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Do the divisome and elongasome share a common evolutionary past?

Piotr Szwedziak and Jan Löwe

The divisome and elongasome are bacterial protein complexes responsible for peptidoglycan (PG) synthesis during cell division and elongation, respectively. We review several lines of evidence, arguing for a shared evolutionary past of the divisome and elongasome. Both integrate closely related penicillin-binding proteins (PBPs) for PG synthesis, use proteins of the RodA/FtsW (SEDS, shape, elongation, division and sporulation) family for Lipid II export and interact with MraY/Mur proteins for Lipid II synthesis. It was recently shown that the actin-like protein FtsA of the divisome polymerises on membranes, adding another parallel, since membrane-associated filaments of the bacterial actin MreB guide the elongasome. Given these similarities, it seems plausible to conclude that the elongasome is a modified version of the divisome, without the membrane-constricting FtsZ-ring and its associated machinery on the inside.

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Introduction

Bacterial morphogenesis and cell division (cytokinesis) are closely linked with peptidoglycan (PG) metabolism. The shape of bacteria depends on the shape of their PG layer — a meshwork made of glycan strands linked by peptide bridges [1]. Two inner membrane- and periplasm-spanning protein complexes govern PG synthesis patterns. The divisome (Figure 1), with varying subunit completeness, is nearly ubiquitous in bacteria, where it is responsible for cell division, specifically inner and outer membrane constriction and PG synthesis at the division site, which produces two new cell poles [2,3]. The elongasome (Figure 2), by contrast, is present only in non-spherical bacteria and directs lateral insertion of PG along the long axis of the cell, thus allowing cylindrical growth [4]. Bacteria first synthesise in the cytoplasm Lipid II, which carries the disaccharide-peptide building block for the polymerisation reaction. Lipid II is then flipped across the inner membrane into the periplasm. PG polymerisation is facilitated by penicillin-binding proteins (PBPs), which are DD-transpeptidases, DD-endopeptidases or DD-carboxypeptidases, and some display transglycosylase activity as well. Hydrolases are needed for breaking bonds in order to provide plasticity. Furthermore, dynamics of the inner membrane and PG layer have to be coordinated with the outer membrane in Gram-negative organisms.

Here we discuss that the divisome and elongasome share features and subunits, arguing that they might have descended from a common evolutionary ancestor.

Divisome and elongasome directly interact with the same Lipid II synthesis machinery

Lipid II, the building block of peptidoglycan is synthesised in the cytoplasm by a single cascade of enzymes: MurA-F, MraY and MurG [5]. Instead of just using the membrane-bound pool of freshly synthesised Lipid II, both divisome and elongasome have been found to interact with the same integral membrane protein MraY (producing Lipid I) and membrane-associated MurG [6]. For the elongasome, more specifically, MurF, G and MraY have been found to interact with MreB [7,8].

Lipid II translocation facilitated by related SEDS proteins

Given that Lipid II synthesis occurs in the cytoplasm and PG synthesis in the periplasm, the divisome and elongasome each contain a protein that translocates Lipid II building blocks across the cytoplasmic membrane: FtsW for the divisome and RodA for the elongasome. At the sequence level, FtsW and RodA are clearly related with over 49% amino acid similarity in *E. coli* (as calculated by a global EMBOSS NEEDLE calculation) and generally have the same size [9]. These integral transmembrane proteins are members of the SEDS (shape, elongation, division and sporulation) family of proteins. FtsW, and most likely RodA contain 10 trans-membrane helices and both termini are located in the cytoplasm [10]. A recent biochemical study of FtsW [11•] has provided an *in vitro* model for translocation, which is thought to involve flipping Lipid II to the periplasmic side. Apart from the assumption that it functions in a similar way to FtsW, not much is known about RodA, except that it is closely associated with the MreBCD proteins [8,12].

