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Molecular dynamics simulation of Toxin–Antitoxin (TA) system in Acinetobacter baumannii to explore the novel mechanism for inhibition of cell wall biosynthesis: Zeta Toxin as an effective therapeutic target

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Abstract

The majority of bacteria and archaea contains Toxin-Antitoxin system (TA) that codes for the stable Toxin and unstable Antitoxin components forming a complex. The Antitoxin inhibits the catalytic activities of the Toxin. In general, the Antitoxin will be degraded by the proteases leading to the Toxin activation that subsequently targets essential cellular processes, including transcription, translation, replication, cell division, and cell wall biosynthesis. The Zeta Toxin-Epsilon Antitoxin system in ESKAPE pathogen stabilizes the resistance plasmid and promotes pathogenicity. The known TA system in Acinetobacter baumannii are known to be involved in the replication and translation, however, the mechanism of Zeta Toxin-Epsilon Antitoxin in cell wall biosynthesis remains unknown. In the present study, molecular docking and molecular dynamic (MD) simulations were employed to demonstrate whether Zeta Toxin can impair cell wall synthesis in A. baumannii. Further, the degradation mechanism of Antitoxin in the presence and absence of adenosine triphosphate (ATP) molecules are explained through MD simulation. The result reveals that the cleavage of Antitoxin could be possible with the presence of ATP by displaying its response from 20 ns, whereas the Zeta Toxin/Epsilon was unstable after 90 ns. The obtained results demonstrate that Zeta Toxin is "temporarily favorable" for ATP to undergo phosphorylation at UNAG kinase through the substrate tunneling process. The study further