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Synthesis of an antimicrobial peptide with a cleavable photolabel for lipid partner identification by mass spectrometry

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Scientific project

1/ Project

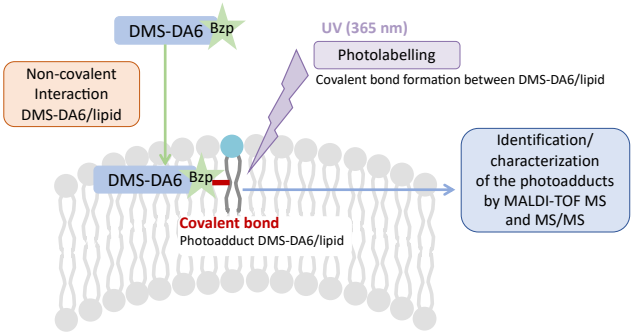
Antimicrobial peptides (AMPs) is a class of membrane-active peptides which kill microorganisms by permeabilizing their membrane or acting on different cytoplasmic targets. Understanding their mode of action is of great interest to develop novel therapeutic peptides. Membrane-targeted AMPs act by interacting with membrane lipids and/or other cell-wall components.

Non-covalent peptide/lipids interactions can be studied by photolabelling coupled to mass spectrometry (MS) by creating a covalent bond between a photoreactive peptide incorporating a UV photoactivatable benzophenone (Bzp) and its lipid partner in the membrane (Walrant & Sachon 2021, Jiao et al. 2017; Bechtella et al. 2019).

We are currently developing this strategy with the AMP DMS-DA6-NH_2 (GVWGIAKIAGKVLGNILPHVFSSNQS-NH_2) and optimized photolabelling yields were obtained by varying the position of the Bzp in the peptide (unpublished data). Due to the dual hydrophilic/hydrophobic properties of the photoadduct, MS analyses are challenging and the introduction of a cleavable linker between the Bzp photolabel and the peptide would greatly simplify sample handling and analysis.

In parallel, a structure activity relationship study has been initiated on DMS-DA6-NH_2. Substituting Asn (N) in position 15 by a Lys (K) enhanced the antimicrobial activity compared to DMS-DA6-NH_2. Interestingly, this analogue remains non-cytotoxic and non-hemolytic.

In the proposed project we first aim to synthesize a Bzp derivative with thiol group that could be reversibly attached to a cysteine residue on the peptide through a disulfide bond. We then aim to further investigate the N15K mutant of DMS-DA6-NH_2 to get more information on its interactions with membranes.



2/ Methods

Solid-phase peptide synthesis, MALDI-TOF MS, Photocrosslinking, Liposomes and model membranes, Calorimetry, Antimicrobial tests, Biochemistry…

3/ References

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-Jiao CY, Sachon E, Alves ID, Chassaing G, Bolbach G, Sagan S, Exploiting Benzophenone Photoreactivity To Probe the Phospholipid Environment and Insertion Depth of the Cell-Penetrating Peptide Penetratin in Model Membranes. *Angew Chem*, **2017**, 56 (28), 8226-30

-Walrant A, Sachon E, Photolabeling strategies to study membranotropic peptides interacting with lipids and proteins in membranes, *Bioconjug Chem*, **2021**, 32 (8), 1503-14