MINI-REVIEW

Regulation of cytokinesis: FtsZ and its accessory proteins

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Abstract

Bacterial cell division is a highly controlled process regulated accurately by a diverse array of proteins spatially and temporally working together. Among these proteins, FtsZ is recognized as a cytoskeleton protein because it can assemble into a ring-like structure called Z-ring at midcell. Z-ring recruits downstream proteins, thus forming a multiprotein complex termed the divisome. When the Z-ring scaffold is established and the divisome matures, peptidoglycan (PG) biosynthesis and chromosome segregation are triggered. In this review, we focus on multiple interactions between FtsZ and its accessory proteins in bacterial cell cytokinesis, including FtsZ localization, Z-ring formation and stabilization, PG biosynthesis, and chromosome segregation. Understanding the interactions among these proteins may help discover superior targets on treating bacterial infectious diseases.

Keywords FtsZ · Z-ring · Bacterial cytokinesis · Divisome · Division protein

Introduction

Most bacteria divide and proliferate through binary fission by splitting into two new daughter cells with equal sizes. A large protein complex called divisome is substantially formed at the future division site. The core component of divisome is the conserved tubulin homologue FtsZ, which regulates bacterial cytokinesis mainly with the help of a series of accessory proteins appearing in a hierarchical manner.

The Min and nucleoid occlusion (NO) system proteins inhibit FtsZ assembly in other places except midcell and localize this protein to the nascent division plane (Fig. 1) to ensure that two progeny cells are equal in size (Shih and Zheng 2013; Schumacher and Zeng 2016). FtsZ monomers then polymerize into single protofilament and form a ring-like structure (Z-ring) at midcell (Fig. 1). Zap proteins stabilize lateral interactions among FtsZ protofilaments and

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promote FtsZ assembly into an integrated Z-ring (Galli and Gerdes 2010; Durand-Heredia et al. 2011; Roach et al. 2016). This ring is also stabilized by anchor proteins FtsA and ZipA, which tether FtsZ to the inner face of the plasma membrane. Z-ring also acts as a dynamic scaffold to recruit downstream proteins with critical regulatory functions of cytokinesis, such as peptidoglycan (PG) remodeling and chromosome segregation (den Blaauwen et al. 2017).

The function of FtsZ and its accessory proteins has been clarified, but their coordinated roles must be further explored. In this review, we summarize the potential properties of FtsZ and its accessory proteins and their multiple interactions to help discover possible targets for the development of novel antimicrobials.

FtsZ localization

FtsZ shares high structural similarity to tubulin because of their ancestral homology. The structure of FtsZ consists of an N-terminal domain (NTD) and C-terminal domain (CTD) linked by central core H7 helices. A globular structure exists within the NTD, which contains the nucleotide-binding site (Ortiz et al. 2016). Following the H7 helices is the catalytic T7 loop at the base of the CTD. The CTD can also be divided into an intrinsically disordered C-terminal linker and a C-terminal conserved peptide, which play vital roles in

