-limiting step that deforms the membrane (142), suggesting that cell wall-driven cytokinesis may be a widely conserved mechanism driving bacterial cell division. Recent work has shown that *C. trachomatis* can also exhibit asymmetric budding-like cell division, which is documented in another FtsZ-less evolutionary relative *Gemmata obscuriglobus*, a member of the Planctomycetes phylum (1, 82, 87) and in L-forms of *B. subtilis* that do not produce FtsZ or peptidoglycan (44). Interestingly the *C. trachomatis* FtsQ ortholog, similar to the *E.coli* divisome protein FtsQ (99), localizes to the site where budding occurs and stays at the asymmetric division septum (1), but it is not yet clear what regulates the choice between symmetric or budding division in this organism (87).

Bacteria that undergo extra-ordinary modes of cell division

Beyond molecular anomalies, such as the absence of certain conserved factors (Min and NO systems, or FtsZ, for example) that are increasingly apparent in the course of studying cell

division in diverse bacterial species, more fundamental physical differences have emerged in certain organisms that violate long-held central premises of bacterial cell division. Chief among these exceptional situations include violating the notion that bacteria must produce exactly two daughter cells by binary fission, and that cell division must occur along the short axis of a rod-shaped cell.

A bacterial endosymbiont that belongs to *Epulopiscium* spp., which hosts the largest known bacterium measuring more than 600 × 80 microns (5), inhabits the intestines of surgeon fish and "gives birth" to multiple live offspring (3). In these organisms, it has been shown that FtsZ assembles into polar rings and a minimum of two (and sometimes up to twelve) live offspring emerge from each pole and grow side by side which are then "birthed" subsequent to programmed mother cell lysis (4, 138), in a manner reminiscent of endospore formation in Firmicutes. Thus, in *Epulopiscium* spp., asymmetric division in the progenitor cell gives rise to multiple progeny and the lysis of the progenitor, not as a stress response, but as part of the normal cell cycle.

A longstanding challenge in bacterial cell biology has been to determine how FtsZ assembles at mid-cell, but septum placement has been assumed to lie along the short axis of a rod-shaped cell - not from pole to pole. A stunning mode of cell division has been observed recently in some marine *gammaproteobacteria* ectosymbionts and are in the process of receiving a proper binomial name (17, 101). A rod-shaped bacterium now referred to as *Candidatus* Thiosymbion oneisti grows as a monolayer, where each bacterium is attached at a bacterial pole on the surface of a marine nematode *Laxus oneistus*. In this organism, fragmented FtsZ rings form parallel to the long axis of the cell, instead of perpendicular to the long axis like in commonly studied model organisms (85) (Fig. 6B). This organism possesses an operon that encodes for a Min system, but it is not yet clear if Z-ring placement is regulated by the Min system. In another ectosymbiont of same family that also undergoes longitudinal division, it was recently shown that FtsZ accumulation occurs first at a pole proximal to the host (84) (Fig. 6C). Interestingly, instead of initiating cell division from both poles at the same time, this organism initiates the process at the host-proximal pole and drives the division and daughter cell separation towards the other pole making use of several FtsZ foci aligned at the division plane, instead of an FtsZ ring. One model posits that division along the long axis permits the continued association of daughter cells with the host surface on which the monolayer of bacteria is formed. Division along the long axis has also been reported for a helix-shaped, *Drosophila melanogaster* endosymbiont, *Spiroplasma poulsonii*, in which longitudinal branching occurs and FtsZ localizes to the branching sites (110).

Concluding thoughts

In recent years, increasingly new observations have been made in non-model organisms. For example, a new operon containing mid-cell associated probable division genes has been reported that is specific for obligate anaerobe *Clostridium difficile* (113). It was also reported that the *C. difficile* Min system, which includes an *E. coli*-like MinE protein in addition to the *Firmicutes*-like DivIVA, is capable of oscillation when produced in *B. subtilis*, suggesting that *C. difficile* may exhibit features that integrate both systems (91).