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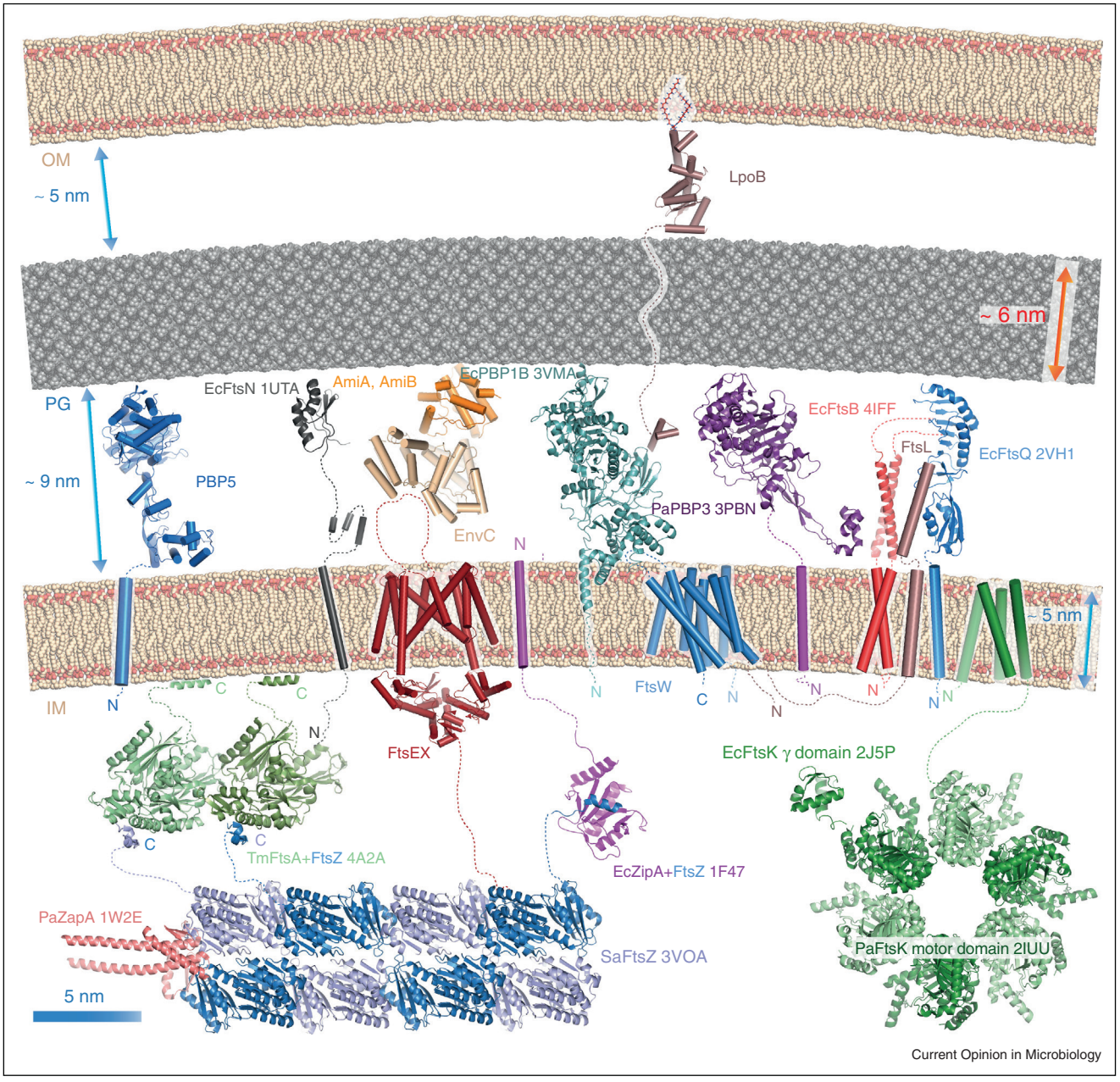
Figure 1



To-scale overview of the divisome. Proteins with known 3D structure are shown in cartoon representation with PDB identifiers indicated. Dotted lines and schematic representations are used for proteins or fragments of proteins with no structural data available. For clarity, NlpD/AmiC are not shown and not all interactions are depicted since they cannot all be represented in two dimensions and it is not currently known how the various proteins interact through their transmembrane segments. All distances and dimensions are approximately to scale (including membrane curvature), except the distance of FtsZ to the cytoplasmic membrane, which is almost certainly larger in *E. coli*, given the linker length between the body of FtsZ and the C-terminal residues that bind FtsA. Structures shown: 1W2E — [55], 3VOA — [56•], 4A2A — [26••], 1F47 — [57], 2IUS — [58], 2J5P — [59], 1UTA — [60], 3VMA — [18], 3PBN — [61], 4IFF — [62] and 2VH1 — [63].