Fig. 1 Schematic model of Min system, nucleoid occlusion (NO) system, and Z-ring. Min system forms bipolar gradients that suppress FtsZ (red spheres) polymerization at both polar sites. As an important protein of NO system, SlmA (green) stretches along the non-terminus-containing (Ter) region of chromosome (black) to inhibit FtsZ assembly. Min and NO systems drive FtsZ monomers to assemble into Z-ring at midcell where Ter region (blue) is located
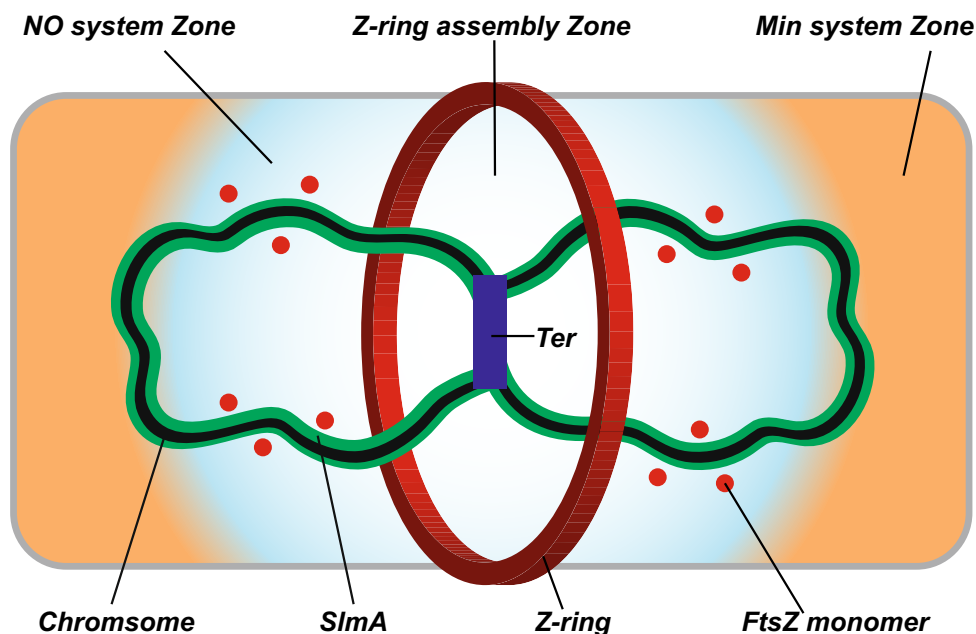
recognizing several FtsZ accessory proteins, such as FtsA, ZipA, SlmA, MinC and ZapD (Schumacher and Zeng 2016; Sundararajan and Goley 2017; Vega and Margolin 2019; Blasios et al. 2013; Huang et al. 2016). When the T7 loop of an FtsZ monomer inserts into the nucleotide-binding site of another FtsZ monomer, the GTPase-active site for GTP hydrolysis is formed at the junction of two FtsZ monomers (Matsui et al. 2014). Linear protofilaments are created when GTP binds to the globular domains of FtsZ monomers.

Min system

MinC and MinD synergistically suppress Z-ring assembly at both polar sites. Considering the roles of these proteins, MinD may function as trucks, whereas MinC serve as cargos. MinC is a critical effector protein in the Min system with two different functional domains. The NTDs of MinC can inhibit the assembly of FtsZ monomers into protofilaments, and the CTDs can weaken the association among FtsZ protofilaments (LaBreck et al. 2019; Park et al. 2018). MinD is tethered to the membrane when bound to ATP, forming a polar zone at one side of the two cell poles. MinC then attaches to ATP–MinD through its CTD, forming a MinCD complex that binds to the CTD of FtsZ (Conti et al. 2015). In this case, the concentration of MinCD is sufficiently high at one cell pole, eventually preventing a division septum from forming at the polar site. In this process, MinD may interfere with cell division by acting as a MinC propeller.

MinE is designated as a restriction factor against the MinCD complex, which guarantees that MinCD only functions at both cell poles. In *Escherichia coli* (*E. coli*), the

MinD and MinE proteins self-organize into a pole-to-pole standing wave oscillator on the membrane to facilitate division initiation at midcell (Conti et al. 2015; Park et al. 2017). At the polar zone, MinC outcompetes MinE for binding with MinD because of its strong binding activity. Thus, MinC can maintain the inhibition of FtsZ assembly at the polar site. When the polar zone covers half of the cell, MinE assembles into an E-ring, which inhibits zone extension, and moves towards the polar site. During this movement, MinE activates the ATPase activity of MinD, which then separates from the membrane. When the polar zone is completely disassembled, the E-ring also dissociates (Loose et al. 2011). Subsequently, MinC, MinD and MinE appear at the opposite pole again and conduct the same procedure. Thus, the old zone disappears at one site, and a new zone develops at the other site. This periodicity of oscillatory behaviour averages approximately 20–50 s. In brief, the MinDE complex is suggested to serve as a reaction–diffusion device that drives oscillation, whereas MinC is like a passenger in this oscillation process (Mizuuchi and Vecchiarelli 2018). Given the pole-to-pole oscillation activity of these Min proteins, the MinC concentration is regulated to be high at polar sites but low at the midcell by the MinDE complex, which ensures the assembly of FtsZ at the midcell.

