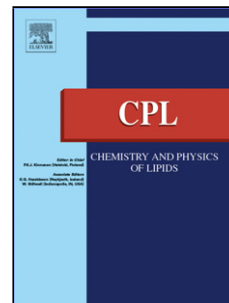


Accepted Manuscript

Title: Mechanistic studies on the effect of membrane lipid acyl chain composition on daptomycin pore formation

Author: David Beriashvili Robert Taylor Braden Kralt
Nooran Abu Mazen Scott D. Taylor Michael Palmer



PII: S0009-3084(18)30168-3
DOI: <https://doi.org/doi:10.1016/j.chemphyslip.2018.09.015>
Reference: CPL 4691

To appear in: *Chemistry and Physics of Lipids*

Received date: 27-8-2018
Revised date: 26-9-2018
Accepted date: 27-9-2018

Please cite this article as: David Beriashvili, Robert Taylor, Braden Kralt, Nooran Abu Mazen, Scott D. Taylor, Michael Palmer, Mechanistic studies on the effect of membrane lipid acyl chain composition on daptomycin pore formation, *Chemistry and Physics of Lipids* (2018), <https://doi.org/10.1016/j.chemphyslip.2018.09.015>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Mechanistic studies on the effect of membrane lipid acyl chain composition on daptomycin pore formation

David Beriashvili¹, Robert Taylor¹, Braden Kralt, Nooran Abu Mazen, Scott D. Taylor, Michael Palmer*

Department of Chemistry, University of Waterloo, Waterloo, ON N2L 3G1, Canada

Abstract

Daptomycin is a lipopeptide antibiotic that binds and permeabilizes the cell membranes of Gram-positive bacteria. Membrane permeabilization requires both calcium and phosphatidylglycerol (PG) in the target membrane, and it correlates with the formation of an oligomer that likely comprises eight subunits, which are evenly distributed between the two membrane leaflets. In both bacterial cells and model membranes, changes in the fatty acyl composition of the membrane phospholipids can prevent permeabilization. We here used liposomes to study the effect of phospholipids containing oleoyl and other fatty acyl residues on daptomycin activity, and made the following observations: 1) Oleic acid residues inhibited permeabilization when part not only of PG, but also of other phospholipids (PC or cardiolipin). 2) When included in an otherwise daptomycin-susceptible lipid mixture, even 10% of dioleoyl lipid (DOPC) can strongly inhibit permeabilization. 3) The inhibitory effect of fatty acyl residues appears to correlate more with their chain length than with unsaturation. 4) Under all conditions tested, permeabilization coincided with octamer formation, whereas tetramers were observed on membranes that were not permeabilized. Overall, our findings further support the notion that the octamer is indeed the functional trans-membrane pore, and that fatty acyl residues may prevent pore formation by preventing the alignment of tetramers across the two membrane leaflets.

Keywords: calcium-dependent lipopeptide antibiotics, phosphatidylglycerol, cardiolipin, membrane fluidity, membrane permeabilization

1. Introduction

The lipopeptide antibiotic daptomycin is used clinically to treat infections with Gram-positive bacteria such as *Staphylococcus aureus* and *Enterococcus faecium*. It

*Corresponding author

Email addresses: dberiashvili@edu.uwaterloo.ca (David Beriashvili), rmtaylor@uwaterloo.ca (Robert Taylor), bjkralt@gmail.com (Braden Kralt), nooran.abumazen@edu.uwaterloo.ca (Nooran Abu Mazen), s5taylor@uwaterloo.ca (Scott D. Taylor), mpalmer@uwaterloo.ca (Michael Palmer)

¹These authors contributed equally to this work.

Download English Version:

<https://daneshyari.com/en/article/11032842>

Download Persian Version:

<https://daneshyari.com/article/11032842>

[Daneshyari.com](https://daneshyari.com)