Marine Bacteria as a Resource for Novel Antimicrobial Peptides against Multidrug-Resistant Pathogens: (meta)Genomic and Metabolomic Approaches to Biotechnological Production

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Abstract

The use of antibiotics has proved of utmost importance to fight bacterial infections; however, their abuse in human and animal healthcare as well as waste generated by pharma-industries, hospitals and livestock producers have led to the spread of antibiotic resistance. Thus, many pathogenic strains have become multidrug resistant (MDR). The pressing need for new antibiotics has boosted scientific efforts toward the discovery of new classes of antibiotics. Antimicrobial peptides (AMPs) are a class of heterogeneous molecules, which represent a promising therapeutic strategy to overcome MDR challenge.

Bacteria produce two main categories of AMPs, as part of interspecific competition strategies. The first are the nonribosomal peptides (NRPs), including approved antibiotics like vancomycin and bacitracin. NRPs are synthesized by large multimodular enzymes, i.e. nonribosomal peptide synthetases. The second class are the ribosomally synthesized and post-translationally modified peptides (RiPPs), which are synthesized by a precursor peptide and modifying enzymes organized in operons, thereby facilitating their identification *in silico*, cloning and expression in heterologous hosts.

Marine bacteria inhabiting extremophilic niches (deep seas and oceans, hydrothermal vents, high polluted areas, tropical and cold regions) are a prolific source of secondary metabolites, which can have potential applications as pharmaceuticals to treat microbial infections. Therefore, this project finds its highly challenging objective in the sustainable production of AMPs from marine bacteria to perform deeper biological studies. This can be achieved through a) optimization of the lead compound production in the native host or b) metagenomic detection of biosynthetic genes and their subsequent transfer into easily culturable heterologous hosts by recombinant technologies. To this aim, this project will focus on the genome- and functional-based screening of the SZN microbial collection to search for producers of AMPs, including RiPPs and NRPs. In addition, available marine metagenomics datasets will be mined for RiPPs biosynthetic gene clusters to synthesize expression vectors for heterologous production of AMPs from uncultivated microbial communities.

The final aim will be a) the development of an optimal lab-scale fermentation process for AMPs production in native and/or heterologous host and b) the assessment of AMPs antimicrobial activity against Gram-positive and Gram-negative clinical isolates with resistance to conventional antibiotics.