Chapter 14

Unique Biochemical Features of the Cytokinetic Protein FtsZ of Mycobacteria

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Abstract

FtsZ, the bacterial cytokinetic protein, a structural homologue of mammalian β-tubulin, is present in bacteria of diverse genera, including mycobacteria. The FtsZ protein of *Mycobacterium tuberculosis* (*M. tuberculosis* FtsZ), the causative agent of tuberculosis, is the most studied among the mycobacterial FtsZ proteins as it is a potential anti-tuberculosis drug target. *M. tuberculosis* FtsZ possesses many unique biochemical features, which include slow polymerisation kinetics, presence of charged amino acids in the C-terminal domain that interacts with a variety of other cell division proteins, and the presence of specific amino acids at unique locations that makes it distinct from the FtsZ of other mycobacterial species and of other bacterial genera. On the other hand, although the FtsZ of *Mycobacterium leprae* (*M. leprae* FtsZ), the causative agent of leprosy, shows high level of conservation with *M. tuberculosis* FtsZ, it has biochemical properties that are very different from those of *M. tuberculosis* FtsZ due to the difference in specific amino acid residues at critical locations on the protein. The present review focuses on these structural features of *M. tuberculosis* FtsZ and *M. leprae* FtsZ, as studied by others and by us, in comparison to those of the FtsZ of other mycobacterial species and of other bacterial genera.

Keywords: mycobacteria, FtsZ, biochemical features, polymerisation, GTPase, GTP binding, bacterial cytokinesis

1. Introduction

Bacterial cell division involves karyokinesis and cytokinesis. The replication and segregation of genetic material occur in karyokinesis. In cytokinesis, the cytoplasm and its contents increase in quantity and get partitioned between two daughter cells with the development of the septum between them and formation of new cell membrane and cell wall in the sacculus.

The process of septation is guided by the cytokinetic protein, FtsZ [1, 2], which is the bacterial structural homologue of mammalian β-tubulin [3]. Polymeric FtsZ, as the inner membrane bound FtsZ ring at the mid-cell site [1, 2], guides septation. A large number of cell division proteins interact with FtsZ at the median (reviewed in [4, 5]). The duration of the whole process of cell division varies from bacterium to bacterium, with different strains of *Escherichia coli* completing cell division in 18–55 min [6], *Bacillus subtilis* taking 120 min [7], whereas *Mycobacterium smegmatis* taking 3 h [8], *M. tuberculosis* 18 h *in vivo* [9] and 24 h in vitro [10], and *M. leprae* completing it in 13.5 days once [11]. Accordingly, since the septation process takes only a part of the whole cell division duration, the polymerisation and depolymerisation dynamics of FtsZ of each bacterium need to be different in different bacteria to suit the septation duration in the bacterium. The required modifications in the polymerisation and depolymerisation dynamics of the cytokinetic protein to suit the time span of septation need to be effected through specific changes in the amino acid residues of FtsZ. Such changes, which can influence polymerisation and depolymerisation dynamics of FtsZ, can be vividly discerned from the evolutionarily purposeful placement of specific amino acid residues at specific structural locations on the protein. Here, we have tried to point out this particular aspect of the structure-function correlation of FtsZ from mycobacteria with that of FtsZ from other mycobacterial species and bacterial genera.

2. Basic common structural features of FtsZ of other bacteria

The biochemical identity of FtsZ was first established through the demonstration of the GTP binding and GTPase activities of *Escherichia coli* FtsZ (*E. coli* FtsZ) [12, 13]. Both the authors showed the presence of a peptide motif (105 GGGTGTG 111), similar to the tubulin signature motif (140 GGGTGSG 147), and postulated that it would form a phosphate-binding loop like in β-tubulin [14]. The GGGTGTG motif is crucial for GTP binding as its change to SGGTGTG in the FtsZ84 mutant of the temperature-sensitive *E. coli* (*ftsZ84*) strain markedly reduced GTP binding ability (by crosslinking) [13] and converted FtsZ into an ATPase *in vitro* [12]. Tubulin and FtsZ share poor primary sequence homology of 10–18%, except in two sequence regions (amino acids 95–175 in β-tubulin and 65–135 in *E. coli* FtsZ, and 305–350 in β-tubulin and 255–300 in *E. coli* FtsZ) where they show clear sequence homology of 85–87 and 51–78%, respectively [15]. The first region contains β-tubulin/FtsZ signature motif, flanked by identical looking secondary structural elements [15]. However, the overall three-dimensional structures of FtsZ and β-tubulin are almost similar [16, 17], which is reflected in the GTP-dependent polymerisation of *E. coli* FtsZ *in vitro* [18, 19] like β-tubulin polymerisation [20].

