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Abstract

Lipopeptide Antibiotics Derived from Polymyxin B with a Broad Spectrum of Activity: Membrane Interaction †

Yolanda Cajal [1,2,*], Roser Segovia [3], Angeles Manresa [4], Ariadna Grau-Campistany [5] and Francesc Rabanal [3]

[1] Department of Pharmacy, Pharmaceutical Technology and Physical Chemistry, Faculty of Pharmacy and Food Sciences, University of Barcelona, 08028 Barcelona, Spain
[2] Institute of Nanoscience and Nanotechnology (IN2UB), University of Barcelona, 08028 Barcelona, Spain
[3] Section of Organic Chemistry, Department of Inorganic and Organic Chemistry, Faculty of Chemistry, University of Barcelona, 08028 Barcelona, Spain; roser_sl_92@hotmail.com (R.S.); frabanal@ub.edu (F.R.)
[4] Laboratory of Microbiology, Faculty of Pharmacy and Food Sciences, University of Barcelona, 08028 Barcelona, Spain; amanresa@ub.edu
[5] Department of Pharmacy, Pharmaceutical Technology and Physical Chemistry, Faculty of Pharmacy and Food Sciences, University of Barcelona, 08028 Barcelona, Spain; a.graucampistany@gmail.com
* Correspondence: Yolanda Cajal, ycajal@ub.edu
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Antimicrobial peptides offer a new class of therapeutic agents to which bacteria may not be able to develop genetic resistance, since they act on the lipid component of the cell membranes [1]. Among these compounds, polymyxin B (PxB) is acquiring new therapeutical relevance and is starting to be considered as a representative of a new class of antibiotics against multiresistant bacteria. PxB and other members of the polymyxin family such as colistin are drugs of last resort to treat Gram-negative multiresistant infections. We have designed new synthetic antimicrobial lipopeptides with Gram-positive and Gram-negative activity derived from the structure of the Gram-negative selective antibiotic PxB [2]. Biophysical studies with model membranes show that the peptides bind to zwitterionic and anionic membranes, but they require the presence of anionic lipids to disrupt the membrane. The inclusion of Arg residues instead of natural Dab favors the insertion in the bacterial lipid membrane and allows passage of the peptides across the bilayer. The presence of (D) Trp favors membrane interaction and confers the molecule intrinsic fluorescence properties that allow the determination of membrane binding. The substitution of Leu by the more flexible NLeu increases the permeabilizing and fusogenic capacity. The new lipopeptides described here are good candidates to become new antimicrobials, although further work needs to be done to ascertain their molecular mechanism of action.

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