experiments. We also performed simulations of systems containing melittin peptides and charged membranes consisting of a DPPC/POPG mixture and using a polarisable water model. We observed that melittin spontaneously inserted into the bilayer and formed transmembrane aggregates consisting of 2-3 peptides. These aggregates then fell apart causing a transient toroidal pore as peptides translocated to the other leaflet of the membrane. Melittin was also found to cause lipid flip-flops between the leaflets.

3101-Pos Board B256

Membrane-Binding Properties of the Antimicrobial Peptide Maximin 3

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Antimicrobial peptides (AMPs) are part of the innate immune system of most organisms, where they protect the organism from a variety of microbial agents. Research is ongoing to utilize AMPs and their derivatives for medicinal purposes, such as antibiotics that are less likely to induce antibiotic resistance in bacteria. This work focuses on the AMP Maximin 3, which is derived from the skin secretions of the toad Bombina maxima. Maximin 3 is a 27 amino acid cationic peptide that has strong activity against a variety of bacterial, fungal, and viral microbes and is thought to cause toxicity by interaction with the plasma membrane, though this interaction has not previously been observed. However, Maximin 3 is also toxic to mammalian cells and cannot be used therapeutically. The goal of this work is to characterize the membrane-binding of Maximin 3 with the ultimate goal of redesigning its sequence to increase selectivity for microbial membranes.

This work examines four aspects of Maximin 3's interaction with membranes. First, fluorescence anisotropy was used to quantify the binding of Maximin 3 to model lipid membranes that mimic the composition of microbial or mammalian membranes. Maximin 3 was also observed binding to E. coli using fluorescence microscopy. Second, Förster resonance energy transfer was used to examine the structural changes that Maximin 3 undergoes upon membrane binding and to probe for structural differences between Maximin 3 bound to bacterial and mammalian model membranes. Third, fluorescence-based vesicle leakage assays were used to directly monitor membrane disruption caused by Maximin 3. And fourth, predicted structures of Maximin 3 and other Maximin peptides bound to membranes were prepared using Rosetta. Our results provide a comprehensive picture of Maximin 3 membrane interactions and suggest sequence modifications that may increase selectivity of the peptide.

3102-Pos Board B257

Insight into the Lytic Mechanism of Antimicrobial Piscidin 1 and 3 using QCM-D

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In this work, we focused on piscidin 1 (P1) and 3 (P3), which are twenty-two-residue-long amphipathic, cationic antimicrobial peptides (AMPs) isolated from hybrid striped bass. Extensive work has been reported on characterizing the atomic-level structure of both P1 and P3 in magnetically and mechanically aligned bilayers using solid-state NMR. Here we investigated the mechanism of action of both P1 and P3 with supported lipid bilayers (SLB), using a quartz crystal microbalance with dissipation monitoring (QCM-D). In order to mimic bacterial cell membranes, we selected a 3:1 ratio of 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) to 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphoglycerol (POPG). Liposomes were deposited onto a QCM-D silicon oxide crystal until SLB formation, then P1 and P3 were introduced into the system and the interaction between the peptide and the lipid system was monitored by changes in frequency (Δf) and energy dissipation (ΔD). Different concentrations (2-20 μM) of the peptide and buffer conditions (pH 6.0 and 7.4) were tested. In particular we observed a Δf increase (~ mass removal) as we increased the concentration of P1 at pH 7.4, suggesting lipid removal, membrane thinning, or pore formation; while at pH 6.0 the Δf decrease (~ mass addition) was probably due to the electrostatic interaction between the more cationic peptide and the anionic POPG. For a quantitative assessment of the effects on the SLB, we have obtained the shear viscosity and shear modulus as a function of piscidin type and concentration via a fit of the well-known Voigt model to the data. In all cases, ΔD values were a clear indication of the destabilization of the SLB. Overall, this study, which demonstrates quantitative P1 and P3 disruption of a bacterial membrane mimic, assists in better understanding the mode of action of piscidins and related AMPs.

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The Antimicrobial Peptides Pore Formation Induce by Ginsenoside Effect in Lipid Bilayers

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The ginsenoside is extracted from the ginseng. Most people believe it is good for health. Ginsenoside has long been reported to be biologically active, most often as having anticancer, anti-transfer for the tumor and will increase the immunity. In the recent research, we found the ginsenoside has obvious thinning effect and we also found the antimicrobial peptides have thinning effect, too. However, how the ginsenosides influences the peptide state in the lipid bilayers is still not clear. In this paper, we used the lamellar x-ray diffraction(LXD) and the oriented circular dichroism(OCD) to study the ginsenosides effect on the peptides pore formation. The result shows the ginsenosides will induce the melittin to transit into the insertion state more easily. That implies the ginsenosides will first bind to the lipid bilayers and reduce most of the head-group volume of the lipid bilayers. Therefore, the melittin binding to the lipid bilayers will enhance larger deformation energy after the ginsenosides. It also supports that the ginsenosides can effectively control the host membrane and then affects the state of the peptdes, so it will induce the peptide to transit into the insertion state from the surface state more easily.

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Investigation of the Mechanism of Antimicrobial Lipopeptides using Coarse-Grained Molecular Dynamics Simulations

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Antimicrobial lipopeptides (AMLPs) are a series of acylated cationic peptides with broad-spectrum antimicrobial activity and low hemolytic activity. We used microsecond-scale coarse-grained molecular dynamics simulations with the MARTINI force field to understand AMLPs' modes of action. Rigorous free energy calculations have been performed to probe the mechanism for their selectivity for different membranes. Although these studies provided useful insights, artifacts arising from the coarse representation of electrostatics in MARTINI force field complicated further interpretation of the simulations. To address this deficiency, we are developing a new coarse-grained force field for AMLPs and lipids based on elliptical Gay-Berne van der Waals potential and electric multipoles. This force field will retain much of the computational efficiency of current coarse-grained models while the detailed representation of electrostatics and molecular shape in this force field will provide more realistic descriptions of molecular interactions among AMLPs and membrane lipids.

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Effects of Arginine and Arginine Mimics on Antimicrobial Peptide Behavior

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Antimicrobial peptides are naturally occurring components of the innate immune system which serve as a first line of defense against bacterial infection. While hundreds of antimicrobial peptides have been identified from natural sources, there is little in the way of consensus sequences that can identify peptides as antimicrobial. Instead, these peptides are more easily defined by the chemical properties of amphiphilicity, cationic net charge, and short length (10-30 aa). In an attempt to further elucidate the chemical mechanisms that play a role in antimicrobial activity, we compared two template peptides (C18G derived from human platelet factor and Ponericin L1 derived from ponerine ant venom) which contain arginine as the cationic moieties to the analgous pair which contain 2 - amino - 3 - guanidinopropionic acid. This effectively shortens the side chain length without modifying the cationic identity. We characterized these systems using a combination of CD spectroscopy for structure formation, fluorescence spectroscopy and quenching for lipid binding affinity, and microbiological techniques to investigate antibacterial efficacy. We found that the arginine analogs behaved similar to the parent peptides with respect to secondary structure formation in the presence of lipid bilayers, ability to permeabilize bacterial membranes, and ability to bind to anionic bilayers with high affinity. The same experiments were carried out on the 2 - amino - 3 - guanidinopropionic acid analogs. Overall this approach allows for SAR-like investigations into peptide structure/function relationships using natural and non-natural amino acids.