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To Fully Exploit the Therapeutic Potential of Antimicrobial Peptides, Additional Research is Required to Develop Improved Bacterial Lipid Membrane Model Systems

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For an antimicrobial peptide to be deemed therapeutically effective it must selectively disrupt bacterial membranes while leaving mammalian membranes intact. The chemical composition, and thus the physicochemical properties, of the lipid membranes of bacteria cells play a defining role in determining the membrane selectivity of antimicrobial peptides. It is therefore critically important to develop an understanding of how the physicochemical properties of antimicrobial peptides interact with the physicochemical properties of lipid membrane in order to maximize membrane selectivity and thus the therapeutic potential of antimicrobial peptides. To address this issue there are two questions that must be answered. One, what types of lipid models are most appropriate to use to mimic the various types of bacterial membranes? And secondly, what types of experiments should be conducted to provide the most useful information in order to design antimicrobial peptide with increased therapeutic potential.

Bacterial membranes are known to contain a much higher concentration of anionic lipids than mammalian membranes. For example the Gram positive strains *s.aureus,* 57 % of its lipid membrane is composed of POPG, while for *s.epidermidis,* 90% of its lipid composition is POPG, and for *B.subtilus,* the percentage of POPG is reduced to 29% [1]. While the membranes of the Gram negative strains *S.typimurium*, *P.cepacia* and *E. coli* contain only 33, 18 and 6 percent POPG respectively [1]. The percentage of POPE found in the Gram positive bacteria *B.subtilus* and *B.megaterium* is 10 and 40% respectively. However, for the Gram negative strains *S.typimurium*, *P.cepacia* and *E. coli* the POPE composition increases to 60, 82 and 82 percent respectively [1]. It is therefore critically important to employ the correct anionic lipid in the proper concentration when conducting investigation of the physicochemical interactions that occur between lipids and antimicrobial peptides. The development of appropriate membrane models for these types of investigations is an area where membrane scientists can have a major impact on the development of new novel antimicrobial peptides into useful therapeutic agents. Clearly to better understand peptide-membrane interactions there is a clear need to develop strain specific membrane model systems. One simple model system of zwitterionic and anionic lipids will not provide the appropriate insight into the physicochemical interactions that occur between antimicrobial peptides and various strains of bacteria. Additional research is needed in this area. For example, a common

model for mammalian membranes consists of 100% POPC lipids; however a better model would also incorporate a small percentage of cholesterol into the lipid to better mimic the local chemical environment of red blood cells. This is important because it has been shown that incorporation of cholesterol into a lipid bilayer can prevent the insertion of membrane penetrating peptides into the lipid bilayer. The incorporation of unnatural amino acids into the primary sequence of antimicrobial peptides induces different physicochemical properties, such as charge density and hydrophobicity, not found in the 20 RNA encoded amino acids normally found in peptides. Therefore, once various lipid compositions have been developed to mimic various strains of bacteria, investigations into the interaction of peptides containing unnatural amino acids with these lipids should be conducted to expand our knowledge of how physicochemical properties affect peptide-lipid interactions. The second issue that must be addressed is the types of experiments that need to be conducted on these new model systems in order to obtain the maximum amount of information. Of course traditional experimental methods such as circular dichroism spectroscopy, isothermal titration calorimetry and induced calcein leakage from LUVs monitored through fluorescence to investigate peptide-lipid interactions must be employed. However, the underutilized technique of High Resolution Magic Angle Spinning Nuclear Magnetic Resonance Spectroscopy will provide three-dimensional structural information concerning the structure adopted by the antimicrobial peptide on binding to small unilamellar vesicles of various compositions unavailable by other techniques. From these structures the contributions of various three-dimensional physicochemical properties can be calculated, thus providing a wealth of currently unavailable information.

These investigations will provide additional insight into how the interactions of the physicochemical properties of peptides and membraneslead to increased antibacterial activity. These investigations also will provide medicinal chemists a "toolbox" of critically needed information to facilitate the development of novel, potent and selective therapeutically useful antimicrobial peptides.

Reference

1. Lohner K, Prenner EJ (1999) Differential scanning calorimetry and X-ray diffraction studies of the specificity of the interaction of antimicrobial peptides with membrane-mimetic systems. Biochim Biophys Acta 1462: 141-156.

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