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Mapping mid-cell: MapZ shows the way

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In the 3 domains of life, cell proliferation relies on the ability to perform accurate cell division in coordination with other events of the cell cycle, such as cell growth and genome segregation. In most bacteria, cell division results in the formation of 2 genetically and morphologically identical daughter cells. Such binary fission process first requires the identification of the cell middle followed by the recruitment of the division machinery, which first component is the highly conserved tubulin-like protein FtsZ. FtsZ forms a ring that eventually constricts to give rise to 2 newborn cells. Understanding the mechanisms that regulate placement and closing of the FtsZ ring is one of the major challenges in bacteriology.

We have recently shown that in *Streptococcus pneumoniae* a unique protein, MapZ (Mid-cell Anchored Protein Z) ensures the 2 fundamental tasks required for the control of cell division.[1] MapZ permanently beacons the future division sites during cell growth and recruits the division machinery by interacting with FtsZ. Then, MapZ phosphorylation controls the constriction of the FtsZ ring during septation. The discovery of MapZ in *Streptococci* that is devoid of previously described system known to regulate FtsZ,[2] demonstrates that nature has evolved alternative ways to regulate the fundamental mechanism of cell division. In the following text, we discuss several questions that arose from these findings and we present several working hypothesis and investigation prospects.

MapZ permanent association with the cell equator is entangled with the fact that *Streptococcus pneumoniae* cells elongate from mid-cell,[3] resulting in what could be termed a "semi-conservative cell growth." PG-synthesis builds the new cell-halves from the cell center while the intact old cell-halves are pushed apart. This process consequently moves away the MapZ rings that are located at the frontier between new and old cell wall material, *i.e.*, at the cell equator. We have been able to show that MapZ localization depends on its extracellular domain, which directly interacts with peptidoglycan. However, the interplay between MapZ and the cell equator remains elusive. We can propose 2 mutually exclusive scenarios: either, the cell equator is a region where the cell wall has a peculiar composition, structure or properties, which could be specifically recognized by MapZ extracellular domain. Or, the MapZ-ring is a physical seal between new and old peptidoglycan that constitutes *per se* the cell equator. In that view MapZ would simply be mechanically pushed as the new cell wall material is incorporated. Distinguishing between these 2 possibilities will require better characterization of the nature of peptidoglycan produced upon cell elongation *vs.* cell constriction together with the structural characterization of the MapZ extracellular domain. One can even imagine that other unidentified proteins contribute to MapZ dynamics.

MapZ-mediated strategy for finding mid-cell differs from those described in rod-shaped organisms such as *Caulobacter crescentus, Escherichia coli* or *Bacillus subtilis*.[4] In those organisms, the current view is that the division site is identified at a particular time in the cell cycle and placed relative to the position of the nucleoid (through nucleoid occlusion systems) and relative to the cell poles (through MinCD systems). We can stress that these systems allow a signaling of the division site that is transient in time and relative in space, whereas MapZ-mediated signaling is permanent in time and absolute and fixed in space. This fundamental discrepancy could correlate to differences in the developmental mode of these different bacteria. In rod-shaped Bacteria, PG-incorporation occurs all along the cell length following a helical pattern.[5] This growth process appears intrinsically incompatible with the existence of a factor that would permanently beacon the cell equator and move as the cell elongates. It then raises the possibility that MapZ-like systems could be associated with a specific mode of peptidoglycan synthesis and/or a specific cell shape. Testing this possibility will require to combine analysis of MapZ conservation in bacterial genomes together with physiological studies of cell growth and division modes.

Another fundamental aspect of cell division regulation concerns the temporal control of Z-ring dynamics during the cell cycle. In *Streptococcus*, the single FtsZ ring splits into 2 rings that migrate along the cell membrane until they coincide with the prepositioned MapZ rings. Importantly, FtsZ splitting and migration still occur in absence of MapZ, which led to the conclusion that MapZ is mainly required to stop and fix the FtsZ-ring at the site of division. Consequently, what rules FtsZ dynamics in the first place remains largely unknown in *Streptococci* as in other bacteria. A tempting hypothesis proposes protein phosphorylation as a main regulator of the cell cycle.[6] We have shown that StkP-mediated phosphorylation of

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MapZ controls septum constriction in a timely manner. Likewise, phosphorylation of other factors involved in division could function as an internal clock that regulates the sequence and timing of the cell cycle events. Supporting this are the reports that FtsZ itself is phosphorylated as well as some of its key regulators (FtsA, EzrA...) in *Streptococci*.[7] One can then envisage that futures investigation will uncover an extensive network of phosphorylation that orchestrates the cell cycle events in prokaryotes, as it is the case in eukaryotic organisms.

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