Divisome and elongasome interact with related or even identical PBPs

Regardless if it is orchestrated by the divisome during cell division or by the elongasome during cell elongation, the next step of PG synthesis after Lipid II translocation is the polymerisation of disaccharide subunits into glycan strands in the periplasm by penicillin binding proteins (PBPs). PBPs may only have transpeptidase activity (TP, in *E. coli* class B PBPs: PBP2, PBP3) or both TP and transglycosylase activity (TG, in *E. coli* class A PBPs:

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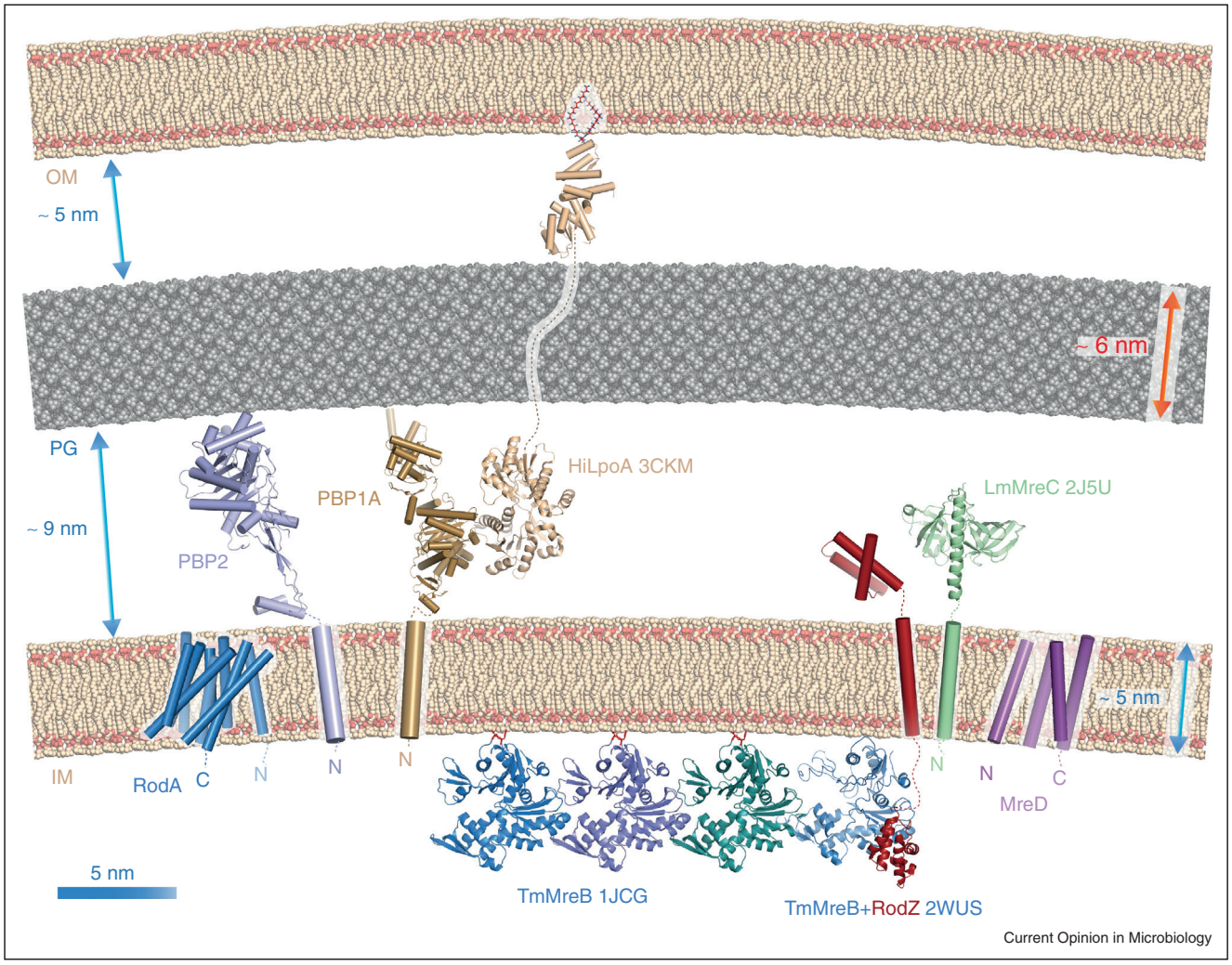
Figure 2



