Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

Research Project Proposal
Academic year 2016-2017

Project Nº 53
Title: Antimicrobial peptides to control biofilms associated with medical implants
Department/ Laboratory: Department of Microbiology and Parasitology; School of Medicine
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Summary Biofilms are complex aggregates composed of microorganisms that are embedded in an extracellular matrix containing exopolysaccharide, proteins and nucleic acids. These structures allow microbial cells to adhere to both biotic and abiotics surfaces. It is estimated that up to 65% of bacterial infections are associated with the presence of biofilms (Lewis, 2001; Lebeaux et al., 2014)). In addition, biofilms are extremely difficult to eradicate with the currently available antibiotics, highlighting the importance of developing effective anti-biofilm therapies. Due to their properties, antimicrobial peptides are well suited to counteract the mechanisms of resistance of biofilms. Thus, these compounds are active against bacterial cells at different stages of growth. In addition, they are rapidly bactericidal, have a wide spectrum of activity, and combined with antibiotics, can form synergistic combinations against multiresistant microorganisms. Finally, resistance to antimicrobial peptides arises at much less frequency than that to conventional antibiotics. Because of all this, our hypothesis is that antimicrobial peptides could form the basis of efficient anti-biofilm treatments. We already have a peptide library containing 240 compounds that were derived from human lactoferricin. In preliminary studies, several of these compounds displayed a potent antimicrobial activity against Gram-positive and Gram-negative planktonic bacteria as well as a high permeabilizing activity on *Pseudomonas aeruginosa* and efficiently protected animals against a lethal septic shock. Furthermore, when used in vitro at ten times their minimum inhibitory concentration, these compounds reduced 10,000 times the viability of mature biofilms of *P. aeruginosa* within 1 h. In the present study, we will determine the activity of antimicrobial peptides on microorganisms producing biofilms of high clinical relevance such as the Gram-negative *P. aeruginosa* and *Escherichia coli*, the Gram-positive *Staphylococcus aureus* and the yeast *Candida albicans*. We will perform structure-activity relationship analysis to determine the structural basis of the different activities evaluated (the peptide bactericidal activity both on planktonic and biofilm cells, as well as the peptide ability to remove and/or inhibit biofilm). These studies will allow us to predict and design an improved generation of peptides

(objective 1). After selecting the most promising compounds, we will investigate two strategies to control biofilms. First, we will immobilize the peptides on polymer surfaces (biomaterials) and assess their ability to inhibit biofilm formation (objective 2). Secondly, we will evaluate the use of the peptides (alone or in combination with antibiotics) as anti-biofilm agents on mature biofilms (objective 3). Furthermore, we will conduct studies on the lead compounds to determine their toxicity in eukaryotic cells and their mechanism of action. Finally, the in vivo effectiveness of the two strategies (therapeutic and prophylactic) will be evaluated in a murine model of infection by biofilm producing bacteria using medical devices surgically implanted in the animals (objective 4).

References

Lewis,K. (2001). Antimicrobial Agents and Chemotherapy 45, 999-1007.

Lebeaux D, Ghigo J-M, Beloin C. (2014) Microbiol Mol Biol Rev, 78:510–543.

POSSIBILITY OF PhD

YES*
* (PhD grant required)