The crystal structures of the FtsZ proteins of *Methanococcus jannaschii* [16], *Thermotoga maritima* [21], *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Aquifex aeolicus* [22] essentially showed independently folding N- and C-terminal domains arranged around a central helix. The N-terminal domain contains GTP-binding site and an incomplete GTPase active site. During the course of polymerisation, the T7 loop of one monomer is supplied in *trans* to the GTP-binding pocket of the next, thus forming the active site for GTP hydrolysis [23–28]. From the co-crystal structure of SulA-FtsZ, it was found that SulA, a cell division inhibitor [29], binds

the T7 loop surface of FtsZ, thereby blocking polymer formation as a part of SOS response [30]. Thus, the T7 loop seems to be critically required for FtsZ polymerisation, thereby carrying the potential to be an antibacterial inhibitor target.

In all the solved structures of FtsZ of *M. jannaschii* [16], *P. aeruginosa* [22], *A. aeolicus* [22], *T. maritima* [21], and of *B. subtilis* [31], the end part of the C-terminus has been found to be unstructured and containing variable residues. It has been found to be a platform for the interaction of a large number of cell division proteins, ZipA [32], FtsA [33], EzrA [34], SepF [35, 36], ZapD [37], and with FtsZ itself [4, 5, 38].

2.1. Specific residues required for the biochemical activities of FtsZ

GTP-binding residues are best conserved between FtsZ and β-tubulin [39]. Monomeric FtsZ binds GTP tightly with a K_d of 5 μM [40]. The FtsZ84 (G105S) mutant protein has an impaired GTPase activity *in vitro* [12]. In other examples, while the mutant FtsZ6460 (G109S) showed nil GTPase activity, FtsZ9124 (P203L) possessed reduced GTPase activity, and both the mutants failed to polymerise *in vitro* [41]. Extensive work has been carried out on the characterisation of FtsZ mutants *in vitro* and *in vivo* [42–44]. Based on a model structure of *E. coli* FtsZ, which was built on the crystal structure of *M. jannaschii* FtsZ [16], the mutants were found to be primarily of three classes [43]. (i) On the front and back surface of protofilament and few on the top and bottom surfaces not in contact with GTP, which were termed as benign mutants as all of them could complement *ftsZ84* strain at non-permissive temperature. Few examples of these mutants are A70T, A81V/F268C (Z100), D158A, D158N, D187A, F268C (Z114), D269A, and D299A. (ii) GTP contact mutants, e.g., N43D, D45A, D45N, D209A, did not complement *ftsZ84* and could polymerise only in the presence of DEAE-dextran. (iii) Mutants, D86K, D96A, E238A, S245F, and E250A, where the mutations were thought to be on the lateral surface of protofilaments and therefore believed to play role in inter-protofilament interactions. These mutants could polymerise *in vitro*, but none of them could complement *ftsZ84* at non-permissive temperature.

Further studies showed that the mutations on the top surface of *E. coli* FtsZ model (e.g., G21K, L68C\D\W, F182C) have far less disturbing effect on the complementation (in plate and liquid culture) and GTPase activity of FtsZ compared to those of the mutations on the bottom surface (e.g. D96A, N207C, D209A\C\K, F210A) [44]. Interestingly, one top surface mutant Q47K that binds GTP at more than 1:1 ratio and having around 30-fold less GTPase activity, compared to that of wild-type FtsZ, failed to complement cell division, both in plate and in liquid culture [44]. The E83 and R85 in the helix H3 bend and lateral residues of *E. coli* FtsZ were found to be important for the polymerisation, GTPase activity, and cellular viability [45]. E93R substitution in *E. coli* FtsZ induces bundling of protofilaments, reduces GTPase activity, and impairs bacterial cytokinesis [46]. Similarly, R191 of *B. subtilis* FtsZ was found to be required for polymerisation [47].

The residue D212G of the T7 loop is conserved among all FtsZ sequences known [48] and all the mutations D212A\N\C, D212G (FtsZ2) impaired GTPase activity [42–44]. The location of FtsZ2 mutation was later validated by the crystallography data that SulA binds to T7 loop

region of FtsZ and a mutation in T7 loop might prevent binding of SulA to block FtsZ polymerisation [30]. There was no other structural abnormality of FtsZ2 to bind GTP and therefore could polymerise in the presence of DEAE-dextran *in vitro* [19] or co-polymerise with wild-type FtsZ [25].

The C-terminal variable (CTV) region residues in *E. coli* FtsZ and *B. subtilis* FtsZ were found to mediate electrostatic interactions to facilitate lateral association of the FtsZ protofilaments to form polymers *in vitro* and *in vivo* [39] and for interaction with other proteins such as ZapD ([49], reviewed in [4, 5]).

