Antimicrobial peptides in the treatment of infectious and inflammatory conditions
Preclinical studies of mechanism of action, efficacy, and safety

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet, kommer att offentligen förvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg, tisdagen den 22 november, klockan 09:00

av

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Avhandlingen baseras på följande delarbeten:


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Abstract

The rapid emergence of antibiotic-resistant microbes worldwide and the urgent need of new antimicrobial agents have stimulated interest in antimicrobial peptides (AMPs) as new therapeutics for treatment of infectious diseases. AMPs are present in all living species and constitute an important part of the innate immune system in multicellular organisms, including humans. AMPs display a remarkably broad spectrum of antimicrobial activity covering both Gram-positive and Gram-negative bacteria, including many antibiotic-resistant strains, as well as fungi, viruses, and protozoa. Further, in contrast to many conventional antibiotics, AMPs rapidly kill bacteria instead of just inhibiting bacterial growth. In addition, AMPs act as modulators of the innate immune system and, importantly, bacteria seem less efficient in developing resistance towards AMPs than towards conventional antibiotics. Together these properties make AMPs highly attractive as a new class of antimicrobials, with clinical potential also extending to diseases where inflammation is part of the pathology.

The aim of this thesis was to study novel AMPs with respect to their mechanism of action (MOA), antimicrobial spectrum, propensity to select for resistance, and in vivo efficacy and safety. To achieve this, we used a number of in vitro and in vivo assays, together generating a comprehensive preclinical evaluation of the peptides. The hypothesis was that the AMPs in this thesis have potential to be developed as therapeutic agents for several infectious and inflammatory conditions, including treatment of skin and soft tissue infections and prevention of postsurgical adhesion formation.

The results showed that all AMPs tested (i.e. PXL03, PXL150, HLR1r, and five variants of CEN1 HC-Br) had broad antimicrobial spectra in vitro with varying sensitivity to salt and serum. Furthermore, PXL150 caused a rapid permeabilization of bacterial membrane in vitro, indicating that this is at least one part of the MOA of this peptide. Under selection pressure in vitro, bacteria did not develop resistance to the peptides tested, i.e. PXL150 and CEN1 HC. Interestingly, all peptides showed anti-inflammatory activity by inhibiting the secretion of proinflammatory mediators from stimulated human cell lines. In addition, PXL01, PXL150, and HLR1r demonstrated fibrinolytic ability in vitro by suppressing the release of plasminogen activator inhibitor-1 (PAI-1). In ex vivo and in vivo skin/wound infection models, the peptides reduced the number of viable bacteria and yeast cells. Further, PXL01 decreased postsurgical adhesion formation in vivo. Notably, nonclinical safety studies showed that PXL150 was safe and well tolerated.

In conclusion, several of the peptides evaluated in this thesis demonstrated a promising preclinical efficacy and safety profile motivating further development as drug candidates for local treatment of infectious and inflammatory conditions.

Keywords: Antimicrobial peptides, AMPs, innate immunity, infection, inflammation, mechanism of action, efficacy, safety, antimicrobial resistance, antibiotic resistance