These advances were aided by new cell biological tools that now permit the use of fluorescence microscopy probes in anaerobes such as *C. difficile* (16, 112). Further variations on existing themes are also now emerging by studying non-model organisms. In a twist on positive regulation of cell division site selection in certain spirochetes such as in the etiological agent of Lyme disease, *Borrelia burgdorferi*, peptidoglycan growth was observed to occur at precise sub-regions within a growing cell, so that the daughter cell division site is actually marked one generation in advance (69). Even the well-studied Min system displays variety, in that Min oscillation can occur in the cyanobacterium *Synechococcus elongatus* even in the presence of physical barriers set-up by thylakoid membranes (90). Similar to *C. difficile*, *S. elongates* also harbors both MinE and DivIVA-like proteins to regulate cell division in this organism (90).

Even in model organisms, new discoveries are continuing to be made such as the one that indicates that MinD in *E. coli* and *B. subtilis* may have an additional role in DNA segregation (28, 75). In *B. subtilis*, for example, the NO protein Noc does not directly interact with FtsZ in the way that the NO protein in *E. coli* (SlmA) does (24, 35, 141). Instead, it was recently proposed that Noc anchors the chromosome to the membrane and physically prevents regions of the cell that are conducive for FtsZ ring assembly during the process of nucleoid segregation (2). Another example of linking chromosome replication to cell division involves a nucleoid replication region organization factor in *E. coli* (MatP) which, together with other divisome proteins, positively facilitates Z-ring assembly and its constriction (7, 19, 92). There is also evidence suggesting the existence of hitherto undiscovered FtsZ regulators, since division site selection may still occur in the absence of the Min and NO systems in *E. coli* and *B. subtilis* (7, 116), and new evidence continues to emerge that links nutrition status to cell division (59, 95). Finally, FtsZ, the well-studied protein central to cell division in most bacteria, is still under active investigation, as new evidence has questioned if FtsZ is the predominant force generator that drives membrane invagination during cytokinesis (42, 94, 142). Instead, an emerging model proposes that assembled FtsZ is a platform to recruit peptidoglycan synthetic enzymes to provide directionality for peptidoglycan synthesis, and that it is peptidoglycan synthesis per se that directly contributes the force for septum formation (142).

The well-established genetics afforded by model systems has provided detailed molecular insights into how these species grow and give rise to progeny. Moving forward, the increasing availability of genome sequences even for unculturable bacteria, combined with the advent of molecular tools that increase the ease of genetic manipulation of these organisms, promises to open avenues of research into traditionally understudied systems to reveal the full repertoire of prokaryotic cell division strategies.

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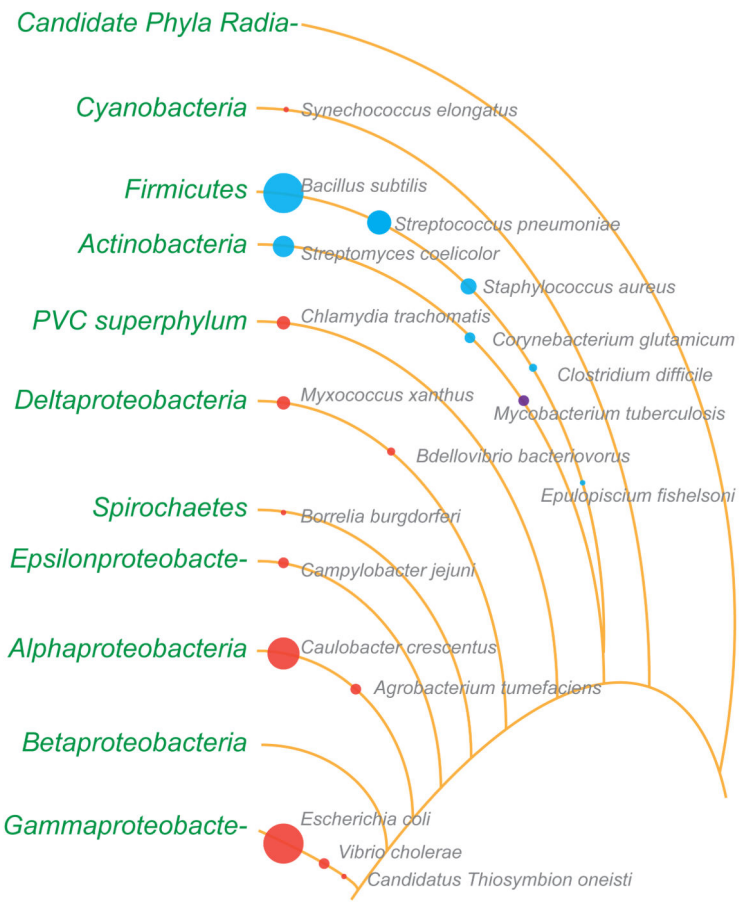