2.2. Polymerisation properties of FtsZ *in vitro* and *in vivo*

FtsZ has been found to exist mostly as dimers [50, 51]. FtsZ assembly process leading to polymerisation has also been found to involve a dimer nucleus [52]. Among the wide variety of FtsZ structures visualised by various methods till date, the simplest one is the protofilament constituted by FtsZ subunits stacked one above the other with a diameter of 5 nm, with each subunit placed at 4.3 nm apart [53]. While straight protofilaments were favoured by high concentration of GTP or by GTPase inhibition, curved conformation was triggered by GTP hydrolysis or in the presence of GDP [54]. Examination of the FtsZ polymers using atomic force microscopy (AFM) showed that individual protofilaments can fragment and re-anneal on a surface [55]. Also, individual protofilaments were found to have tendency to form bundles in the presence of GTP and singular curved protofilaments were observed in the presence of GDP-AlF_3 [55]. This observation might have implications on the assembly dynamics of FtsZ ring on the inner cell membrane during bacterial cell division.

The *E. coli* FtsZ-Q47K mutant, which does not support cell division [44], formed bundles and rings in yeast cytoplasm [56]. They found that the double mutant *E. coli* FtsZ-Q47K-**D86K**, which carries a lateral mutation (indicated in bold letters) formed long linear cables but did not assemble into a ring. In a separate observation, the authors have reported that FtsZ cables laterally assemble to form bundles in yeast cytoplasm. Thus, these observations indicated that the lateral contacts in FtsZ are important *in vivo* for FtsZ polymeric ring formation. Interestingly, it was found that the C-terminal unstructured tail, or region equivalent to it, is completely dispensable for *in vitro* and/or *in vivo* polymerisation of *E. coli* FtsZ [57, 58], *P. aeruginosa* FtsZ [30], and *B. subtilis* FtsZ [34].

In *in vivo* studies, FtsZ rings constituted by FtsZ polymers have been observed at the mid-cell site using fluorescence microscopy [1, 2] and super resolution 3D-structured illumination microscopy (3D-SIM) [59]. *In vivo* studies in *E. coli* [60] and *B. subtilis* [61] have shown oscillation of FtsZ in a helical pattern throughout the length in the presence of FtsZ ring in *E. coli* [60] and later constricting to the median as the Z-ring form in *B. subtilis* [61].

3. Unique structural features of mycobacterial FtsZ and their role in biochemical activities

Like in the case of FtsZ from other bacterial systems [50–52], *M. tuberculosis* FtsZ exists as a dimer [62] and the assembly process leading to polymerisation has also been found to involve

a dimer nucleus [63]. Like in the case of FtsZ from other bacterial systems, the T7 loop of one monomer is supplied in *trans* to the GTP-binding pocket of the next, thus forming the active site for GTP hydrolysis [64]. In a FRET-based system, *M. tuberculosis* FtsZ was found to take about 60–100 s to reach polymerisation saturation, about 10 times slower compared to *E. coli* FtsZ [63]. At steady state also, subunit turnover and GTPase activity were about 8–10 times slower than those of *E. coli* FtsZ [63]. FRAP experiments showed that *M. tuberculosis* FtsZ has a slower recovery than *E. coli* FtsZ in yeast cytoplasm also [56], which is consistent with the slower polymerisation of *M. tuberculosis* FtsZ [65]. Thus, the FtsZ polymerisation and assembly dynamics of FtsZ of *M. tuberculosis*, which divides once in 18–24 h [9, 10], are much slower than those of the FtsZ of *E. coli*, the different strains of which divide once in 18–55 min [6].

3.1. The role of N-terminal domain residues

The N-terminal domain of the FtsZ proteins of all mycobacterial species is highly conserved (**Figure 1**). In spite of this conservation, conspicuous drastic differences exist at specific amino acid locations. A typical example is the glaring presence of T172 in *M. leprae* FtsZ as the lone exception in lieu of A172 in the FtsZ proteins of all the other mycobacterial species. *M. leprae* FtsZ was found to be polymerisation-lethargic *in vitro*, even in the presence of DEAE-dextran and under a variety of other conditions [66]. However, interestingly, change of T172 to A172, as it exists in *M. tuberculosis* FtsZ, showed dramatic polymerisation as in the case of *M. tuberculosis* FtsZ [66]. Conversely, the reciprocal replacement of A172 with T172 in *M. tuberculosis* FtsZ, as it exists in *M. leprae* FtsZ, completely abolished the polymerisation potential of *M. tuberculosis* FtsZ. These observations showed the crucial nature of A172 residue for polymerisation of FtsZ of all mycobacterial species that have generation time of 24 h or less. On the contrary, the change of A172 to T172, exclusively in *M. leprae* FtsZ, seems to be an evolution-driven modification, probably to dramatically tone down FtsZ polymerisation rate, as *M. leprae* divides only once in 13.5 days [11]. The positioning of T172, which can wield such dramatic influence on FtsZ polymerisation, is well justified to be in the N-terminal domain that is known to be important for polymerisation, as found in *E. coli* FtsZ [21, 57]. Modelling of *M. leprae* FtsZ and *M. tuberculosis* FtsZ showed that probably the presence of Thr, which is a hydrogen-bonding and branched residue, at 172 position in the T6 loop might have imposed rigidity on the T6 loop-H10 helix-T7 loop segment and thereby affecting the polymerisation potential of *M. leprae* FtsZ [66]. Conversely, at position 172, the presence of the non-branched residue Ala that does not engage in hydrogen bonding might not impose rigidity on the T6 loop-H10 helix-T7 loop, thereby facilitating polymerisation of *M. tuberculosis* FtsZ. The link of T6 loop, which contains the 172 residue, to the T7 loop, which might be crucial for polymerisation *in vitro* [66], via the H10 helix, supports this possibility. In view of these observations, it is needless to state that there have to be cellular factors that might enable polymerisation of *M. leprae* FtsZ in a very slow manner suiting the slow generation time of the bacterium when *M. leprae* divides inside human cells. The D84 and D94 of *M. tuberculosis* FtsZ are equivalent to D86 and D96 of *E. coli* FtsZ, respectively [42], and both the residues form salt bridge at the dimer interface [62]. The D94 and N22 form salt bridge with R181 and E136, respectively, in the other subunit [62]. Such interactions might be necessary for the protofilament association during *M. tuberculosis* FtsZ polymerisation as found necessary for the *E. coli* FtsZ polymerisation [42]. While G103 was found to be involved in GTP binding [67], C155 has also been found to play an important role in the assembly of *M. tuberculosis* FtsZ into protofilaments during polymerisation [68].