NO system

In *E. coli*, the NO system is mediated by the SlmA protein, an FtsZ antagonist and DNA-binding protein. SlmA binds to the specific SlmA-binding sequences (SBSs) dispersed on the chromosome, except for the terminus-containing (Ter) region stretched along the cell's short axis (Fig. 1)

(Schumacher and Zeng 2016; Tonthat et al. 2013). Given that the Ter region is the last chromosomal region to split, only FtsZ is allowed to polymerize at the midcell. The activated SlmA–SBS complex can bind to the CTD of FtsZ without affecting its GTPase activity. However, by stimulating FtsZ–GDP formation, SlmA–SBSs promote the disassembly of preassembled FtsZ polymers (Tonthat et al. 2013; Cabre et al. 2015; Cho et al. 2011). After SlmA binds with DNA, its conformational change and its antagonistic activity are enhanced by the SBSs. In *Bacillus subtilis* (*B. subtilis*) and *Staphylococcus aureus*, the Noc proteins act as SlmA and participate in the NO system (Pang et al. 2017).

Z-ring formation and stabilization

Early in cytokinesis, FtsZ polymers migrate to the midcell and then assemble into a highly dynamic Z-ring at the division site (Fig. 1). The Z-ring may contain a cluster of short and overlapping filaments that are roughly perpendicular to the long axis of the cell (Huecas et al. 2017). These single-stranded filaments can assemble laterally and form bundles or sheets with the help of other regulatory proteins, such as ZipA, ZapA and ZapC (Guan et al. 2018; Ruiz-Martinez et al. 2018; Bhattacharya et al. 2015). Before cell division is initiated, FtsZ filaments on the inner membrane are arranged loosely and are not completely aligned. The Z-ring also exhibits a loose helical structure rather than a closed ring. However, when division begins, FtsZ filaments condense, and the Z-ring becomes a tight structure (Viola et al. 2017; Wang and Wingreen 2013).

ZapA

ZapA consists of an N-terminal globular head domain and a C-terminal coiled-coil domain in *B. subtilis*, *E. coli* and *Pseudomonas aeruginosa* (Galli and Gerdes 2010; Nogueira et al. 2015). The amino acid residue K42 within the N-terminal globular domain of ZapA is required to interact directly with residues K51 and K66, which are close to the GTP-binding site of FtsZ (Roseboom et al. 2018). The tetramer of ZapA cross-links adjacent FtsZ protofilaments and promotes Z-ring stability by inhibiting GTPase activity (Ruiz-Martinez et al. 2018; Low et al. 2004). However, GTPase activity is not affected after ZapA directly binds to FtsZ in *Caulobacter crescentus*, indicating that the interaction site of ZapA and FtsZ varies across different bacterial species (Woldemeskel et al. 2017).

ZapB

ZapB exists as a dimer that contains a 100% coiled-coil domain. High-resolution 3D reconstruction images indicate that ZapB forms a highly ordered structure concentric to the Z-ring (Soderstrom and Daley 2017). ZapB indirectly binds to FtsZ via ZapA, the N terminus of which is responsible for its interaction with ZapA. The dimers of ZapB cross-link ZapA molecules between two FtsZ protofilaments, which further stabilize Z-ring assembly (Buss et al. 2017; Galli and Gerdes 2012). ZapB directly connects with the MatP protein, which binds to the Ter region of the chromosomes. MatP, ZapB and ZapA interact with one another in a sequential order and form a MatP–ZapB–ZapA structure, which anchors the Ter region of the chromosomes to the Z-ring (Mannik et al. 2016; Espeli et al. 2012). ZapB serves as a linker to stabilize the Z-ring and coordinate chromosome segregation between the chromosome and Z-ring within this structure.

