The bacterial cell division protein FtsZ assembles into cytoplasmic rings in fission yeast

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Keywords: FtsZ; cytokinesis; tubulin; yeast

During cytokinesis, most bacteria assemble a ring-like structure that is composed of the tubulin homolog FtsZ. The mechanisms regulating assembly and organization of FtsZ molecules into rings are not fully understood. Here, we express bacterial FtsZ in the fission yeast Schizosaccharomyces pombe and find that FtsZ filaments assemble into cytoplasmic rings. Investigation of the Escherichia coli FtsZ revealed that ring assembly occurred by a process of closure and/or spooling of linear bundles. We conclude that FtsZ rings can assemble in the absence of all other bacterial cytokinetic proteins and that the process might involve hydrolysis of FtsZ-bound GTP and lateral associations between FtsZ filaments.

Received February 7, 2008; revised version accepted May 5, 2008.

Results and Discussion

Previous studies have shown that EcFtsZ expressed in fission yeast assembles into ring-like structures and cables [Fig. 1A, panels i, ii; Srinivasan et al. 2007], which are largely abolished upon coexpression of SulA (Srinivasan et al. 2007), a known inhibitor of FtsZ polymerization in bacterial cells. These spot-like structures were very similar in appearance to the spots observed when FtsZ was expressed in mammalian cells by Cabral and coworkers [Yu et al. 1999]. In addition, as in fission yeast cells, FtsZ expressed in mammalian cells was also observed to form a filamentous network interconnecting the dots [Yu et al. 1999]. Fluorescence recovery after photobleaching experiments (FRAP) revealed that FtsZ turns over with a recovery half-time \( t_{1/2} \) of \( \sim 11 \text{ sec} \) \( (n = 22) \), which is very close to the FtsZ turnover rates determined in bacterial cells [Anderson et al. 2004]. FRAP was carried out on both spot- and cable-like structures of EcFtsZ. Both the spots and cables showed similar turnover rates of 10.82 ± 4.5 sec \( (n = 7) \) and 10.88 ± 4.2 sec \( (n = 15) \), respectively [Fig. 1B, C; Supplemental Table 1]. Based on these two criteria, we concluded that FtsZ polymerization in fission yeast occurred by mechanisms similar to those in bacterial cells.

A closer examination of the polymeric structures formed by EcFtsZ using 3D confocal microscopy revealed that the FtsZ patches were indeed ring-like structures with diameters of 0.51 ± 0.04 \( \mu \text{m} \), \( n = 100 \) [Figs. 2A–C, 3H]. EcFtsZ also assembled into linear cables, and in many instances, cables appeared to be connected with...
myces cerevisiae. E. coli FtsZ formed cables (panel i) and spots or patches (panel ii). [B–G] Fluorescence recovery after photobleaching (FRAP) of the various FtsZ-GFP-containing structures. [B] EcFtsZ ring. (C) EcFtsZ cable. (D) MtFtsZ ring. (E) MtFtsZ cable. (F) EcFtsZQ47K ring. (G) EcFtsZQ47K cable. Fission yeast cultures expressing FtsZ-GFP were mounted onto agarose slides, and a Zeiss Meta 510 confocal microscope was used for the FRAP experiments. The FtsZ-GFP structures were bleached at 0 sec (using 100% laser power and 100 iterations), and the recovery of the fluorescence was followed by time-lapse imaging. Images were obtained at 4-sec intervals in the case of wild-type FtsZ and 30-sec intervals for the FtsZQ47K mutant. Quantification of the fluorescence recovery of a representative experiment is shown in the adjoining graphs. Normalized fluorescence intensities were used for graphical representations. The $t_{1/2}$ values mentioned in the text were obtained by fitting the fluorescence recovery curves to a single exponential curve $F(t) = C \cdot (1 - e^{-kt})$ and calculated from $t_{1/2} = \ln(2)/k$. (EcFtsZ) E. coli FtsZ; (MtFtsZ) M. tuberculosis FtsZ. Bar: 2 µm (except in the case of F), 1 µm.

