ISSN: 0975-3583, 0976-2833 VOL 13, ISSUE 05, 2022

A REVIEW ON ROLE OF DIVIVA PROTEIN IN BACTERIA

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INTRODUCTION

DivIVA is a membrane binding protein that clusters at curved membrane regions such as cell poles and membrane invaginations occurring during cell division. DivIVA protein recruit many other proteins to these subcellular sites through direct protein-protein interactions. DivIVA is a strongly conserved cell division protein found in most gram positive bacteria. Cell poles and the invaginating septum during cell divisions are regions where the membrane is naturally bent and consequently, DivIVA typically clusters at these sites. DivIVA serves as a central scaffold protein for the recruitment of other factors and the list of recognized proteins, the localisation of which depends on DivIVA. DivIVA protein generally consist of two domains, a strictly conserved N-terminal domain required for lipid bind and a lesser-conserved C-terminal domain, both forming parallel coiled-coil dimers. N-terminal extensions of two heluies forming the coiled-coil in the N-terminal domain cross each other and fold back onto the coiled-coil structure. Hydrophobic amino acids are exposed to the solvent at the apical end of this structure, and DivIVA interacts with membranes through the insertion of these side chains into phospholipid layer. In addition to membrane binding, the lipid binding domain also mediates the interaction of DivIVA with biding partners, such as MinJ. C-Terminal domain of DivIVA, which is oriented towards the cytoplasm, also associates with binding partners, such as centromere-binding protein RacA contributing to chromosome segregation in B. Subtilis cells. Considering that RacA is a soluble cytoplasmic protein, it therefore seems that DivIVA interacts with transmembrane proteins via its lipid binding domain and with cytoplasmic proteins through its C-terminal domain. Bacillus Subtilis possess a septum determining Protein named DivIVA[1], which recognizes membranes of negative curvature[2], Hence its localization at the cell poles and the septum during the initiation of septation [1]. DivIVA is responsible for maintenance of a high concentration of FtsZ Inhibition, MinC, at the cell poles, ensuring correct positioning of septum formation at the mid cell [3]. Majority of widely studied rod-shaped bacteria such as

ISSN: 0975-3583, 0976-2833 VOL 13, ISSUE 05, 2022

E.coli and bacillus subtilis elongate by the lateral deposition of new cell wall material along the whole length of the bacterium. It is the highly regulated septal positioning and formation that results in the formation of morphologically identical daughter cells. The essential bacterial tubulin homologue FtsZ[4] is crucial in the initiation of a contractile protofilament ring, the Z ring at the site of septum formation.

DISCOVERY OF DivIVA

Studies of cell division Mutants in B. Subtilis isolated in the early 1970s (DivIV-A1 and DivIV-B1 [5],[6] led to the eventual mapping and Discovery of the DivIVA gene more than 2 decades later[7]. The Name "DivIVA" was chosen on the basis of the recommendation that division mutants that exhibited abnormal off-centre septum placement be named Div IV mutants [8]. B. Subtilis DivIB-A1 mini cell producing mutant, as well as the parent wild-type strain into which the DivIV-A1 mutation was transferred, was examined. During studies it became apparent that the lengths of mini cell producing cells of the DivIV-A1 mutant were much greater than lengths of wild-type cells grown in like manner. In DivV-A1 system extreme length of mini cell producing cells is primarily a result of division suppression rather than division dislocation. The mutation in another Div IV mutant, Div IV-B1, Which mapped to the min CD Cluster (adjoining mre BCD genes encode cell shape-determining proteins), Specifically disrupted the mind gene [9, 10],. Min CD, together with the help of the spatial determinant DivIVA (and of MinJ), regulate the assembly of the FtsZ ring (Z-ring), a central component of the cell division machinery required for cell division [11, 12].

STRUCTURE OF DivIVA

Four different interaction partners are known: (i) the transmembrane protein Min J, which acts as a molecular bridge between DivIVA and the FtsZ-inhibiting Min CD complex [13-15]; (ii) the DNA-binding protein RacA, which is required for chromosome segregation during spore formation [15-17]; (iii) the competence-specific inhibitor of cell division Maf [17]; and (iv) the competence regulator ComN [18]. Highly conserved N-terminal domain that forms a dimeric structure with a characteristic cap structure and a less conserved C-terminal domain that is rich in coiled coils but varies in length among the different bacterial species [19]. These domains are connected by a flexible 20-amino-acid linker. The N-terminal domain is required for the lipid binding of DivIVA and for localization. The crystal structure suggested that the central coiled region of the C-terminal domain contributes to DivIVA dimerization (Fig. 1B) and that the end of this domain (amino acids 130 to 153) forms an antiparallel four-helix bundle constituting the tetramerization domain (TD) whereby two DivIVA dimers are linked together in an end-to-end orientation [19](Fig. 1A and B).