ZapC

ZapC is a small cytoplasmic monomeric protein. It does not share any sequence identity to ZapA or ZapB but exhibits similar phenotypic and functional characteristics to other Zap proteins (Durand-Heredia et al. 2011; Schumacher et al. 2016). As an early divisome protein, ZapC co-localizes with FtsZ at the midcell in an FtsZ-dependent manner. Both the N- and C-domains of ZapC possess hydrophobic cavities that serve as FtsZ-binding sites. ZapC binds close to the GTPase globular core of FtsZ with high affinity through its hydrophobic pockets. ZapC can bind and stabilize FtsZ protofilaments by inhibiting GTPase activity of full-length FtsZ polymers. Superfluous ZapC leads to lethal filamentous morphology or cell division block (Bhattacharya et al. 2015; Ortiz et al. 2015; Hale et al. 2011).

ZapD

ZapD forms a symmetrical dimeric structure that consists of an α-helical domain and β-strand domain in *E. coli*. Residues R116, R221 and R225 in ZapD are critical for forming a positively charged binding pocket, which is required for bundling FtsZ protofilaments (Roach et al. 2016; Schumacher et al. 2017). As a molecular cross-linking reagent, ZapD binds to the CTD of FtsZ with a set of ZapD arginine residues. Similar to ZapC, FtsZ is also required for ZapD to localize at the midcell and inhibit GTPase activity. ZapD is also believed to participate in the condensation of loose FtsZ filaments (Roach et al. 2016; Huang et al. 2016; Choi et al. 2016). ZapD overexpression causes the separation of FtsZ away from the midcell, leading to elongated cells.

FtsA and ZipA

In many bacterial species, FtsZ filaments are tethered to the cytoplasmic membrane by interacting with the anchor

proteins FtsA and ZipA, forming a functional cytokinetic ring. FtsA is an actin-related protein that can insert itself into the bacterial membrane through its C-terminal amphipathic helix. ZipA, a bitopic membrane protein restricted to Gammaproteobacteria, integrates into the membrane through its N-terminal transmembrane domain (Krupka et al. 2019; Pichoff and Lutkenhaus 2005). Cross-linking data show that FtsA and ZipA interact directly with each other through the exposed surface of the FtsA helix 7 (Vega and Margolin 2019). Both FtsA and ZipA bind to the conserved CTD of FtsZ.

The conformation of the FtsA protein can affect the formation of the Z-ring and the process of bacterial division. Purified *E. coli* FtsA protein can be assembled into a mini-ring structure to inhibit FtsZ bundling and ring formation (Krupka and Margolin 2018; Krupka et al. 2017). The gain-of-function variant protein FtsA* cannot be normally polymerized, and a mini-ring structure cannot be formed on the lipid monolayer, thereby suppressing the inhibition of the FtsZ bundling process. The monomeric FtsA protein can promote FtsZ bundling and recruitment of downstream division proteins into the Z-ring. In normal bacteria, ZipA can prevent the FtsA protein from polymerizing to maintain monomeric forms or oligomers (Schoenemann 2018; Pichoff et al. 2012). The *E. coli* FtsA protein can remodel the bacterial membrane structure and is essential for membrane division. Given that the C-terminal amphipathic helix of FtsA can be inserted into membrane phospholipids, FtsA protein conformation changes when FtsA binds to ATP; this change causes cell membrane deformation, which eventually leads to contraction of the middle membrane (Conti et al. 2018).

Cytokinesis after divisome assembly

The Z-ring functions as a scaffold and recruits another set of conserved proteins in a hierarchical and roughly temporal order when Z-ring is assembled at the division site with the help of the aforementioned FtsZ localization and stabilization proteins (Fig. 2). This large protein complex is defined as a divisome or division machine, which is not a static structure. FtsZ filaments within the Z-ring bind with PG synthases, treadmill on the inner face of the cell membrane and promote PG synthesis (Bisson-Filho et al. 2017; Ramirez-Diaz et al. 2018). Besides, the ring indirectly binds to chromosomes and participates in its segregation.