Figure 2. FtsZ assembles into rings in fission yeast. (A–C) EcFtsZ-GFP assembled into ring-like structures in fission yeast. The medium-strength nmt42 promoter was used for the expression of FtsZ-GFP in S. pombe. Cultures were grown for 16–20 h at 30°C in the absence of thiamine to allow the expression of the proteins. Panel i in A–C show the boxed region in panel i in A–C, respectively. (C, panel iii) The white ring labels the region used to measure the diameter of the rings and labels the center of the outer and inner diameters of the fluorescence of the FtsZ ring. (D) Assembly of EcFtsZ into cable-like structures. The inset shows a ring connected to a cable. (E) Assembly of rings and cables upon expression of EcFtsZ-GFP in budding yeast. Expression of FtsZ was achieved by the addition of 1% galactose for 3 h. (F, panels i,ii) Expression of MtFtsZ-GFP in fission yeast showing both rings (panel i) and cable (panel ii). The inset shows the assembly of FtsZ into a ring-like structure. (G, panels i,ii) Expression of XoFtsZ-GFP in fission yeast. Panel i shows cells with FtsZ rings and panel ii shows a cell with both FtsZ rings and cables. The inset shows the assembly of FtsZ into a ring-like structure. (H) Ring-like structures of FtsZ are formed from the FtsZ cables. Time-lapse images showing the formation of FtsZ ring-like structures from the cables. Cells were grown in minimal medium without thiamine for 16 h and were mounted onto agarose pads and imaged using a confocal microscope. Images are shown at 3-min intervals. Bars: except for those in the insets, 2 µm; insets, 1 µm.

MtFtsZ has been reported to display a reduced GTPase activity (White et al. 2000) and a concomitant reduction in the rate of filament turnover in vivo (Chen et al. 2007). Consistently, rings and cables of MtFtsZ displayed a significant increase in $t_{1/2}$ in FRAP experiments [Fig. 1D,E; Supplemental Table 1], suggesting that MtFtsZ was potentially using similar mechanisms of assembly and polymerization in fission yeast. FtsZ from the Gram-negative plant pathogen Xanthomonas oryzae [XoFtsZ] was also able to assemble into rings and cables upon expression in fission yeast [Fig. 2G, panels i,ii]. We conclude that FtsZ polymers have an intrinsic ability to assemble into cytoplasmic ring-like structures upon expression in the yeasts S. pombe and S. cerevisiae.

We then imaged fission yeast cells expressing EcFtsZ to determine the relationship, if any, between FtsZ rings and FtsZ cables. Time-lapse microscopy revealed that the rings were formed from the linear cables (Fig. 2H; Supplemental Movie 1). However, due to the excessive number of cables and rings and the dynamic nature of these structures, it was difficult to visualize the steps leading to assembly of FtsZ rings in fission yeast.

Since the time-lapse studies were typically performed by transfer of cells grown in liquid medium to agar containing solid pads, it was possible that the act of transferring or placement on the solid surface itself might initiate ring assembly. However, since FtsZ spots and rings, giving a lariat-like appearance (Fig. 2D). In order to see whether assembly of a FtsZ ring-like structure was peculiar to expression in Schizosaccharomyces pombe, we expressed EcFtsZ in another host, Saccharomyces cerevisiae. EcFtsZ formed cables and rings with a diameter of 0.48 ± 0.042 µm, $n = 100$, in this yeast as well (Fig. 2E), showing that assembly into ring-like structures was an intrinsic property of FtsZ polymers. We then asked whether FtsZ from other bacterial species also showed similar behavior. To this end, we first expressed FtsZ from the Gram-positive human pathogen Mycobacterium tuberculosis [MtFtsZ]. MtFtsZ assembled into spots, rings, and cables upon expression in fission yeast [Fig. 2F, panels i,ii, and insets therein], although the rings were less clear in these cases compared with those observed upon expression of EcFtsZ in fission yeast.
the GTPase activity of which has 1.05 GTP/FtsZ (Redick et al. 2005). However, 1.19 GTP/FtsZ compared with that of wild-type FtsZ, lysis mutant FtsZQ47K revealed that the over of FtsZ filaments (Anderson et al. 2004; Chen and consistent with the idea that GTP hydrolysis regulates turn-

ation of fewer FtsZQ47K rings per cell. FtsZQ47K also those formed by wild-type FtsZ. In addition, expression 3C,E,F) that were, curiously, consistently larger than those formed by wild-type FtsZ. In addition, expression of FtsZQ47K in fission yeast led consistently to the formation of fewer FtsZQ47K rings per cell. FtsZQ47K also assembled into linear bundles and cables [Fig. 3D]. Consistent with the idea that GTP hydrolysis regulates turnover of FtsZ filaments [Anderson et al. 2004; Chen and Erickson 2005], ERAP experiments with the slow-hydro-

lysis mutant FtsZQ47K revealed that the $\frac{1}{2}$ of FtsZQ47K cables and rings was significantly higher [Fig. 1F,G; Supplemental Table 1]. It is noteworthy that minimal fluorescence recovery was detected upon photo bleach-

