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EDITORIAL

Classic Spotlight: Staying in Shape and Discovery of the *mrdAB* and *mreBCD* Operons

Piet A. J. de Boer

Department of Molecular Biology & Microbiology, School of Medicine, Case Western Reserve University, Cleveland, Ohio, USA

How nonspherical bacteria maintain their shape is a long-standing question in bacteriology. That the peptidoglycan (PG) sacculus is critical to maintain both cell shape and integrity was established early on when treatment of bacterial rods with lysozyme was found to convert them into protoplasts that are both spherical and osmotically unstable (1). The first evidence that cell shape is also controlled by factors that are not required for building a sacculus *per se* came from a famous "large-scale" screen of 400 temperature-sensitive *Escherichia coli* mutants at the Pasteur Institute. Some of these formed spherical cells at 42°C. Moreover, these cells were osmotically stable, indicating that they still possessed an intact but spherical PG sacculus (2). The next decade saw the isolation of additional cell shape mutants of both *E. coli* and *Bacillus* species by various laboratories. Many of these propagated as osmotically stable spheroids in a nonconditional fashion, and corresponding mutations in *E. coli* mapped to two regions of the chromosome: near *lipA* at ~14 min (*mrd*, *rodA*, and *rodX* alleles) and near *rpsL* at ~73 min (*mre*, *mon*, *envB*, and *rodY* alleles). Meanwhile, the β-lactam amdinocillin (compound FL1060) became available as an important drug and tool (3). The drug causes *E. coli* to phenocopy spherical mutants (3), and Spratt and Pardee identified its target as a penicillin-binding protein that they named PBP2 (4). Several groups then showed that selection for amdinocillin resistance (Mec^r) frequently yields mutants with a spherical cell phenotype very similar to those described earlier. In a series of 1980s *Journal of Bacteriology* papers, Michio Matsuhashi and colleagues used this Mec^r selection to (i) obtain a set of isogenic cell shape mutants, (ii) map mutations on the chromosome, and (iii) isolate and study the affected genes. Mutations in the spherical Mec^r mutants again mapped to either of the *mrd* or *mre* regions identified before (5). Work by Matsuhashi, Spratt, and others then first established that the *mrd* region contains two genes in an operon that are essential for rod shape maintenance. One was shown to encode PBP2 and is called *pbpA* or *mrdA*, and the other is designated *rodA* or *mrdB* (5, 6). The subsequent identification and isolation of the relevant cell shape genes in the *mre* region started with a classic paper from 1987 (7). The authors isolated a specialized transducing λ phage that could correct the shape defect of *mre* mutants, one of which contained a sizeable chromosomal deletion (Δ*mre-678*). Phage DNA was then used to construct a set of plasmids carrying different fragments of the *mre* locus, and cell shape complementation assays with the plasmids implied that the locus contains at least two genes required for maintenance of rod shape (7). This was confirmed soon after by additional complementation results, DNA sequencing, and *in vitro* translation assays, demonstrating that the protein products of three contiguous genes in the locus (*mreB*, *mreC*, and *mreD*) are all required to convert spherical Δ*mre-678* cells back to rod shape (8, 9). The discoveries of the *mrdAB* and *mreBCD* operons form the basis of all subsequent work on understanding how the proteins they encode collaborate to dictate a cylindrical shape to the PG sacculus. Of course, the discovery of MreB (7, 8) was also more broadly important, as it eventually led to the realization that bacteria invented not just tubulin (FtsZ) but actin (MreB) as well.

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Address correspondence to pad5@case.edu.