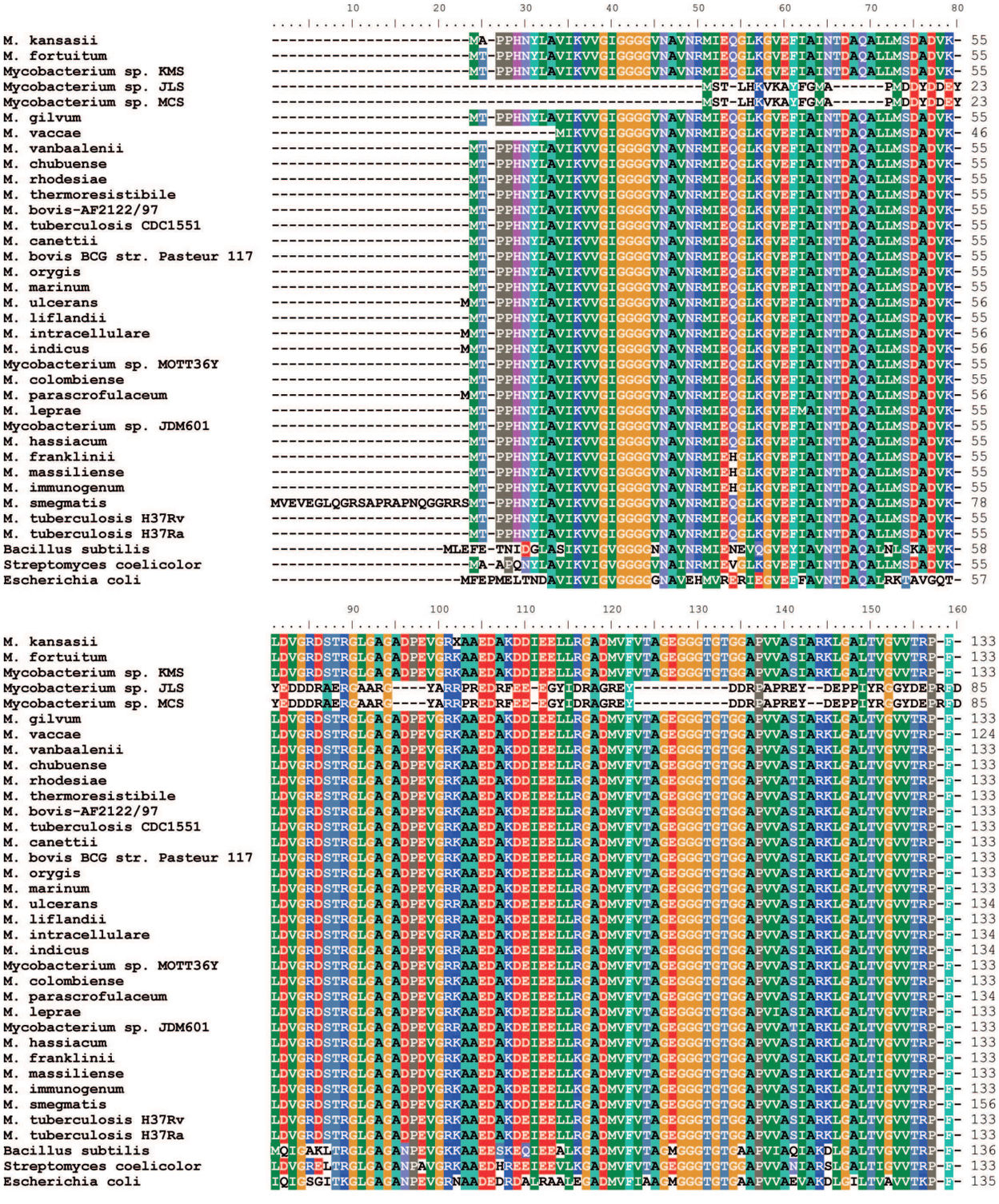

Figure 1. Homology comparison of the amino acid sequences in the N-terminal domain of FtsZ of various mycobacterial species.