Figure 1.

Representation of the relative number of reports describing cell division in various bacterial species. The diameters of the circles roughly indicate the number of cell division publications available for organisms highlighted in this review. Note: The diameter of the circles for *E. coli* and *B. subtilis* are capped at an arbitrary number so that other circles are visible. Red circles, Gram-negative; blue circles, Gram-positive; violet, *M. tuberculosis*. Lines depict phyla and lineages loosely based on the bacterial branch of the tree of life (PMID: 27572647). Several phyla and lineages were omitted for clarity. PVC superphylum comprises of *Planctomycetes*, *Verrucomicrobia*, and *Chlamydiae*. The branch length, spaces between them, and the order in which some organisms are listed are not based on phylogeny.

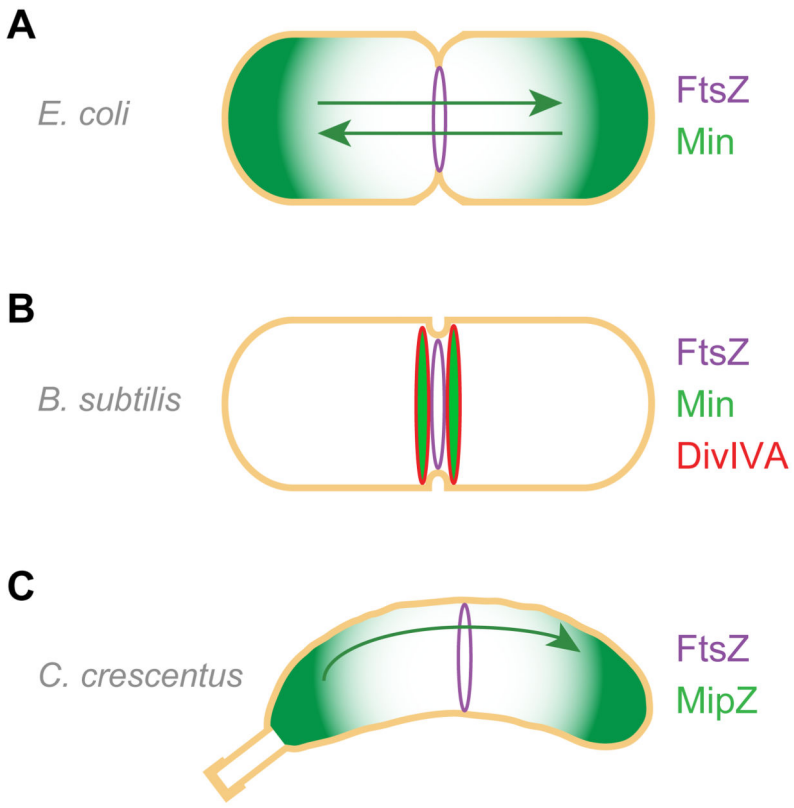

Figure 2.

Regulation of cell division in model organisms is achieved predominantly by negative regulators. (A) In *E. coli*, proteins that comprise the Min system (green), which prevent FtsZ (purple) ring assembly, oscillate between the poles and inhibit cell division close to cell poles. (B) In *B. subtilis*, the Min system (green) is recruited to sites adjacent to newly forming septa by DivIVA (red); it does not mediate division site selection, but maintains cell division fidelity by preventing aberrant septation from occurring at mid-cell adjacent to a newly formed septum. (C) In *C. crescentus*, MipZ (green)interacts with chromosome-bound ParB and co-migrates to the stalk-less pole and displaces polar-localized FtsZ (not shown), to permit FtsZ ring assembly at mid-cell. The negative regulators of FtsZ are shown in green. Nucleoid occlusion system is not depicted for clarity.