Figure 3. GTP binding and GTP hydrolysis are crucial for assembly of FtsZ into multiple rings in fission yeast. [A] A GTP-binding mutant (FtsZF182S) fails to assemble cables, spots, and rings in fission yeast and exhibits only diffuse cytoplasmic fluorescence. [B] FtsZG105S (ftsZ84), a well-characterized temperature sensitive allele of FtsZ forms only cable-like structures. (C,D) Assembly of FtsZQ47K-GFP into rings (C) and cables (D) in fission yeast. [E] Linear filaments seemed to connect with the FtsZQ47K-GFP ring structures in some cells. [F] Magnified images of the FtsZQ47K rings. (G) The white ring marks the region used to measure the diameter of the rings and marks the center of the outer and inner diameters of the fluorescence of the FtsZ ring. [H] Quantification of the ring diameters of FtsZ-GFP and FtsZQ47K-GFP expressed in fission and budding yeasts. The diameters of 100 rings were measured in each case. The error bars represent the standard deviation from the mean. Bars: F,G, 1 µm; others, 2 µm.

rings are observed in cells grown and fixed in liquid medium [data not shown], it is likely that assembly of FtsZ rings starting from cables might represent a property of the FtsZ polymer, rather than an artifact of the experimental procedure used.

We then expressed several previously characterized EcFtsZ mutants [Redick et al. 2005] in fission yeast and found that abolishing GTP binding [FtsZF182S] completely abrogated polymer formation of FtsZ and gave rise to only diffuse cytoplasmic fluorescence [Fig. 3A]. This experiment suggested that GTP binding was important for assembly of FtsZ cables. FtsZG105S, the product of a well-characterized conditional lethal allele of FtsZ [ftsZ84] [Lutkenhaus et al. 1980; RayChaudhuri and Park 1992, Redick et al. 2005], was able to assemble into cables, but was unable to organize into rings [Fig. 3B].

Interestingly, expression in fission yeast of the FtsZQ47K mutant provided novel insight into the mechanism of FtsZ ring assembly. Previous studies have shown that EcFtsZQ47K mutant has a GTP-binding activity of 1.15 GTP/FtsZ compared with that of wild-type FtsZ, which has 1.05 GTP/FtsZ [Redick et al. 2005]. However, the GTPase activity of EcFtsZQ47K is only 0.5/FtsZ per minute as compared with that of 14.5/FtsZ per minute of the wild-type FtsZ [Redick et al. 2005]. FtsZQ47K expressed in fission yeast formed ring-like structures [Fig. 3C,E,F] that were, curiously, consistently larger than those formed by wild-type FtsZ.

In addition, expression of FtsZQ47K in fission yeast led consistently to the formation of fewer FtsZQ47K rings per cell. FtsZQ47K also assembled into linear bundles and cables [Fig. 3D]. Consistent with the idea that GTP hydrolysis regulates turnover of FtsZ filaments [Anderson et al. 2004; Chen and Erickson 2005], FRAP experiments with the slow-hydro-

lysis mutant FtsZQ47K revealed that the $\frac{1}{2}$ of FtsZQ47K cables and rings was significantly higher [Fig. 1F,G; Supplemental Table 1]. It is noteworthy that minimal fluorescence recovery was detected upon photo bleach-

ing of FtsZQ47K rings [Fig. 1F,G; Supplemental Table S1]. The diameters of the rings formed by the EcFtsZQ47K averaged 0.63 ± 0.05 µm [Fig. 3H], with maximum diameters reaching 0.77 µm. EcFtsZQ47K when expressed in S. cerevisiae also assembled similar structures [Supplemental Fig. 1A,B] with an average diameter of 0.71 ± 0.1 µm [Fig. 3H].

Interestingly, in many cells, ring-like structures appeared to be linked to a linear filament, again giving rise to a lariat-like appearance [Fig. 3E]. Thus, we considered two scenarios. First, it was possible that FtsZ ring unraveling led to the presence of a cable of FtsZ connected to a ring structure. Alternatively, it was possible that a ring of FtsZ might assemble from cable-like FtsZ structures. To distinguish between these possibilities, we imaged cells containing cables and those containing rings. Fully formed rings of EcFtsZQ47K did not unravel into cables in 15 cells imaged, each followed for up to 2 h [data not shown]. Strikingly, however, linear filaments of FtsZQ47K were found to organize into FtsZQ47K rings. As shown in Figure 4A and Supplemental Movie 4, the linear FtsZQ47K filaments formed lariat-like structures and subsequently organized into a ring structure in what appeared to be a spooling-like mechanism. Photobleaching experiments [Fig. 4B, Supplemental Fig. 1C; Supplemental Movies 3, 4] wherein a part of the ring was bleached and the recovery of fluorescence was followed by time-lapse microscopy suggested the assembly of the filament tails into the ring. Additional experiments in which a part of the linear bundle that was associated with the ring was photobleached showed that the bleach mark moved toward the ring [Fig. 4C], further providing evidence that the organization of the FtsZQ47K bundles into rings might involve a spooling-like mechanism.

