Cyclic di-AMP Modulates Cellular Turgor in Response to Defects in Bacterial Cell Wall Synthesis

Brogan AP, Bardetti P, Rudner DZ. *Nat Microbiol*. June 2025

Presenter: Tzu-Yu, Chen
Advisor: Hashimoto Masayuki Ph.D.

Date/Time: 2025/12/04, 17:20 – 18:10
Location: Room 601, Med College Building

Background

In Gram-positive bacteria, mutations leading to higher c-di-AMP levels enhance resistance to cell wall–targeting antibiotics like β-lactams. Intriguingly, c-di-AMP does not appear to directly interact with cell wall synthase. Instead, earlier studies hypothesized that this enhanced resistance results from an alteration in turgor pressure: high c-di-AMP is hypothesized to reduce turgor pressure. However, direct experimental evidence confirming that c-di-AMP alters turgor pressure was lacking.

Objective

To elucidate the signaling pathway and regulatory mechanisms by which c-di-AMP modulates cytoplasmic turgor pressure in response to cell wall defects.

Result

Bacillus subtilis was used as the model organism in this study. This study demonstrates that CdaA-dependent synthesis of c-di-AMP is essential for maintaining cellular integrity when peptidoglycan biogenesis is compromised. Moreover, the regulatory protein CdaR—and specifically its Intrinsically Disordered Region (IDR)—is required for sensing cell wall defects caused by impaired activity of the major cell wall synthase, PBP1. Using an in vivo c-di-AMP reporter based on a riboswitch, the study shows that c-di-AMP levels increase rapidly in response to defects in PBP1-mediated cell wall synthesis. The data further reveal that chronically elevated c-di-AMP decreases cytoplasmic turgor, leading to thinner cells, whereas excessively low levels yield swollen cells with higher internal pressure. In addition , the data show that either extreme—too much or too little c-di-AMP—is detrimental and can ultimately lead to cell death, underscoring the necessity of precise regulation of this second messenger for bacterial survival.

Conclusion

Altogether, this study demonstrates that when facing cell wall defects, the Diadenylate cyclase CdaA increases c-di-AMP levels to reduce cytoplasmic turgor pressure, and that decreasing the second messenger increases turgor.