3.2. The role of C-terminal domain residues

The C-terminal stretch of FtsZ protein has been found to have structural and functional roles in different bacterial systems (reviewed in [4, 5]). The crystal structure of *M. tuberculosis* FtsZ

did not contain the co-ordinates for the 66 residues at the C-terminal portion [62], indicating its unstructured nature like in the case of the C-terminal stretch of the full-length FtsZ of *M. jannaschii* [16], *Pseudomonas aeruginosa* [22], *Aquifex aeolicus* [22], *Thermococcus maritima* [21], and *B. subtilis* [31]. On the tubulin dimer template, the molecular model for the complete structure of *M. tuberculosis* FtsZ, inclusive of the extreme C-terminal 66 residues [69], the co-ordinates of which were not visible in the crystal structure of *M. tuberculosis* FtsZ [62], also showed an unstructured C-terminus [69].

Like in the case of *E. coli* FtsZ and *B. subtilis* FtsZ, the C-terminal region of the FtsZ proteins of all the mycobacterial species contain charged residues towards the C-terminal end. FtsZ of diverse mycobacterial species also shows wide variations in the nature of the residues in the C-terminal region (**Figure 2**). These residues show high levels of divergence from the residues on the FtsZ of *B. subtilis* (Gram-positive) and *E. coli* (Gram-negative) and even from the FtsZ of *Streptomyces coelicolor*, which is also an Actinobacteria like mycobacteria. Many mycobacterial species have an insertion of GGIAD in the C-terminal variable region, the function of which is under investigation.

The *M. tuberculosis* FtsZ dimer model showed a possible role for the C-terminal Arg residues (R378 and R379) on the stability of the dimer and hence on the polymerisation of the protein. In fact, biochemical studies showed that the deletion of the extreme C-terminal residues, R378 and R379 in the C-terminal extreme stretch of $_{373}$PPFMRR$_{379}$ of *M. tuberculosis* FtsZ, completely abolished polymerisation *in vitro* [69]. Besides the deletion of R379, the deletion of the R378 or its replacement with Lys, His, Ala, or Asp completely abolished polymerisation activity, indicating the crucial nature of the residues in the unstructured region of the protein for polymerisation. However, the polymerisation potential of the protein was not affected by the deletion of the single R379 residue alone [69]. The C-terminus of most of the mycobacterial FtsZ ends with $_{377}$MRR$_{379}$ and very few with $_{377}$MRH$_{379}$, with the conservation of M377 (**Figure 2**).

M. tuberculosis FtsZ has been found to interact with *M. tuberculosis* FtsW *in vitro* [70] and *in vivo* [71]. The presence of three of the four aspartate residues, D367 to D370, was found to be critically required for the interaction of *M. tuberculosis* FtsZ with a cluster of positively charged residues in the C-terminal tail of *M. tuberculosis* FtsW *in vitro* [70] and *in vivo* [71] (**Figure 2**). Similarly, PknA-dependent phosphorylation of T343 in *M. tuberculosis* FtsZ is required for FtsZ function during oxidative stress [72]. Like in the case of FtsZ-SepF interaction in *B. subtilis* [35, 36], the C-terminal tail of *M. tuberculosis* FtsZ was found to be required for the interaction of SepF with FtsZ [73]. These and other studies showed that *M. tuberculosis* SepF is found to be an essential part of the mycobacterial cell division machinery [74], probably in assisting FtsZ localisation at the mid-cell site [73].

3.3. The role of other residues in the protein

Like in the case of the mutations D212A\N\C, D212G (FtsZ2) in *E. coli* FtsZ, which impair GTPase activity [42–44], the equivalent mutant D210G of *M. tuberculosis* FtsZ also showed impaired GTPase activity [67] (**Figure 3**). Although *M. tuberculosis* FtsZ-D210G polymerised *in vivo* to the mid-cell ring in a merodiploid *Mycobacterium smegmatis* background, it failed

