Antimicrobial peptide-grafted PLGA-PEG Nanoparticles to Fight Bacterial Wound Infections

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The treatment of chronic wound infections (CWI) using antimicrobial peptides (AMPs) is not yet effective as they lose their activity *in vivo*. In this work, the AMP MSI-78(4-20) was grafted to poly(D,L-lactide-co-glycolide)-polyethylene glycol (PLGA-PEG) nanoparticles (NPs) through a thiol-maleimide (Mal) Michael addition reaction. As opposed to encapsulation, this strategy prevents AMP aggregation and accelerates AMP action. MSI-78(4-20) is a shorter derivative of MSI-78, that shows equivalent antimicrobial action and further selectivity towards bacterial cells [1]. Different ratios of PLGA-PEG/PLGA-PEG-Maleimide (Mal) were tested, and the formulation containing 40% PLGA-PEG-Mal displayed the best colloidal properties and the highest AMP content, as evidenced by NPs zeta potential (+8.6±1.8mV) and AMP quantification (326µg/mL). Regarding the antimicrobial performance, AMP-NPs proved to be as effective as the free AMP with a minimal inhibitory concentration (MIC) of 8-16µg/mL against *Pseudomonas aeruginosa* and 32-64µg/mL against *Staphylococcus aureus*. In addition, AMP grafting reduced the time for complete killing from 1-2h to 15min for *P. aeruginosa* and from 6-8h to 0.5-1h for *S. aureus* (Figure 1). When tested in simulated wound fluid, AMP-grafted NPs maintained the antimicrobial activity against *S. aureus* while loss of activity was observed against *P. aeruginosa*. Importantly, at the MIC concentrations (16 and 32µg/mL) AMP-NPs did not cause cytotoxic effects on human foreskin fibroblasts with respect to their metabolic activity. To sum up, our findings support that AMP-PLGA-PEG NPs represent a promising approach to manage CWI.

References

[1] Monteiro, C., et al., A 17-mer Membrane-Active MSI-78 Derivative with Improved Selectivity toward Bacterial Cells. Mol Pharm, 2015. 12(8): p. 2904-11.

Figures

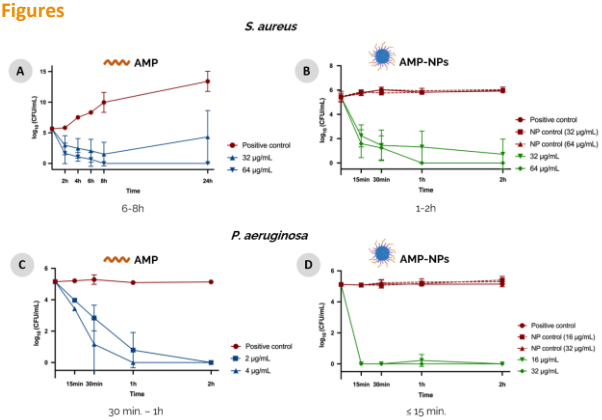

Figure 1: Time–kill assay of AMP (A) and AMP-NPs against *S. aureus* (B); and AMP (C) and AMP-NPs against *P. aeruginosa* (D).