Bioactive peptides: biomolecules to fight antimicrobial resistance

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Antimicrobial resistance (AMR) is actually one of the principal public health threats. Pathogens, like bacteria virus or fungi, are becoming resistant to conventional antibiotics and new tools are needed to fight their infections, especially at a nosocomial level. Antimicrobial peptides (AMP) are studied as a promising response because they are the first line of defence of the immune system in all organisms. They have usually a broad spectrum of activity and their common target is the cell membrane of the pathogen. Our work is focused on AMPs identified in Antarctic fishes, like chionodracine and trematocine, which are adapted to live in an extreme environment and, therefore, have evolved particular physiological arrangements. Our aim is to find new weapons to fight especially bacteria identified with the acronym ESKAPE (i.e., *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginos*a and *Enterobacter* species) that are among the most common causes of life-threatening infections acquired in health facilities. Usually, the identified peptides are not highly active against human pathogens but, using them as a scaffold and with few amino acids mutations, we have been able to generate molecules with interesting bactericidal activity. Chionodracine mutants showed, as an example, MIC and MBC values between 0.6 (2 μg/mL) and 5 μM (16 μg/mL) against clinical isolates from ESKAPE pathogens, whereas trematocine values ranged between 3 (8 μg/mL) and 10 μM (32 μg/mL). Successively, we studied their selectivity towards cell membranes, and cytotoxicity versus human cell lines. Moreover, we determined *in vitro* their toxicity versus mammalian erythrocytes, and also *in vivo* using an invertebrate model (insect pupae). In conclusion, these AMPs could be considered as new potential drugs for pharmacological applications.

Key words: antimicrobial peptides; ESKAPE pthogens, chionodracine, trematocine, toxicity