A peptidomimetic strategy to improve the antimicrobial properties of calcitermin

Project goal

The objective of this project is to **synthesize and characterize novel antimicrobial agents with high efficacy against pathogenic microorganisms**, based on **calcitermin**, a natural antibiotic peptide found in human airways. Different classes of mutants will be designed, in order to improve the calcitermin enzymatic stability and biological activity; the physicochemical properties of the most promising products will be deeply investigated, in view of a possible use as treatments against infectious diseases. Since the antimicrobial activity of calcitermin is connected to its interaction with some biological relevant metal ions, chemical modifications will take care of preserving its ligand properties.

Reasons for undertaking the research topic

The reasons behind this research topic are to be found in the **need of innovative antimicrobial therapies**. In fact, despite the improvement of antimicrobial agents over the last decades, there is currently only a limited number of effective drugs against infectious diseases and the phenomenon of **antimicrobial resistance** (the resistance developed by pathogenic microorganisms against a previously effective treatment) still represents a clinical and financial burden on the world health care system. However, the use of antimicrobial peptides (AMPs) represents a promising strategy for the design of new drugs, mostly thanks to their scarce attitude to induce antimicrobial resistance. AMPs are naturally present in the human organism and they are involved in the immune response during infections.

First of all, in order to design an effective antimicrobial peptide-based therapy, it is necessary to optimize the metabolic stability of the employed AMPs. This can be achieved changing the structure of the peptide through the insertion of unnatural amino acids or other chemical alterations. Our first candidate as novel antimicrobial agent is calcitermin, a bioactive peptide found in human airways. This choice arises from its ability to inhibit bacteria and fungi growth, with better performances when it is bound to zinc or copper ions, two crucial metals for the subsistence of both humans and pathogens.

Description of research

The first aim of this project is to design and synthesize novel peptides deriving from calcitermin. There are different possible strategies, and we will explore a variety of possibilities, including several syntheses of peptides containing amino acids which are not recognized by human enzymes, so that they can trick the biodegradation processes.

Synthesis of the peptide sequences will be achieved by means of well-known standard procedures, while purification of the products will be performed using liquid chromatography.

The enzymatic stability of all the new molecules will be tested. Their antimicrobial activity in the presence and absence of metal ions will then be studied against the most common pathogens (Gram positive and negative bacteria, fungi). Special attention will be devoted to the SARS-CoV-2 virus, since calcitermin is present in mucous fluid of the human respiratory tract. Such analyses will allow us to choose the most promising novel calcitermin-derived peptides and corresponding metal complexes. In fact, calcitermin exhibits a better antimicrobial activity in the presence of metal ions.

Finally, this project will focus on how the metals interact with our synthesized molecules, in order to find connections with their biological activity. A broad range of experimental techniques will be employed in order to obtain the thermodynamic parameters of the metal-ligand interaction and to identify the binding sites and the coordination geometry of the formed metal complexes.

Expected results

We expect to find new non-natural peptides or peptidomimetics with improved enzymatic stability and promising antimicrobial activity. Modifications of the peptide structure will confer higher proteolytic stability. Furthermore, the ability to interact with metals will be possibly preserved and checked for the new synthesised and most promising peptide derivatives. We expect that the microbicidal activity is linked to the metal coordination ability of the peptide, considering that metals can act as cofactors (molecules which interact with a peptide/protein to guarantee its biological activity), having a structural function and intervening as “nutrient” for both the human and the pathogen. Taking into account the possibility to find a correlation between biological activity and metal interaction, we are also quite confident to obtain novel classes of antimicrobial agents that will serve as starting material for new therapeutic strategies against infectious diseases.