All the studies performed with FtsZQ47K involved the only available reliably regulatable fission yeast promoter [nmt1], which requires ~16 h for full induction. As a result, we were unable to trace the events leading to the formation of FtsZQ47K bundles, although we were able to image the assembly of FtsZQ47K rings from linear bundles. Recently, Bahler and colleagues [Watt et al. 2008] have described a uracil-regulatable promoter [urg1], which allows a faster induction. We therefore made a plasmid under the urg1 promoter control that allowed expression of FtsZQ47K. Upon induction of gene expression with uracil, FtsZQ47K assembled into multiple short filaments [Fig. 5A, marked by white arrowheads], which appeared to either become ligated or laterally bundled leading to the formation of a thick bundle [Fig. 5A,B, Supplemental Movies 5, 6]. As shown in previous examples, spooling of these bundles led to the formation of FtsZQ47K rings [Fig. 5A, Supplemental Movie 5]. We also found examples in which FtsZQ47K assembled short cables that underwent closure directly leading to the formation of FtsZQ47K rings [Fig. 5B, Supplemental Movie 6, marked by arrows]. The intensity of GFP fluorescence in these FtsZQ47K rings increased with time. It is currently unclear if this increase in fluorescence intensity reflects direct association of shorter protofilaments of FtsZQ47K with the pre-

formed ring or if it arises from spooling of weakly fluorescent tails. The fact that FtsZQ47K assembled first into cables and then into rings was also established by quantification over time of the various structures present in fission yeast cells expressing FtsZQ47K [Supplemental Fig. 2B].
et al. 2001; Stricker and Erickson 2003; Redick et al. studies have identified several lateral contact mutants FtsZ protofilaments. Earlier biochemical and in vivo of FtsZ) might also involve lateral associations between spiral (generated by closure and/or spooling of a long cable linear bundles. We reasoned that the compaction of a ther by closure of linear cables or by apparent spooling of a cable of FtsZ into the ring. A part of the filament attached to the ring structure (at 22 min) and the subsequent disappearance (probably by spooling) of the filament to assemble the ring structure. (B) Spool- ing-like behavior of the filament into the ring structure shown by fluorescence recovery after photobleaching (FRAP). The movement of the unbleached region of the ring is seen in the time-lapse images. The cultures were grown for 16–20 h at 24°C in minimal medium without thiamine and mounted onto agarose slides for time-lapse microscopy and FRAP experiments. (C) Apparent spooling of linear cable of FtsZ into the ring. A part of the filament attached to the ring was photobleached. The white rectangle shows the bleached region. The bleached region was seen to move toward the rings, implying a spooling-like behavior. Bars: B, 1 µm; others, 2 µm.

Our studies showed that FtsZQ47K rings assemble ei- ther by closure of linear cables or by apparent spooling of linear bundles. We reasoned that the compaction of a spiral [generated by closure and/or spooling of a long cable of FtsZ] might also involve lateral associations between FtsZ protofilaments. Earlier biochemical and in vivo studies have identified several lateral contact mutants that are known to be essential for FtsZ ring assembly [Lu et al. 2001; Stricker and Erickson 2003; Redick et al. 2005]. We therefore created a double mutant in EcFtsZ, FtsZQ47KD86K (the positions of which are shown in Supplemental Fig. 2A), to test whether lateral contacts were required for FtsZ ring compaction. EcFtsZQ47KD86K formed long linear cables and occasionally large closed loops that covered the entire circumference of the fission yeast cell [Fig. 4C, panels i,ii], but were never found to form rings of 0.6–0.7 µm in diameter.

In summary, we show that E. coli FtsZ assembles into rings of diameter 0.51 ± 0.04 µm in fission yeast cells. Although it is clear that the bacterial cell diameter establishes the diameter of the FtsZ ring, it is curious that the diameter of FtsZ rings expressed in fission yeast is roughly similar to the cell diameter of several bacterial species. Interestingly, several studies using electron microscopy and atomic force microscopy approaches have demonstrated the ability of FtsZ to assemble into rings [Chen et al. 2005; Gonzalez et al. 2005; Mingorance et al. 2005; Michie et al. 2006]. These rings have been predominantly reported to be composed of a single protofilament. Although we conclusively established that FtsZ can assemble into cytosolic rings in fission yeast, the numbers of overlapping protofilaments that make up this ring structure are currently unknown.