To-scale overview of the elongasome. Same symbols and restrictions as for Figure 1. Structures shown: 1JCG — [20], 2WUS — [64], 2J5U — [65] and 3CKM — [66].

PBP1A-C). Only some of the PBPs are specific to either the divisome or elongasome [13]. Importantly, all large PBPs are related by sequence, for example 41% amino acid similarity between PBP2 and 3 (FtsI) or 32% similarity between PBP1A and B, all from *E. coli*. In *E. coli*, both divisome and elongasome contain PBP2 and PBP5, a carboxypeptidase class C PBP [14,15•]. FtsW of the divisome interacts directly with PBP3 (FtsI), which is specific for division [16]. In terms of PBPs, perhaps the strongest evidence for our theory of a common ancestor is that both the divisome and the elongasome contain one of the closely related class A bifunctional PBPs: the divisome PBP1B and the elongasome PBP1A [17]. High-resolution crystal structures of synthetic class A PBPs are available, highlighting expected molecular similarities of various enzymes [18,19]. For instance, the structure of PBP2 from *Staphylococcus aureus* (note: *Sa* PBP numbering is different) [19] (PDB 3DWK) revealed two distinct domains: the N-terminal membrane-bound TG domain and the C-terminal periplasmic TP domain. The two active sites lie ~70 Å apart. In the structure of *E. coli* PBP1B (PDB 3VMA) [18], for example, the TG and TP domains are closely related to PBP2 from *S. aureus* in fold and adopt a similar elongated shape. They may bridge the 9 nm distance between the cytoplasmic membrane and the PG layer. Synthetic PBPs are anchored in the membrane by single transmembrane helices, but the periplasmic domain of class A PBPs still exhibits significant hydrophobicity, mainly due to the membrane attachment sites of the TG domain, indicating that it may also interact closely with other proteins of the divisome and elongasome [18]. Hence the closely related PBP enzymes can be considered integral parts of the divisome and elongasome, adding to their similarity.

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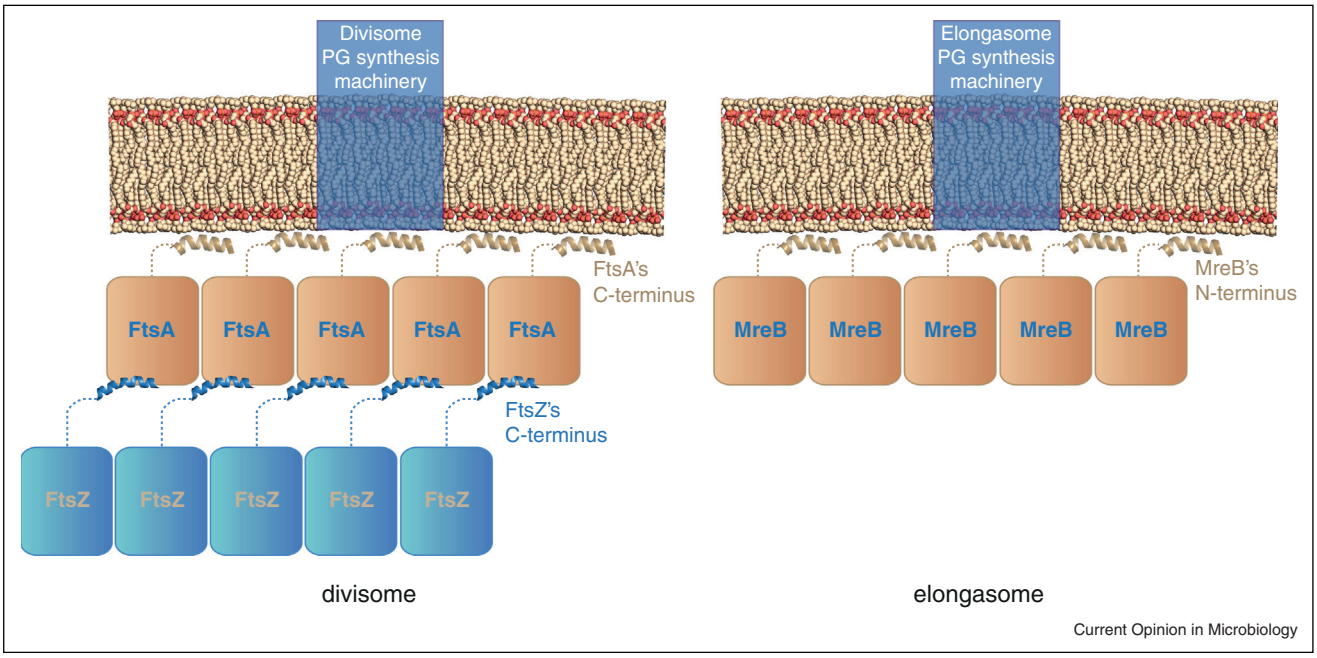
Figure 3