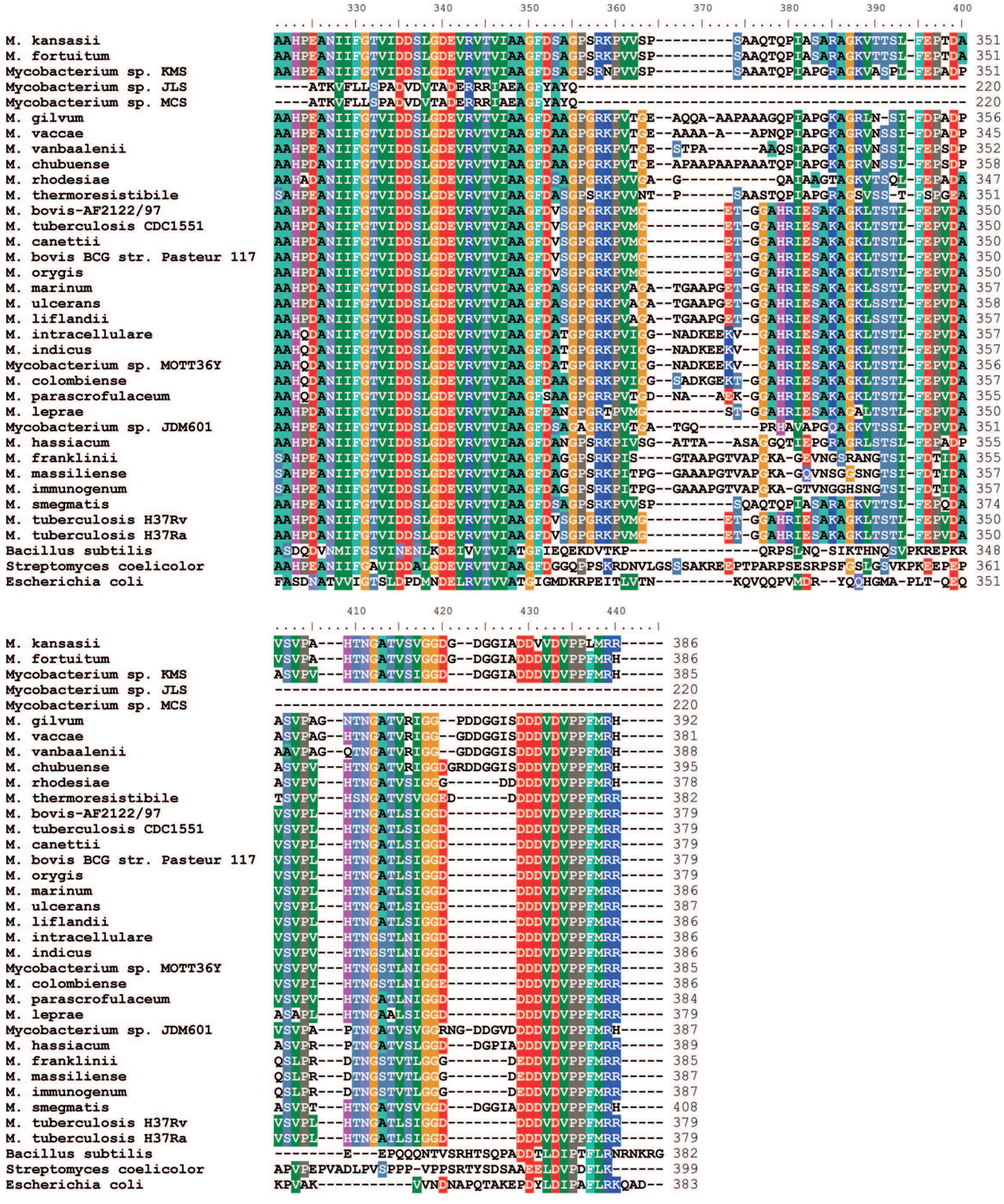

Figure 2. Homology comparison of the amino acid sequences in the C-terminal domain of FtsZ of various mycobacterial species.

to act as the sole source of FtsZ *in vivo* and showed 100-fold impaired GTPase activity *in vitro* [67]. The authors suggested that the mutation on the T7 loop might not prevent FtsZ self-association or association with the wild-type protein but rather specifically affect GTP