Our studies also established that FtsZ can assemble into rings in the absence of all other known bacterial proteins implicated in cytokinesis. Our conclusions are consistent with the recent study by Osawa et al. 2008. These authors using purified FtsZ [with a membrane tether] and reconstituted liposomes have shown that FtsZ can organize into rings in the absence of all other bacterial cytoskeletal proteins [Osawa et al. 2008]. Finally, our studies begin to provide a mechanism for assembly of FtsZ rings starting from protofilaments. As in the case of tubulin, GTP hydrolysis by FtsZ has been shown to generate curvature in FtsZ protofilaments [Lu et al. 2000]. Thus, it is likely that FtsZ ring assembly might be mediated by nucleotide hydrolysis coupled with further lateral associations among the protofilaments. This idea...
is in agreement with the recent structural studies, which have shown that lateral associations play an important role in the determination of the curvature of FtsZ protofilaments (Oliva et al. 2007; Horger et al. 2008). Our results are also consistent with imaging studies in E. coli, B. subtilis, and Streptomyces coelicolor (Addinall and Lutkenhaus 1996, Schwedock et al. 1997, Ben-Yehuda and Losick 2002, Thanedar and Margolin 2004; Grantcharova et al. 2005). In all these bacteria, FtsZ rings at the midcell site as well as at the cell ends, during sporulation, have been shown to involve compaction of spiral structures, although the biochemical basis of this compaction was unclear. Our studies might thus provide a biochemical framework to understand FtsZ ring assembly in bacteria. We also note that although FtsZ rings can assemble in fission yeast cells, we did not observe any of these to undergo constriction. Future studies should test whether coexpression of FtsZ with other known bacterial cytokinesis proteins can stimulate FtsZ ring constriction in fission yeast cells.

Materials and methods

Strains, plasmids, and constructs

Transformation of S. pombe strain MY192 (ΔURA4 ura4-D18; lab collection) with the various plasmids was carried out using the lithium acetate method (Keeney and Boeke 1994). FtsZ-GFP and FtsZ mutant versions were expressed from the medium-strength ura4-D2 promoter (Basi et al. 1993). FtsZQ47K was also expressed under control of the ura1 promoter. The construction of the plasmids is described in the Supplemental Material.

Expression of GFP fusion proteins and fluorescence microscopy

FtsZ-GFP and its mutant versions (under the ura4-D2 promoter) were expressed in S. pombe by growing the transformed cultures in the absence of thiamine for 16–20 h at 24°C or 32°C. Induction of expression of FtsZQ47K-GFP under the ura1-inducible ura1 promoter was carried out by adding 0.5 mg/mL uracil. For time-lapse imaging, the cells were mounted onto agarose slides, and images were acquired at fixed time intervals. In the case of the ura1 promoter, cultures were induced with uracil for 15 min and then mounted onto the agarose slides, which also contained uracil. A Zeiss Meta 510 confocal microscope, with an apochromat 100×/1.3 NA oil-immersion objective was used for acquiring images, and for time-lapse imaging and fluorescence recovery after photobleaching experiments. Photobleaching was carried out with 100% laser power and with 100–150 iterations. Z-stack images were acquired at fixed intervals with a Z-depth of 0.2 or 0.3 μm. An unbleached region in the same field/cell was used to correct for acquisition bleach. Ring diameters and fluorescence recovery were analyzed using Zeiss 3D for LSM software. Other image manipulations were done using ImageJ [http://rsb.info.nih.gov/ij/] and Adobe Photoshop. The FRAP data were fit to a single exponential equation F(t) = C1 – e^-t/τ and recovery half-times (τ/2) were calculated as ln[2]/(E) (Anderson et al. 2004; Sprague et al. 2004). MATLAB and the open source software R [http://www.R-project.org/] were used for curve fitting by the method of nonlinear least squares regression analysis.

Acknowledgments

We thank Huang Yingyi for the construction of MtrftsZ-gfp plasmid and the uracil inducible vector; Zhang Wei for the construction of the budding yeast expression construct of FtsZ-GFP; and Anup Padmanabhan, Uttamam Surana, Umesh Varshney, and Seshadri Anuradha for other agents/help. We thank Rahul Thadani, Arumugam Madhumular, and Srikant Parameswaran for computational help. We thank all members of the Cell Division Laboratory for discussions and/or critical reading of the manuscript. R.S. and M.M. acknowledge the Singapore Millennium Foundation for a fellowship. This work was funded by research funds from the Temasek Life Sciences Laboratory.

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*Genes Dev.* 2008, 22:
Access the most recent version at doi:10.1101/gad.1660908

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