PG biosynthesis

PG is one of the main components of the bacterial cell wall. During cell division, PG biosynthesis occurs at the midcell mainly under the control of the downstream proteins FtsW, FtsI, FtsQLB, FtsN and FtsEX (Soderstrom et al. 2019). FtsW is an integral membrane protein that belongs to the shape, elongation, division and sporulation (SEDS) family. FtsW facilitates the transport of cytoplasmic lipid II, the PG precursor, into the existing cell wall for PG synthesis. FtsW also acts as a PG polymerase, which polymerizes lipid II into PG (Taguchi 2019; Perez et al. 2019). FtsI is a penicillin-binding protein (PBP3) with monofunctional transpeptidase activity. In *E. coli*, FtsI is required for septal PG synthesis in coordination with PBP1b, which demonstrates both transglycosylase and transpeptidase activities. FtsW directly interacts with FtsI and PBP1b, forming a PBP1b–FtsW–FtsI

Fig. 2 Overview of the apparatus of divisome. Z-ring, which is composed of FtsZ protofilaments, is anchored to the membrane by FtsA and ZipA within the divisome. Peptidoglycan (PG) synthase (PBP1b–FtsW–FtsI subcomplex) is linked to the Z-ring by FtsQLB subcomplex, dominating PG synthesis. PG synthesis will not be initiated until FtsN appears and relieves the inhibition of PG synthase by FtsQLB. Transmembrane FtsEX is responsible for septal PG hydrolysis when the cell wall needs to split. FtsKc and MatP–ZapB–ZapA bind to the Ter region and participate in chromosome segregation. The Fts family proteins are represented by capital letters
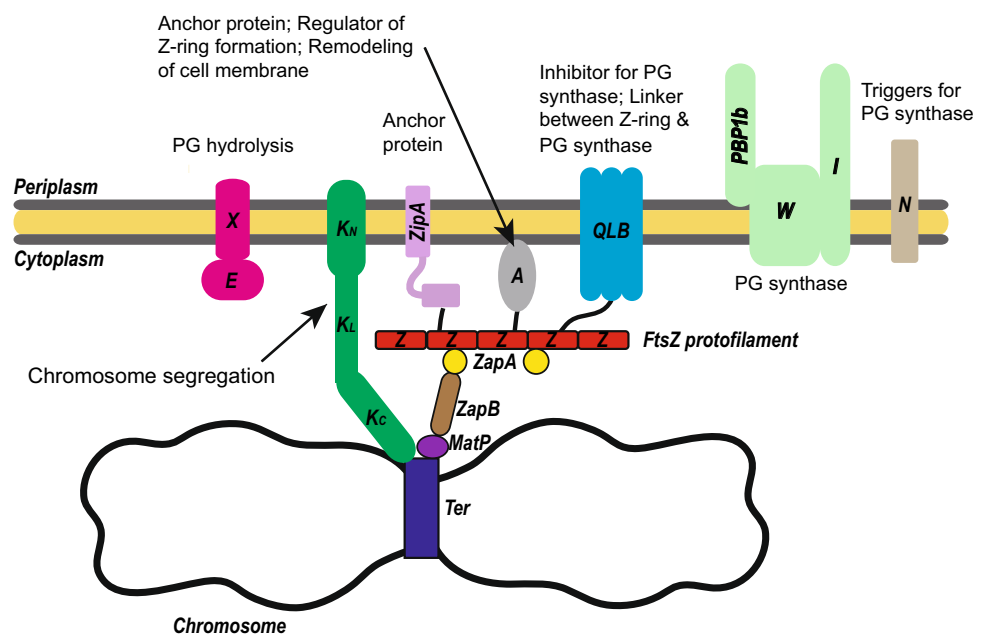
synthase subcomplex within the divisome (Boes et al. 2019; Fraipont et al. 2011; Wissel and Weiss 2004). FtsQ, FtsL and FtsB are all bitopic membrane proteins that assemble into an FtsQLB subcomplex. Without enzymatic activity, FtsQLB appears to serve as a link between the Z-ring and PG synthase (Condon et al. 2018; Kureisaite-Ciziene et al. 2018; Villanelo et al. 2011). FtsQLB also inhibits the glycosyltransferase activity of PBP1b and the transpeptidase domain of PBP3 and eventually suppresses PG synthesis. FtsN is the last protein that arrives at the division site, which is believed to trigger cell constriction. When FtsN accumulation at the midcell relieves the inhibition of PBP1b and FtsI by FtsQLB, PG synthesis starts (Weiss 2015; Liu et al. 2015; Pichoff et al. 2018).