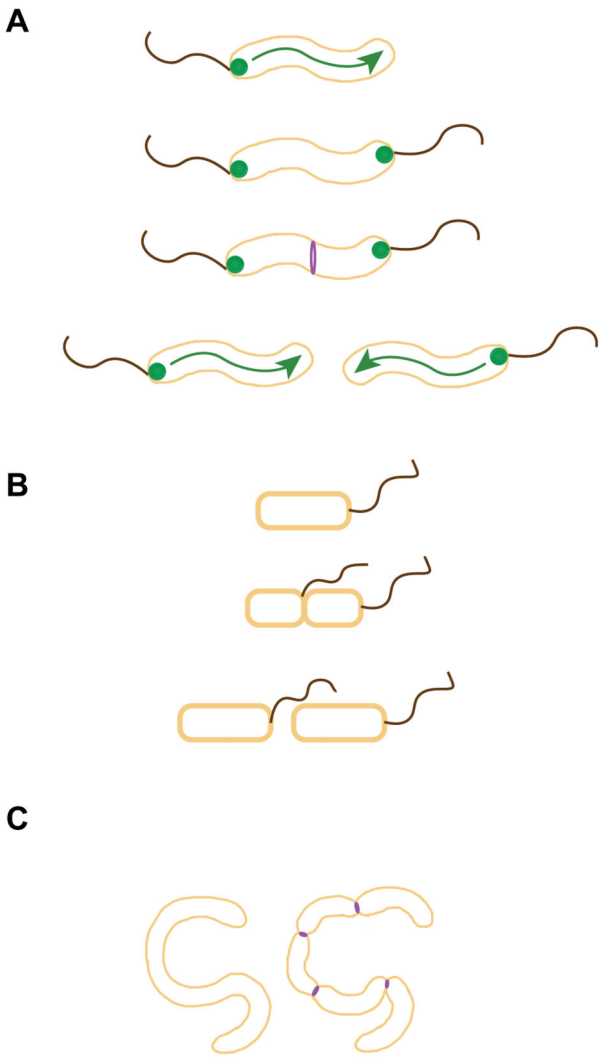

Figure 3.

Cell division regulation in polar flagellates. (A) In *C. jejuni*, FlhG (green circles), a MinD/ParA-like ATPase that regulates flagellar copy number, also participates in negatively regulates FtsZ (purple) assembly near poles. (B) In a magnetotactic Gammaproteobacterium, flagella arise from the site of cell division (suggesting positive cell division regulation), perhaps to ensure that the flagella of daughter cells are oriented in the same direction as the parental cells along earth's the magnetic dipole. (C) Cells of *B. bacteriovorus* grow as filaments inside the periplasm of Gram-negative bacteria. Just prior to host cell lysis, the filamentous cell undergoes synchronous septation (reminiscent of sporulating *S. coelicolor* cells) to liberate motile daughter cells. Possible sites of FtsZ ring assembly (purple) are shown; flagella arising from the site of septation are not depicted.