Hypothesis: FtsA of the divisome is functionally equivalent to MreB of the elongasome. Both proteins are actin-like, polymerise into actin-like protofilaments, bind the cytoplasmic membrane through amphipathic helices (N-terminal for MreB, C-terminal for FtsA) and interact with the cytoplasmic surface of the divisome/elongasome. The tubulin homologue FtsZ polymerises into a ring that is separated from the divisome through a long flexible linker and the Z-ring organises the divisome into a small band around the division site through interaction with FtsA. No such organiser exists for the elongasome, leading to cylindrical growth, rather than invagination and cell division.

Equivalence between FtsA of the divisome and MreB of the elongasome?

Adding to our list of parallels between the divisome and elongasome, it now appears that both the divisome and elongasome, at least in some organisms, contain membrane-bound, actin-like filaments (Figure 3). More than a decade ago it was demonstrated that MreB, being part of the elongasome, has the canonical actin fold and assembles into actin-like protofilaments [20]. Later it was appreciated that MreB binds directly to membranes via a hydrophobic loop and in Gram-negative organisms also by an N-terminal amphipathic helix [21••]. The monomeric FtsA structure was solved more than a decade ago [22] and surprisingly, it displayed deviant subdomain architecture with actin's subdomain 1B replaced by a similarly sized domain 1C at the opposite end of the molecule. Only later it was shown that *E. coli* FtsA contains a C-terminal amphipathic helix and binds to the inner membrane [23]. And recently it was demonstrated unambiguously that FtsA polymerises into canonical actin-like protofilaments, despite the altered subdomain architecture [24•,25,26••]. Given the fold and properties of the two actin-related proteins FtsA and MreB, we propose that they perform similar functions for the divisome and elongasome, respectively (Figure 3). FtsA is thought to be the main membrane anchor for tubulin-like FtsZ in *E. coli* [27] and is also involved in the assembly of downstream divisome proteins [28]. Strikingly, the cytoplasmic part of late divisome protein FtsN seems to bind in a cleft between the body of FtsA and its subdomain 1C [29••]. This is reminiscent of the PilM–PilN interaction, PilM being a structural homologue of FtsA involved in pilus assembly [30•] (PDB 2YCH). Taken together, it may suggest that FtsA's activity is regulated by FtsN and we speculate that a similar role may be exerted by the cytoplasmic tail of MreC in the elongasome, since the MreB-MreC interaction has been reported [31]. It is interesting to note that MreB's movement in cells seems to be driven or controlled by the PBPs in the periplasm [32•,33•,34•], requiring a feedback mechanism that most likely involves MreC and/or MreD. The newly discovered parallel between the two actins, FtsA and MreB, indicates that FtsZ, which forms a ring at the division site is probably a functional alteration required only for division (Figure 3). The Z-ring organises synthesis and remodelling of PG in a small band at midcell that coincides with membrane constriction, which may be facilitated by FtsZ alone or both FtsZ and FtsA [35,36••]. By contrast, the elongasome does its work all round the straight section of the cell. FtsZ, being solely cytoplasmic, interacts with membrane-tethered FtsA through a long flexible linker. Hence FtsZ, and some FtsZ-interacting proteins (for example ZapABC) are some distance away from the membrane (and the

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divisome) and should be considered functionally separate [28].