FtsE (a cytoplasmic ATPase) and FtsX (an integral membrane protein) form a widely conserved ATP-binding cassette transporter-like complex, which functions as transmembrane regulator for septal PG hydrolysis. When PG synthesis is complete, the newly synthesized cell wall must be equally split into two daughter cells by hydrolytic enzymes called amidases (Arends et al. 2009; Yang et al. 2011). In *E. coli*, the amidases AmiA, AmiB and AmiC are responsible for cleaving bonds between stem peptides and glycan strands at the septum. To hydrolyse PG efficiently, these amidases must be activated by EnvC (for AmiA and AmiC) and by NlpD (for AmiC), both of which contain the critical LytM domains for cell separation. EnvC is recruited to the division site by FtsEX (Ercoli et al. 2015; Rued et al. 2019; Dubey and Priyadarshini 2018).

Chromosome segregation

DNA replication and chromosome segregation are crucial for bacterial reproduction. Several proteins are associated with this process, such as the aforementioned SlmA and MatP. During cytokinesis, FtsK is another key protein responsible for chromosome segregation. FtsK is a membrane-bound DNA translocase that belongs to the FtsK/SpoIIIE/Tra family. The multifunctional FtsK coordinates chromosome unlinking, segregation and cytokinesis. The structure of FtsK is mainly divided into three domains, namely the N-terminal domain (FtsK$_N$), linker domain (FtsK$_L$) and CTD (FtsK$_C$) (Grainge 2010; Berezuk et al. 2018). FtsK$_N$ is a membrane anchor domain with four transmembrane helices and is involved in septum constriction. FtsK$_L$ is poorly conserved with various length sequences among species and is required for the recruitment of FtsI. FtsK$_C$ is an ATP-dependent DNA translocase and facilitates the disassembly of chromosome dimers in coordination with the XerCD/*dif* resolvase system (Sherratt et al. 2010; Misra et al. 2018). The *dif* sites are located in the Ter region of the chromosome, which is close to the midcell. Upon stimulation by FtsK, the tyrosine recombinases XerC and XerD resolve the dimeric chromosomes into monomers at the *dif* sites. The chromosome monomers can then be segregated into daughter cells (Kennedy et al. 2008; Galli et al. 2017).

Conclusions and perspectives

Cytokinesis is important to living organisms because any aberrant fission leads to abnormal cell morphology or even cell death. Bacterial cell division is a sophisticated process, in which the emergence of proteins is strictly ordered, and the amount of proteins is precisely regulated. FtsZ plays a major role during cytokinesis by recruiting other accessory proteins to immobilize and stabilize the Z-ring and then accurately triggering and regulating bacterial cytokinesis.

The position of Z-ring needs to be limited precisely at the future division site by the Min system and NO system. The Min system proteins, namely MinC, MinD and MinE, and the NO system protein SlmA are responsible for directing FtsZ localization to midcell. FtsZ cannot function alone during bacterial cytokinesis. A diverse array of accessory proteins appears in a hierarchical manner and binds to FtsZ. Zap proteins, namely ZapA, ZapB, ZapC and ZapD, stabilize lateral interactions among FtsZ protofilaments and facilitate the Z-ring formation. The Z-ring, tethered on the inner membrane by FtsA and ZipA, acts as a dynamic scaffold for recruiting downstream proteins with regulatory functions of cytokinesis, forming a multiprotein machine termed the divisome. When the divisome matures, it dominates septum PG synthesis, chromosome segregation, and triggers the constrictive force for cell division.

This review focuses on the potential properties of FtsZ and its accessory proteins, as well as their multiple interactions. Investigating this problem may help reveal bacterial binary fission in depth and develop novel cytokinesis inhibitors in the future.

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