

An Unprecedented Molecular View of Lipopeptides Antibiotics Actions on Membranes with Drug Discovery Implications

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DESCRIPTION

The world is running out of antibiotics. In the last decades, antibiotic development has stagnated, while antibiotic resistance continues to rise. The European Centre for Disease Prevention and Control estimates that currently in Europe, 25,000 patients die per year due to antibiotic-resistant bacterial infections.

Lipopeptides (LPs) are a promising class of antibiotic drugs against the bacterial membrane only investigated to a limited degree. The characterization of the lipid-lipopeptide interactions has been proven to be difficult. One of the advantages of the LPs is that they develop less bacterial resistance than other antibiotic drugs. LPs have unique structural composition (a cyclic head group attached to a single lipid chain) different from other antimicrobial agents; consequently, their mode of action also differs from most antimicrobial agents. LPs action is multifaceted and complex, hence, the correlation of their structures with their precise actions is challenging. Our lack of knowledge on LPs mechanisms of action has hindered the potential of medical development of the LPs [1]. In the last years, the approval for medical use of the antimicrobial LPs Daptomycin (Dap) in 2003 and, more recently, Oritavancin, Dalbavancin, and Telavancin shows there is increasing activity in the medical application of LPs as antibiotics.

The complex chemical structure of the LPs also poses problems for production, as chemical synthesis of LPs has seldom been achieved. Recently, progress has been made in this direction. Recent advances in chemical peptide synthesis are providing us new tools, and the chemical optimization and tuning of the structures of the LPs, there are numerous homologues and isoforms is becoming increasingly possible, as well as an alternative to fermentation, and a route for industrial production, hence, further improving the future outlook for the LP family of antibiotics [2].

Despite their biomedical usefulness, a detailed comprehension of the action of the LPs has remained elusive. Importantly, the mode of action of LPs differs from other drugs, while most drugs target the specific regions of specific molecules, the ligand-drug interaction, the action of the LPs does not associate, in most cases, to a specific target, alternatively, the LPs modify the bulk properties of the bacterial membrane on heterogeneous pathways of action.

The particularity of the action of the LPs makes its characterization by the conventional techniques used for other drugs challenging.

Despite the approval of Dap for the treatment of skin infections caused by Gram positive bacteria in 2003, the mechanism of action of Dap remains unclear. Dap is a paradigm for the mechanisms of action of LPs; contrary to most drugs, Dap does not count with any nonspecific molecular target. Only the initial simpler steps of Dap action are known. Initially, Dap inserts in the outer membrane of the bacterial membrane where it raises the lateral pressure, and, thus, creates a pressure difference between the inner and outer leaflets that will give yield to a plethora of membrane deformations that in combined action will destabilize the structure of the bacterial membrane and kill the bacteria. The multiple combined action strategy of Dap differs from that of most drugs that target specific locations on specific biomolecules to alter specific stages of a metabolic pathway. Logically, given the difference in the action of Dap with respect most drugs, the conventional techniques employed in the study of most drugs are not optimal for the Dap case, because they focus on specific drug-ligand interactions and for its study they obtain and average the information from large amounts of molecules which lowers their sensitivity for the multiple and parallel actions of the drugs. In our recent publication, we showed that thanks to an implementation of the High-Speed Atomic Force Microscopy (HS-AFM) for the study of LP drug actions, we could, for the first time, visualize and quantify the pathways of action of Dap on membranes [3].

Our work is unique as it is the first time the HS-AFM was used for assessment of the action of drugs on membranes at the molecular-level. The HS-AFM is a young technique little more than 15 years old that achieves imaging speed around 1000 times faster than conventional atomic force microscopes [4]. Thanks to the HS-AFM that is capable of imaging under infection-like conditions we identified for the action of Dap the stoichiometry and energy profile of interaction of the antimicrobial oligomers, the structure of trans-membrane pores that permeabilize the membrane, as well as the mechanism of formation of the pores, or the mechanism of creation of tubulations that eject material out of the membrane, among others. Overall, our unprecedented time-sequences of the

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heterogeneous actions of Dap on membranes provided us with a novel and powerful tool for the analysis of the mechanisms of action of this LP.

CONCLUSION

In the future, we will continue to work on the application of the HS-AFM for drug discovery with special focus on LPs. We hope that the unique information the HS-AFM can provide will, one day, be incorporated to the protocols of drug discovery, for example for the training of in-silico drug discovery algorithms. HS-AFM analysis can be especially useful for those drugs that present high-levels of heterogeneous and non-specific activity on the cell membrane.

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