BACILLUS SUBTILIS

DIVIVA has a quite separate role in sporulating cells of bacillus subtilis. The bacillus subtilis DIVIVA protein targets to the division spectrum and controls the site specificity of cell division. The bacillus subtilis DIVIVA gene encodes a coiled – coil protein that shows weak similarity to eukaryotic organisms. DivIVA is capable of localization by sensing negative (concave) membrane curvature within the cell, presumably independently of the action of

ISSN: 0975-3583, 0976-2833 VOL 13, ISSUE 05, 2022

FtsZ at cell poles [20], and at sites where the division septum intersects the lateral cell surface [2, 21]. In fact, an earlier report indicated that DivIVA targets the sites of cytokinesis even when artificially expressed in unrelated organisms—E. coli and fission yeast Schizosaccharomyces pombe [22]. It is possible that DivIVA is able to localize to nascent division sites by recognizing negative curvature elicited by the constriction of Z-rings [12, 20]. Super resolution microscopy revealed that DivIVA localizes and forms two rings at mid cell, likely sandwiching a constricting Z-ring [12]. DivIVA localization appears to be dynamic in actively dividing cells, and transfer of molecules between the old and the nascent division sites has been observed [23]. DivIVA is localized at division sites during vegetative growth and prevents aberrant assembly of Z-rings immediately adjacent to newly formed septa [12, 14, 24]. Furthermore, localization of DivIVA, a peripheral membrane protein, appears to depend on the presence of a translocate subunit, SecA, of the protein secretion apparatus [25].

Bacillus Subtilis DivIVA has dual functions

It is required for appropriate septum placement by confining the MinCD cell Division Inhibitory complex at the cell poles. It facilitates chromosome segregation by Interacting with oric complex in sporulating cells.

FIRMICUTES

In the rod-shaped bacterium Listeria monocytogenes, the absence of DivIVA leads to a cell separation defect [26] which mimics the chaining phenotype seen in a S. Pneumonia DivIVA null strain[27, 28]. Defective cell separation was attributed to the dependency of autolysins p60 and MurA on DivIVA for subsequent secretion via the SecA2 pathway [26]. Furthermore, an L. monocytogenes strain lacking DivIVA is unable to swarm (a process which is independent of MinJ, unlike the case in B. subtilis[14] or build biofilms and exhibits attenuated virulence [26, 29]. DivIVA also appears to play a role in cell division in L. monocytogenes by directly interacting with MinD, thereby circumventing the need for MinJ [30]; the direct MinD-DivIVA interaction has also been documented in Clostridium spp[31]. In the spherical bacterium Staphylococcus aureus (which also lacks min genes, similarly to other non-rod-shaped bacteria), the absence of DivIVA does not lead to significant changes in cell morphology or produce cell division defects[32], even though S. aureus DivIVA localizes to division sites [32, 33]. A role for DivIVA in chromosome segregation, possibly through a direct interaction with SMC condensin, was observed previously [33]. Bacterial two-hybrid and protein abundance analyses revealed that DivIVA interacts with and is stabilized by DnaK[33]. Additional DivIVA-interacting proteins include the cell division proteins FtsZ, FtsA, EzrA, DivIC, penicillin-binding protein 1 (PBP1), and GpsB[33].

