that arginine binding to phosphatidylglycerol is more favorable by only ~1 kcal/mol, suggesting that lipid binding domains and antimicrobial peptides likely require many charged side chains acting together to promote membrane localization.

434-Pos
Physical Modeling of Membrane-Lytic Antimicrobial Peptides: Toward Optimizing Their Membrane Disrupting Activity
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Antimicrobial Peptides (AMPs) are fast microbe-killing molecules found in virtually-all living organisms. Membrane-active AMPs are of particular interest, since they do not easily induce bacterial resistance. Accordingly, these peptides offer promising design principles for developing potent peptide antibiotics, especially for fighting conventional antibiotic-resistant bacteria. Here, we present a physical basis for optimizing the selective membrane-disrupting activity of cationic AMPs. Our approach explains the vital feats of the peptide, shedding quantitative insights into their design principles: Threshold peptide coverage on the membrane surface required for disruption can easily be reached for microbes, but not for the host cell - large peptide charge (> 4) is shown to be the key ingredient for determining the optimal activity-selectivity of AMPs (in an ambient-salt dependent way). Our results also illustrate how reduced fluidity of the host cell membrane by cholesterol enhances the selectivity.

435-Pos
The Role of Hydrophobicity in Peptide-Membrane Interactions: Insights Through Coarse-Grained Molecular Dynamics Simulations
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Peptide-membrane interactions are complex and diverse phenomena, highly important for various biological processes, such as antimicrobial defence mechanisms, viral translocation, membrane fusion and different functions of membrane proteins. Despite the extensive theoretical and experimental on-going research in the area of these interactions, the underlying mechanisms remain unclear. Here, we will present the latest results of our study on simulations of peptide-membrane interactions, based on the coarse-grained MARTINI force field [1, 2]. We will discuss about the possibility of classifying α-helical peptides into groups according to their hydrophobicity and predicting their interaction with cell membranes [3, 4]. Structural and dynamical properties related to various interaction patterns will be presented. Moreover, results of the potential of mean force (PMF) for peptide translocation across the lipid bilayer calculated for each class of peptides will be presented and compared. Finally, we will examine the possibility of simulating stages of the endocytic pathway and discuss about the reliability as well as wider implications of these results.
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436-Pos
A Comparative Study on the Effect of Hydrophobicity and Net Positive Charge on the Antibacterial and Anti- Endotoxin Activities of Antimicrobial Peptides
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The bacterial outer membrane, lipopolysaccharide (LPS), can serve as a barrier that protects bacteria from antimicrobial peptides (AMPs). However, LPS can also activate immune cells that in sever cases may cause death. This activity can also be neutralized by several AMPs. However, it is difficult to determine common denominators required for antimicrobial and LPS neutralizing activities. To this end, we synthesized and investigated a series of 12-mer D,L-amino acid peptides and their fatty acid-conjugated analogs composed of Leu and Lys with increasing number of positive charges and decreasing hydrophobicities, and with preserved positions for the D-amino acids. The overall altered helical structure in the membrane is similar for all of them as determined by FTIR spectroscopy. All the peptides were tested for their antibacterial and hemolytic activity, their ability to permeate LPS vesicles, to neutralize LPS activation of macrophages, as well as their effect on LPS morphology, determined by negative staining electron microscopy. The data reveal that whereas antimicrobial activity increases linearly with the increase in the peptides' hydrophobicity, peptides with different hydrophobicities are endowed with similar LPS neutralizing activities. Besides its importance to the understanding of antimicrobial and LPS neutralizing activities, this study suggests the use of such diastereo-mers as potential templates for the development of simple molecules that carry out both types of functions.

437-Pos
Cationic Antimicrobial Peptides: A Physical Basis For Their Selective Membrane-Disrupting Activity
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Antimicrobial peptides (AMPs) are not only fast microbe-killing molecules deployed in the host defense of living organisms but also offer valuable lessons for developing new therapeutic agents. While the mode of action of AMPs is not clearly understood, membrane perturbation has been recognized as a crucial step in the microbial killing mechanism of many AMPs. Here, we present a physical basis for the selective membrane-disrupting activity of cationic AMPs. In particular, we calculate the surface coverage of peptides embedded in the lipid headgroup-tail interface and the resulting membrane-area change, in terms of peptide and membrane parameters (e.g., peptide charge and the fraction of anionic lipids). We find threshold peptide coverage on the membrane surface required for disruption can easily be reached for microbes, but not for the host cell - large peptide charge > 4) is shown to be the key ingredient for the optimal activity-selectivity of AMPs (in an ambient-salt dependent way). Intriguingly, we find that in a higher-salt environment, larger charge is required for optimal activity. Our results also illustrate how reduced fluidity of the host cell membrane by cholesterol is implicated in the selectivity.

438-Pos
Energy Barriers and Helix Plasticity in the Membrane Insertion of pHLIP
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The pH (low) insertion peptide (pHLIP) is a 36-aa monomeric peptide which is both soluble in water and able to insert as a transmembrane helix in lipid membranes at low pH. Thus, pHLIP has three major states with characteristic secondary structure: it is unstructured in solution (state I) and when bound to the surface of lipid membranes at neutral pH (state II). However, it forms a transmembrane helix in membranes at acid pH (state III), with a pKa of insertion between states II and III of 6.0. The lipid insertion of pHLIP is mediated by the protonation of at least two Asp residues. Thus, pHLIP has to deal with the translocation of acidic residues through the membrane to insert.
Here, we designed several mutant peptides where the number of aspartic residues in the hydrophobic region of pHLIP was modified. Some mutations altered peptide behavior in solution and their interaction with lipid. At the same time, we observed that there was an apparent linear relationship between the number of Asp and both the observed pKa and the cooperativity of the insertion and/or folding in the membrane.
In order to study the role of transmembrane helix formation in the lipid insertion of pHLIP, we designed a mutant peptide where the key residue Pro20 had been mutated to Gly. This peptide retained the overall properties of pHLIP, however both the interfacial (II) and the transmembrane (III) states had a higher helical content than wt pHLIP, and the pKa of insertion was also higher.
Our data suggest that i) the number of Asp and their location at the water-lipid interface affect the pKa and/or cooperativity of the transition and ii) the formation of the membrane interfacial helix promotes peptide insertion into the membrane.

439-Pos
Lipid Membrane Destabilisation By Arginine Peptides Is Chain Length Dependent
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The intracellular delivery of proteins and other bioactive molecules using membrane-permeable carrier peptide vectors is a way to elucidate and control cell functions with therapeutic potentials. One of the most typical peptide vector is a short arginine-rich peptide segment derived from the human immunodeficiency virus (HIV)-1Tat protein as well as various arginine-rich oligopeptides. These peptides seems to translocate with their cargo into eukaryotic cells through a physical mechanism which is neither receptor-mediated and does not implicate endocytosis. Other studies have however implicated an endocytic pathway involving macropinocytosis. We provide here evidence that arginine peptides induce membrane destabilisation in DMPC and DMPG liposomes which is dependent of the arginine peptides length. Evolution of the CH_2- vibration of lipids was monitored by ATR-IR (Attenuated Total Reflection