Mechanisms of resistance to antimicrobial peptides in Gram-negative pathogens

Introduction

Since antibiotic resistance is spreading among bacteria and only few new antibiotics are currently developed, it is essential to find alternative weapons able to fight multiresistant bacteria. Antimicrobial peptides (AMPs) are potential alternatives to classical antibiotics. They originate from diverse sources, have various structures, and mainly disrupt bacterial membranes. It was first believed that emergence of resistance towards AMPs was negligible. However, it was recently shown that resistance to AMPs is more common than previously thought. In this context, it is essential to investigate mechanisms involved in bacterial resistance to AMPs. We recently observed that modifications of the bacterial surface (outer membrane proteins, lipopolysaccharide) were involved in resistance to AMPs. Interestingly, resistance can be either specific to one AMP or cause cross-resistance to other AMPs.

Aim of this project

In this project, we want to better understand how changes in bacterial surface induces resistance to AMPs. We want to identify and characterize the exact modifications that cause resistance to AMPs and understand the underlying mechanisms that make some of them cause a specific resistance to one AMP, while others induce cross-resistance to several AMPs.

Experimental approaches

We will use microbiological, biochemical and microscopy tools to investigate the role of mutations of outer membrane proteins and changes in lipopolysaccharides structure in the resistance of *Escherichia coli*, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* to AMPs. We will first select in vitro resistance in different bacterial strains and identify by sequencing the mutations causing resistance. These mutations will be inserted in a wild-type strain using CRISPR-Cas9 based targeted mutagenesis, to confirm their role in resistance. We will then investigate the influence of these mutations on bacterial fitness, morphology, and virulence to understand whether acquisition of

resistance has side-effects for the bacteria. Furthermore, we will use biochemical techniques to characterize modifications of bacterial envelope properties, which may explain the resistance to AMPs.

Significance

Resistance to antibiotic is a growing concern for modern medicine. New antimicrobial strategies need to be developed. Antimicrobial peptides may be an interesting alternative to classical antibiotics, but we need to better characterize resistance mechanisms bacteria can develop towards them. This will help to develop strategies to combat the development of resistance and thus avoid that AMPs become rapidly useless.

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