The antimicrobial lysine-peptoid hybrid LP5 inhibits DNA replication and induces the SOS response in Staphylococcus aureus - DTU Orbit (25/12/2018)

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ABSTRACT: BACKGROUND: The increase in antibiotic resistant bacteria has led to renewed interest in development of alternative antimicrobial compounds such as antimicrobial peptides (AMPs), either naturally-occurring or synthetically-derived. Knowledge of the mode of action (MOA) of synthetic compounds mimicking the function of AMPs is highly valuable both when developing new types of antimicrobials and when predicting resistance development. Despite many functional studies of AMPs, only a few of the synthetic peptides have been studied in detail. RESULTS: We investigated the MOA of the lysine-peptoid hybrid, LP5, which previously has been shown to display antimicrobial activity against Staphylococcus aureus. At concentrations of LP5 above the minimal inhibitory concentration (MIC), the peptoid caused ATP leakage from bacterial cells. However, at concentrations close to the MIC, LP5 inhibited the growth of S. aureus without ATP leakage. Instead, LP5 bound DNA and inhibited macromolecular synthesis. The binding to DNA also led to inhibition of DNA gyrase and topoisomerase IV and caused induction of the SOS response. CONCLUSIONS: Our data demonstrate that LP5 may have a dual mode of action against S. aureus. At MIC concentrations, LP5 binds DNA and inhibits macromolecular synthesis and growth, whereas at concentrations above the MIC, LP5 targets the bacterial membrane leading to disruption of the membrane. These results add new information about the MOA of a new synthetic AMP and aid in the future design of synthetic peptides with increased therapeutic potential.