Mechanisms of Antimicrobial and Anti-Endotoxin Activities of a Triazine-Based Amphipathic Polymer

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Abstract

Recently, numerous synthetic small molecular peptidomimetics have been designed to overcome the shortcomings of antimicrobial peptides (AMPs), such as protease instability and high production cost. TZP4 is a triazine-based amphipathic polymer designed to mimic the amphipathic structure found in AMPs. Compared to melittin, TZP4 showed superior antimicrobial activity against antibiotic-resistant pathogens, such as methicillin-resistant Staphylococcus aureus and multidrug-resistant Pseudomonas aeruginosa. Results of membrane depolarization, SYTOX Green uptake, flow cytometry, and gel retardation assays suggested that the mechanism of antimicrobial action of TZP4 involved an intracellular target rather than the bacterial cell membrane. Furthermore, TZP4 suppressed the mRNA levels of inducible nitric oxide synthase (iNOS) and tumor necrosis factor-α (TNF-α) and inhibited the release of NO and TNF-α in lipopolysaccharide (LPS)-stimulated RAW264.7 cells. BODIPY-TR-cadaverine displacement and dissociation of Fluorescein isothiocyanate (FITC) labelled lipopolysaccharides (LPS) assays revealed that TZP4 strongly bound to Escherichia coli-derived LPS and disaggregated the LPS oligomers. Additionally, flow cytometric analysis revealed that TZP4 inhibited the binding of FITC-conjugated LPS to RAW264.7 cells. These observations indicate that TZP4 may exert its anti-endotoxin activity by directly binding with LPS and inhibiting the interaction between LPS and CD14+ cells. Thus, we propose that TZP4 is a promising drug candidate for the treatment of endotoxic shock and sepsis caused by gram-negative bacterial infections.

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