DEVELOPMENT OF ANTIMICROBIAL PEPTIDES USING THE JOKER ALGORITHM

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INTRODUCTION: Health care-acquired infections (HAIs) represent a major cause of mortality and increase hospital costs in developing countries. The emergence of resistant microorganisms stimulates the pharmaceutical and biotechnology companies to search for new antibiotics. Antimicrobial peptides (AMPs) are promising candidates as immunomodulatory and anti-infective agents. Here, we analyzed the antimicrobial properties of three synthetic AMPs that were developed using the Joker algorithm. MATERIALS AND METHODS: From a set of 23 peptides designed with the Joker algorithm and screened against a bioluminescent strain of Pseudomonas aeruginosa, three best active AMPs (PaAMP1B1, EcAMP1R4 and mastoparamR4) were selected and further evaluated. Minimal inhibitory concentrations (MICs) were determined against several Gram-positive (Staphylococcus aureus, Streptococcus pyogenes, Enterococcus faecalis, Listeria ivanovii) and Gram-negative (Escherichia coli, Acinetobacter baumannii, P. aeruginosa, Klebsiella pneumoniae) bacteria and against yeasts (Candida albicans, C. parapsilosis). In order to address the antimicrobial mechanism, time-kill studies and membrane permeabilization and depolarization assays were performed. The cytotoxicity of PaAMP1B1 and mastoparamR4 was also determined. RESULTS AND DISCUSSION: All peptides were highly active against Gram-negative bacteria (MIC = 1.5–12.5 μM). PaAMP1B1 was the most potent peptide against Gram-positive bacteria (MIC = 3 μM; MIC = 12.5–50 μM for EcAMP1R4 and mastoparamR4) except for E. faecalis (MIC = 50 μM). Only mastoparamR4 showed activity against C. albicans (MIC = 12.5 μM). At a concentration 2-fold above the MIC, a rapid bactericidal activity was observed for PaAMP1B1 and EcAMP1R4 against E. coli within 5 and 15 min, respectively. However, killing of S. aureus was faster for EcAMP1R4 (15 min) compared to PaAMP1B1 (30 min). Preliminary results showed no cytotoxicity against murine RAW 264.7 macrophages for PaAMP1B1 and mastoparamR4 at antimicrobial concentrations. CONCLUSION: The Joker algorithm is a promising tool for the design of potent AMPs opening the possibility of therapeutic applications.

Keywords: Bacterial resistance, antimicrobial peptides, rational design.
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