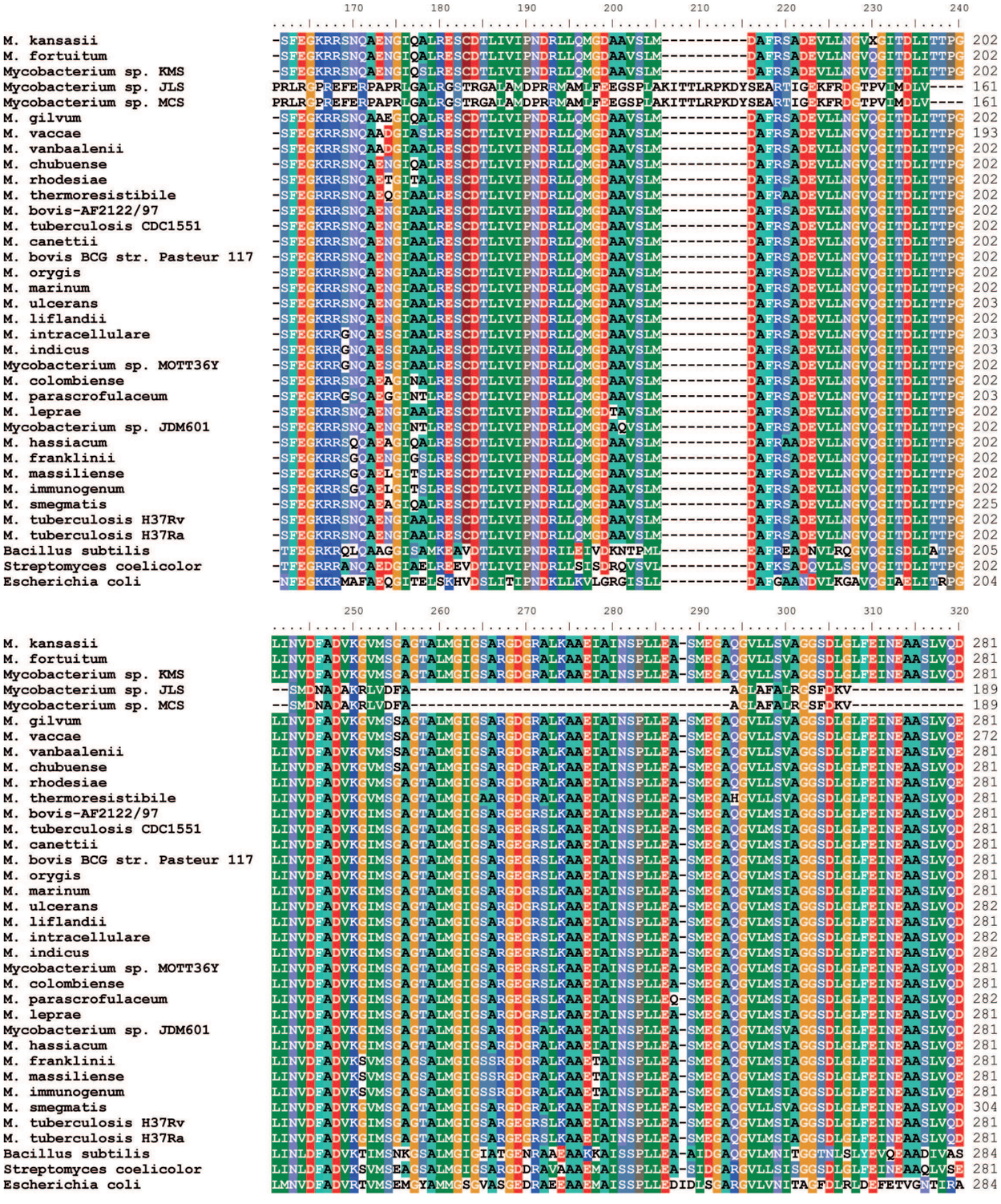

Figure 3. Homology comparison of the amino acid sequences at other parts of FtsZ of various mycobacterial species.

hydrolysis, thereby uncoupling GTPase property from polymerisation. The specific residues, which have been found to be involved in the polymerisation or interaction of *M. tuberculosis* FtsZ with itself or with other cell division proteins, are listed in **Table 1**.

Residue in *M. tuberculosis* FtsZ	Interacting protein of *M. tuberculosis*	Functional role of the interaction	Reference
N22	E136 of FtsZ	Polymerisation	[62]
D94	R181 of FtsZ	Polymerisation	[62]
G103	FtsZ	GTP binding	[67]
C155	FtsZ	Polymerisation	[68]
A172	FtsZ	Polymerisation	[66]
D210	FtsZ	GTPase	[67]
T343	PknA	FtsZ function*	[72]
D367-D370	FtsW	FtsZ function*	[70]
R378, R379	FtsZ	Polymerisation	[69]
C-terminal tail	SepF	FtsZ function*	[73]

*The exact biochemical activity of the FtsZ, in which these residues participate, is not known.

Table 1. Residues in ***M. tuberculosis*** FtsZ that interact with residues in another subunit or with other cell division proteins.