Beyond parallels

Given the likely evolutionary distance between the divisome and elongasome, it is not surprising that there are differences, additions and deletions beyond the conserved core as discussed above. The divisome currently contains more subunits that do not seem to have parallels in the elongasome. Amongst these are FtsQLB [37], Tol-Pal [38] and FtsEX [39,40•] in *E. coli*. FtsQ is very conserved but currently no function is known apart from many interactions with other divisome proteins. FtsEX is an ABC transporter that uses ATP hydrolysis to induce conformational changes in EnvC, the most important activator of amidases in the periplasm. The Tol-Pal complex is essential for outer membrane dynamics during division [38]. PG remodelling requires the breaking of amide bonds between PG strands in order to be able to add or remove material. Specialised hydrolytic enzymes (AmiA-C) reside in the periplasm and they are part of the divisome since they require tight regulation [41]. The DL-endopeptidase LytE is part of the *Bacillus subtilis* elongasome [42] but it is perhaps a bit early to conclude similarities since not much work has been published in this area. Two recent reports [43••,44••] indicate that PBP action is regulated from the outside of the cell: PBP1A of the elongasome is regulated externally by its outer membrane cognate lipoprotein activator LpoA. This interaction is affected by the sacculus thickness since LpoA has to reach through the ~6 nm PG layer and in addition ~5 nm between the PG and the outer membrane, as measured in *E. coli*, to physically contact PBP1A and this is only possible in the regions where the most and largest pores in the PG occur [45]. A similar, LpoB-orchestrated regulatory mechanism of PBP1B exists in the divisome. However, in the context of possible similarities between divisome and elongasome it is important to note that LpoA and LpoB are not related by sequence and LpoA and LpoB are restricted to γ-proteobacteria only. This could mean that LpoA and B are niche-related, late additions to the divisome and elongasome. Pushing speculation to the limit, it is possible to detect weak amino acid sequence similarity between the N-terminal domain of FtsK in the divisome and MreD in the elongasome, when large alignments are constructed (data not shown). The C-terminal domain of FtsK is a DNA translocase [46] but the N-terminal domain is a 4-helix transmembrane protein of unknown function. MreD has currently no known function, but is of very similar size to FtsK-N and is predicted to contain four transmembrane helices.

What has been the evolutionary path?

Given that cell division is a very basic requirement of life and being a sphere might be considered the default state of primordial bacteria, one might speculate that the elongasome developed as a specialised form of the divisome, losing FtsZ in the process. Proteins downstream starting from FtsA evolved into MreB and the proteins of the elongasome. One argument against this order of events is the deviant domain architecture of FtsA, compared with all other actin-like proteins [22]. We counter that the deviation in FtsA is a domain swap that conserves function, namely polymerisation [26••] and hence is an event that could have occurred later, after MreB evolved. Another problem is that FtsA is not as conserved as MreB or FtsZ. It seems that at least in some organisms and many Archaea [47], FtsA has been substituted with another polymerising membrane anchor, SepF, that substitutes its function but not the fold [48,49•].

If the role of FtsZ is to constrict the membrane and to organise the divisome machinery in one single ring around the cell via its interaction with FtsA then this opens up the questions what guides the elongasome? This goes back to old questions about what guides cell width. It may well be that the default mode of action of the elongasome is to not alter width, copying whatever PG network is present, as determined by the new poles, which the divisome generates [50]. In this context it is interesting that there are several reports highlighting contacts between the divisome and the elongasome [15•,51–53]. And most directly, it has been shown that MreB, the actin of the elongasome, interacts with the tubulin FtsZ of the divisome, which might provide answers to questions about what provides the guide to the elongasome in terms of cell width, for example [54••].

It will be essential to obtain more molecular data on the divisome and elongasome before exact evolutionary relationships may be determined.

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