Control of bacterial cell wall autolysins by peptidoglycan crosslinking mode

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Presenter: Yi-Chen Liu **Date/Time**: 2025/12/18, 15:20-16:10

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Background

The bacterial cell wall is composed of peptidoglycan (PG), a mesh-like polymer essential for structural integrity. To allow for cell growth and division, the cell wall must be dynamic; this requires autolysins, such as Lytic Transglycosylases (LTs), to cleave existing bonds and create space for new material. While essential, LTs are dangerous and must be tightly regulated to prevent cell lysis. PG strands are crosslinked by two main enzyme families: Penicillin-Binding Proteins (PBPs), which form DD-crosslinks, and LD-transpeptidases (LDTs), which form LD-crosslinks. The physiological role of LD-crosslinking in regulating PG turnover has remained unclear.

Objective

This study investigates whether the mode of peptidoglycan crosslinking acts as a structural checkpoint to regulate the activity of lytic transglycosylases (LTs) and defend against external lytic threats.

Results

Through high-throughput peptidoglycan profiling of *Vibrio cholerae*, the authors identified a strict inverse correlation where conditions favoring LD-crosslinking significantly reduced the levels of anhydromuropeptides, the catalytic products of LT activity. Genetic analysis using *Δldt* mutants and copper-mediated inhibition confirmed that a reduction in LD-crosslinks leads to increased LT activity. Crucially, in vitro assays demonstrated that purified LTs are directly inhibited by LD-crosslinked substrates due to steric hindrance, a specific effect not observed with other glycan-degrading enzymes like lysozymes, which retained full activity. Furthermore, this structural modification was shown to function as a defense mechanism; increasing LD-crosslinking in E. coli effectively protected the cells from lysis by the T6SS effector Tse4 and LT-encoding bacteriophages such as Lambda, significantly reducing plaque formation.

Conclusion

The authors identified a widespread mechanism where LD-crosslinks function as a structural inhibitor of Lytic Transglycosylases. This "safety lock" allows bacteria to fine-tune PG degradation during growth and provides a critical defense strategy against predatory enzymes and phage infection. This discovery highlights the physiological importance of PG crosslinking plasticity in bacterial survival and stress adaptation.