4. Correlation between FtsZ polymerisation kinetics and bacterial generation time

Mycobacterium leprae is one of the slowest growing bacteria with a generation time of 13.5 days *in vivo* [11]. The generation time of *M. tuberculosis* is 18 h *in vivo* [9] and 24 h *in vitro* [10]. Similarly, while *M. smegmatis* divides once in 3 h [8], *S. coelicolor* A3(2), which is classified under Actinobacteria like mycobacteria, has a generation time of 2.31 h, except that some of the strains grow as slow as 28.9 h depending upon growth conditions [75]. Meanwhile, different strains of *E. coli* show generation time of only 18–55 min [6]. In agreement with the slower generation time of *M. tuberculosis*, compared to that of *E. coli*, *M. tuberculosis* FtsZ showed slower polymerisation *in vitro* [63, 65]. Interestingly, the FtsZ of *M. leprae*, which divides once in 13.5 days [11], did not polymerise at all *in vitro* even in the presence of DEAE-dextran [66]. Comparatively, the time taken by *M. smegmatis* and *S. coelicolor* to reach steady state of FtsZ polymerisation is about 4 min [76]. Similarly, the time taken by the FtsZ of *Caulobacter crescentus*, which has a generation time of 3 h [77], to reach steady state of polymerisation is 5 min [78]. On the contrary, while *E. coli* FtsZ takes only 1–6 s to reach steady state of polymerisation [18, 79], FtsZ of *B. subtilis*, which divides once in 120 min [7], takes approximately 200 s [47]. These observations on the comparative polymerisation kinetics of FtsZ proteins of *E. coli*, *M. tuberculosis*, *S. coelicolor*, *M. smegmatis*, and *M. leprae* and the generation time of the respective bacterium (**Table 2**) probably allude to the existence of a correlation between the generation time of the bacterium and the time taken by the respective FtsZ to reach steady state kinetics *in vitro*, which may hold true *in vivo* as well. Mechanistically, such a correlation needs to be necessarily in-built so that kinetics of FtsZ polymerisation during division of the cell keeps pace with the overall generation time of the bacterium. The presence of A172 in the FtsZ of

Bacterium	Time taken to reach steady state of FtsZ polymerisation (from light scattering data)[a] [with reference]	Generation time of the bacterium[a] [with reference]
M. smegmatis	~4 min [76]	3 h [8]
S. coelicolor	~4 min [76]	2.31 h [75]
M. tuberculosis	~6–10 min [65]	24 h [10]
M. leprae	ND[b] [66]	13.5 days [11]
E. coli	~1–6 s [18]	18–55 min [6]
B. subtilis	~200 s [47]	120 min [7]
C. crescentus	~3 min [78]	3 h [77]

[a]The studies from which the respective values were taken are given in the parenthesis.
[b]Not determined as *M. leprae* FtsZ does not polymerise *in vitro* [66].

Table 2. Correlation between the time taken to reach FtsZ polymerisation steady state and generation time of the bacterium.

all mycobacterial species, except in *M. leprae* where it is T172, is a typical example for such a correlation. The homology comparison of mycobacterial FtsZ sequence vividly shows the existence of several such minor differences in terms of specific amino acid residues at crucial positions that may play significant role in conferring differences in the polymerisation kinetics of the FtsZ protein of the respective bacterium. Structure-function studies on the polymerisation kinetics of a large number of FtsZ molecules from diverse bacterial genera differing widely in their generation time might establish such correlation.

5. Application of the FtsZ structure-function studies in public health

FtsZ being the principal essential cytokinetic protein in bacterial systems, it has been examined as a potential target for the design of inhibitory compounds that could be used as antibacterial drugs against diverse pathogenic bacteria (reviewed in [80]). Although the overall sequence conservation between FtsZ and β-tubulin is only 10–18% except at two stretches [15], it is important to ensure that anti-FtsZ compounds do not inhibit β-tubulin in humans. Owing to the overall conservation of the three-dimensional structure of FtsZ proteins from diverse bacterial genera, developing broad spectrum antibiotics, which are equally effective against the FtsZ of pathogenic bacteria of diverse genera, by designing inhibitor against the FtsZ molecule of a single bacterium, seems to be an attractive possibility [81].

6. Perspectives and challenges

The vast regions of homology and overall conservation of the three-dimensional structure of FtsZ proteins of diverse bacterial systems may seem attractive to design common inhibitors directed against these regions expecting them to be effective against the FtsZ proteins.

However, the structure-function studies on FtsZ revealing the subtle differences among the primary, secondary, and tertiary structures of FtsZ proteins from diverse bacteria give the hint that an anti-FtsZ inhibitor designed against the FtsZ of a select pathogenic bacterium may not act effectively with the same MIC/MBC against the FtsZ proteins of other pathogenic bacteria, as found [81]. Thus, the design of a common inhibitor that may be expected to act against FtsZ proteins from diverse pathogens remains a big challenge in the development of inhibitors against bacterial cytokinetic protein, FtsZ. Secondly, identification of the residues contributing to the structure that is required for the generation of force by FtsZ for cell wall/membrane constriction [82] during the physical division of the mother cell also remains a challenge for future studies.

7. Conclusions

The essential cytokinetic protein, FtsZ, of different Mycobacterial species and of other bacteria has evolved to possess specific amino acid residues at crucial positions on the protein to suit the polymerisation kinetics that befit cell division duration. Thus, each FtsZ protein is unique in terms of the specific types of amino acid residues at crucial positions on the protein in spite of the regions of homology and overall conservation of the three-dimensional structure. It is these unique differences in the residues at specific crucial positions on the FtsZ protein that confer subtle differences on the FtsZ structure and hence on the cytokinetic function of the protein in the respective bacterium.

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