Canadian Association of Physicists | Association canadienne des physiciens et physiciennes

Contribution ID: **1887** Type: **CLOSED - Oral (Student, Not in Competition) / Orale (Étudiant(e), pas dans la compétition)**

Membrane Cholesterol Protects Against Polymyxin B Nephrotoxicity in Renal Membrane Analogues

Tuesday 30 May 2017 14:45 (15 minutes)

At the dawn of the post-antibiotic era, the use of "last-line"antibiotics continues to rise due to emergence of antimicrobial resistant bacteria. Until 2015, polymyxin B (PmB), a membrane rupturing antibiotic, was the last without known resistance. Unfortunately, the drug has been clinically hindered from conception due to the occurrence of kidney-related side effects. However, the mechanisms by which PmB damages kidney tissue has remained unknown. We have prepared analogues for renal membranes to uncover the mechanisms of PmB nephrotoxicity and the carpet model of insertion through X-ray diffraction, Molecular Dynamics (MD) simulations, and electrochemistry.

By probing the membrane at angstrom level resolution, we observe cubic phases with the incorporation of PmB indicating the formation of a "spongy"porous membranes. We find that PmB exists in two states, either membrane-bound or inserted. PmB in the membrane-bound state is able to form aggregates, induce membrane thinning and increase membrane curvature, whereas PmB in an inserted state can increase water permeation. The presence of cholesterol in the membrane greatly diminishes the membrane-damaging interaction of PmB. With MD simulations, we show that inserted PmB have 4-fold decreased lateral diffusivity when cholesterol is present. From this, we show that antimicrobial peptides induce membrane damage by puncturing the membrane and subsequent membrane effects. Membrane cholesterol inhibits the following resulting membrane effects. In summary, we provide mechanistic understanding of PmB's mechanism of action and the carpet model of antimicrobial insertion.

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Session Classification: T3-7 Soft Matter and Molecular Dynamics (DPMB) | Matière molle et dynamique moléculaire (DPMB)

Track Classification: Physics in Medicine and Biology / Physique en médecine et en biologie (DPMB-DPMB)