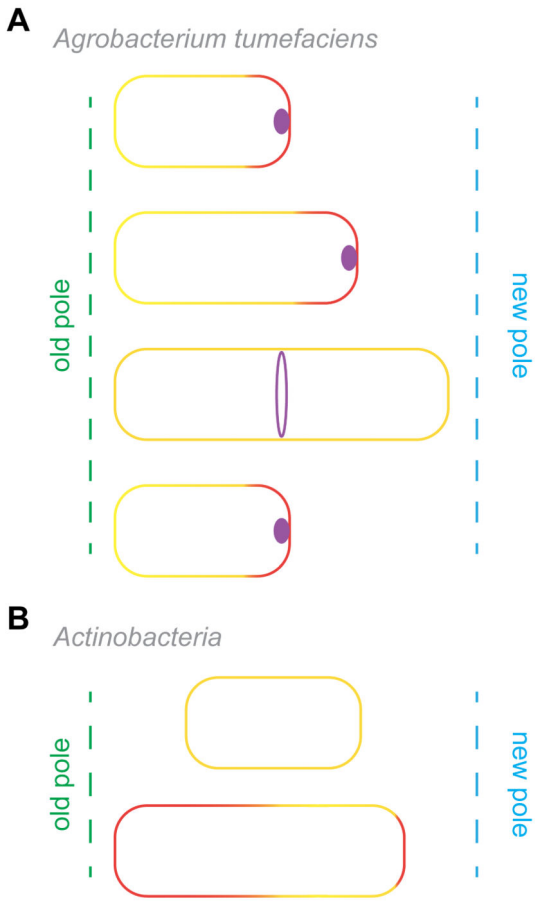

Figure 4.

Cell division in bacteria that display polar growth. (A) FtsZ (purple foci) in *A. tumefaciens* remain localized at the pole after cell division and likely facilitate polar elongation specifically at the new pole (red line). Subsequently FtsZ relocates to the mid-cell site (purple ring) to assemble the divisome and mediate cell division. (B) Cells of both *C. glutamicum* and *M. tuberculosis* (labeled "Actinobacteria") undergo uneven growth at cells poles with older poles exhibiting faster growth than the new pole.

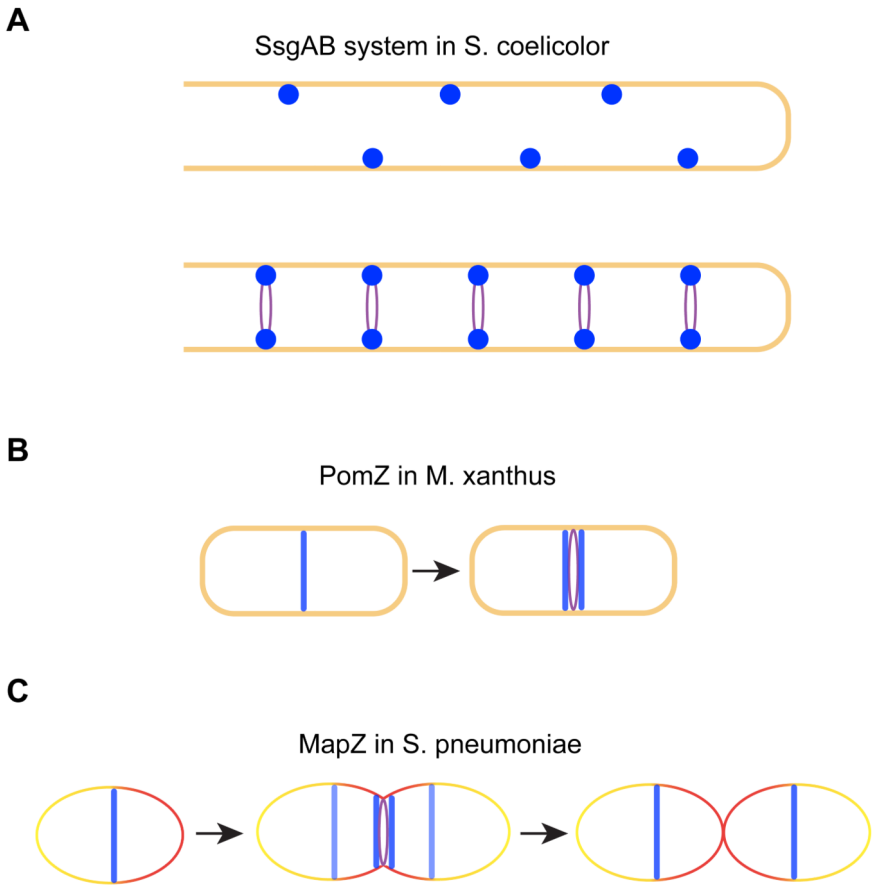

Figure 5.