STREPTOCOCCUS PNEUMONIAE

GpsB is essential in S. pneumonia, but accumulation of suppressor mutations that allow GpsB to become nonessential in some strain back-grounds has been clearly delineated [28, 34]. Depletion of GpsB results in cell elongation and formation of constriction-deficient Z-rings [35]. In a different strain background, deletion of gpsB resulted in cell elongation

ISSN: 0975-3583, 0976-2833 VOL 13, ISSUE 05, 2022

because of improper helical localization of division proteins and concomitant peptidoglycan insertion[28]. This phenotype appears to be corrected in cells in which DivIVA is also absent, highlighting that coordination of cell wall synthesis in Pneumococcus requires both DivIVA and GpsB [28]. However, the corrective effect was not reproducible in other strain types [34].The interaction between GpsB and PBP2a has been established by genetic, biochemical, and structural methods, and the residues involved in the interaction between GpsB and PBP2a are similar to those of B. subtilis GpsB and PBP1[34, 36]. In addition, GpsB was found to be in a complex with EzrA, MreC, StkP, and multiple penicillin-binding proteins: PBP1a, PBP2b, and PBP2x [34, 36]. The interaction between GpsB and PBP2b observed via coimmunoprecipitation analysis may not be direct, as the interaction was not seen in bacterial two-hybrid or fluorescence polarization assays [36]. Together, multiple lines of evidence indicate that GpsB plays a vital role in linking peptidoglycan synthesis at division sites for septation and cell periphery for cell elongation[34]. The S/T kinase StkP plays a critical role in cell wall synthesis and virulence in multiple Streptococcus species [37-39]. Known StkP substrates include GpsB, DivIVA, FtsA, EzrA, MapZ, and FtsZ [37-39]. Bacterial two-hybrid and surface Plasmon resonance experiments revealed that pneumococcal GpsB interacts with both EzrA and DivIVA and that GpsB is required for proper localization and auto phosphorylation of StkP [28]. In a different pneumococcal strain, however, the interaction between GpsB and DivIVA (based on immunoprecipitation assay) and GpsB-mediated localization of StkP were not evident[34]. StkP auto phosphorylation and phosphorylation of its substrates, on the other hand, are dependent on GpsB in multiple strain backgrounds [34].

MYCOBACTERIUM SPECIES

DivIVA, also known as Wag31, was initially characterized as the highly immunogenic antigen Ag84 in Mycobacterium tuberculosis and Mycobacterium leprae strains [40, 41]. In Mycobacterium species (which, unlike Firmicutes, undergo apical growth [42]), DivIVA is essential[43-45] and localizes to the septum, cell poles, and branching sites[45-48]. Overproduction of DivIVA leads to polar bulging and branching in Mycobacterium smegmatis [46], a fast-growing cousin of M. tuberculosis, where DivIVA dictates the site of peptidoglycan insertion [49, 50]. An indirect link between DivIVA and Z-ring assembly was revealed by the elucidation of direct interactions between DivIVA and a cell wall synthesis protein (CwsA) and FtsZ-interacting FtsI/PBP3[51-54] .Localization of DivIVA depends on Ami1 amidase, as there was a higher rate of unusual lateral budding in an Ami1 amidase mutant due to DivIVA mislocalization to the sites of lateral branching[55], which resembles the localization pattern of DivIVA in Streptomyces. In addition to assisting in cell wall synthesis, DivIVA also interacts with proteins involved in the biosynthesis of mycolic acids [49, 56, 57]. Mycolic acids are an integral part of the mycomembrane and play a crucial role in pathogenesis[58]. A role for S/T kinases and cognate phosphatases in regulating cell shape and division in M. tuberculosis has been observed previously [59, 60]. Of the 11 S/T kinases encoded by this organism[61], at least one of them, PknA, phosphorylates DivIVA at T73[59, 62]. It was also elucidated that a phosphomimetic variant of DivIVA displays an increased rate of peptidoglycan synthesis compared to the phosphoablative mutant [47]. Furthermore, the phosphorylation status of DivIVA is also regulated by the essential MtrAB two-

ISSN: 0975-3583, 0976-2833 VOL 13, ISSUE 05, 2022

component system and FtsI[54]. Similarly to DivIVA in other organisms, M. smegmatis DivIVA also interacts with the chromosome segregation machinery—in this case, with the ParA ATPase component [63] and possibly with ParB as well[64]. In M. smegmatis, which lacks the Min system, a paralog of DivIVA, SepIVA, is involved in cell division regulation[65]. Apart from the functions described above, there are additional roles for DivIVA in oxidative stress response[51] and bacterio-phage infection[66].

ACKNOWLEDGEMENT

The authors express sincere gratitude to the management of Raghavendra Institute of Pharmaceutical Education and Research (RIPER) for giving us opportunity to write the review.

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