Examples of positive regulation of cell division. (A) During sporulation in *S. coelicolor*, SsgB interacts with SsgA (complex depicted in dark blue) to mark potential division sites and recruit FtsZ (purple). (B) Cells of *M. xanthus* uses PomZ (blue) to indicate the site for FtsZ localization and assembly. (C) In *S. pneumoniae*, MapZ (LocZ; depicted in blue) localizes to the mid-cell division site facilitate the process of FtsZ ring assembly. Just prior to septum formation, a subpopulation of MapZ (light blue) binds to the nascent peptidoglycan during the lateral cell wall synthesis (shown as red line) and hitchhikes to mark the future division sites.

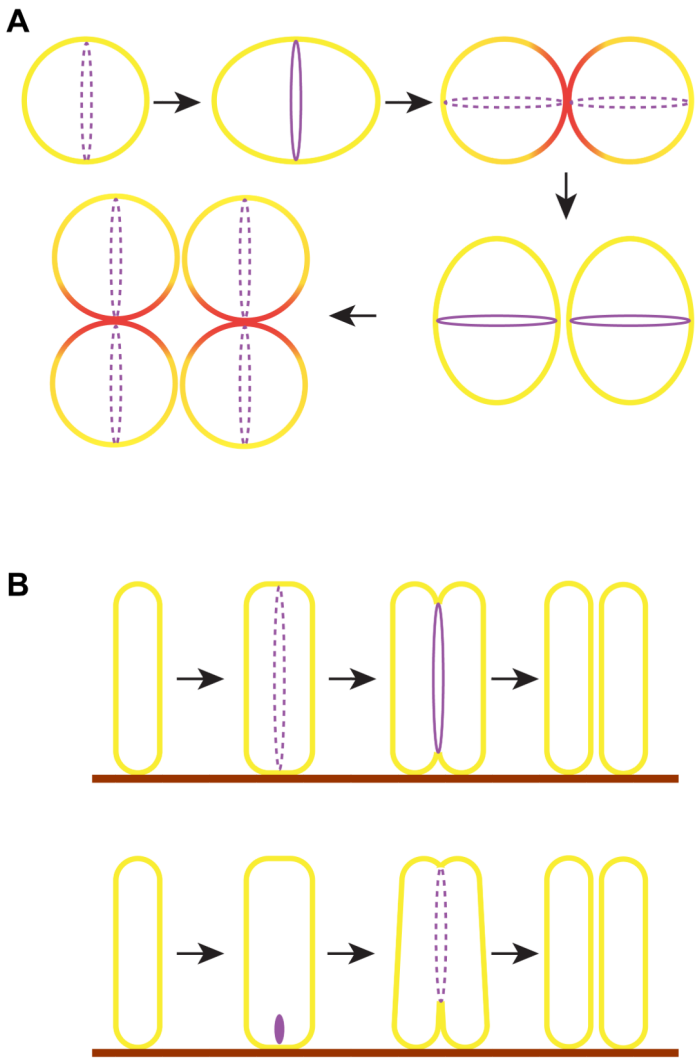

Figure 6.

Other modes of bacterial cell division. (A) Subsequent generations of the spherical *S. aureus* divide in a plane orthogonal to the two previous generations. Although cell wall synthesis was speculated to occur only during septum synthesis, new evidence suggests that circumferential cell wall synthesis also occurs in this organism. Subsequent to cell division, the septum-derived cell wall material (red) contributes to less than half of the newly formed daughter cell. The division plane of the next generation lies orthogonal to that of the preceding generation. (B) Top: The marine gammaproteobacterium *Candidatus* Thiosymbion oneisti attaches via one pole to the surface (brown lines) of the nematode *Laxus oneistus*. This bacterium grows wider along the short axis prior to FtsZ (purple) assembly, which occurs at mid-cell parallel to the long axis of the cell, presumably to permit both daughter cells to remain adhered to the host. Bottom: In another gammaproteobacterial relative of this organism (yet to be named), that lives on the surface of a different nematode *Robbea hypermnestra*, FtsZ localizes closer to the host-proximal pole and trigger septum formation. Subsequently, several fragmented FtsZ foci continue to mediate septum synthesis

towards the distal pole. The factors involved in the regulation of longitudinal division remains to be elucidated.