Structure Of Complexes Of Helix-5 From Bax With Lipid Membranes

ARTICLE *in* BIOPHYSICAL JOURNAL · JANUARY 2009

Impact Factor: 3.97 · DOI: 10.1016/j.bpj.2008.12.726

5 AUTHORS, INCLUDING:

Gustavo Fuertes Vives

European Molecular Biology Laboratory

23 PUBLICATIONS **210** CITATIONS

SEE PROFILE

Santiago Esteban-Martín

Barcelona Supercomputing Center

31 PUBLICATIONS **622** CITATIONS

SEE PROFILE

Jesús Salgado

University of Valencia

95 PUBLICATIONS **1,751** CITATIONS

SEE PROFILE

bilayers, a body centered tetragonal crystal packing of Alm channels is formed. As the hydration level increases closer to biological conditions, the separation between bilayers increases, the interbilayer interactions weaken, and the crystalline order disappears while considerable diffuse scattering remains. The effect of hydrophobic mismatch is examined for two mono-unsaturated lipids, diC18:1PC and diC22:1PC, that differ in bilayer thickness by 7.3 Å. There is also additional in-plane scattering at a medium q of 0.7 $Å^{-1}$ that our analysis suggests may not be from the Alm channel structure.

820-Pos Board B699

Characterization of the Dynamic Structural Changes of Melittin - Lipid Bilayer Interactions

Usha Devi[1], **Mark Gostock[2]**, Jonathan F. Popplewell[1], Marcus J. Swann[1].
[1]Farfield Group Ltd., Crewe, United Kingdom, [2]Farfield Scientific Inc., Pittsburgh, PA, USA.

Melittin, the soluble peptide of bee venom, has been demonstrated to induce lysis of phospholipid liposomes. We have previously explored the dependence of lysis on liposome composition and now explore the interaction in more structural detail at the level of the lipid bilayer. Supported Lipid Bilayers are probed optically using the waveguide technique Dual Polarization Interferometry (DPI) to obtain data on the mass and birefringence of the lipid bilayer structures. The birefringence is a measure of the degree of alignment and compression of the lipid tails and is highly sensitive to changes of ordering within the membrane. The interaction of the bilayers with Melittin is probed as a function of peptide concentration and the resultant mass and birefringence changes related to the interaction mechanism. For the zwitterionic phosphatidyl choline the lytic ability of melittin is dependent on the degree of acyl chain mobility, with melittin able to induce lysis of liposomes in the liquid crystalline state, whilst those in the gel state show strong resistance to lysis. Thus the interaction of Melittin with Dimyristoyl-Glycero-Phospho-choline (DMPC) lipid bilayers is probed both above and below its transition temperature.

821-Pos Board B700

Experiments Meet Hydrophobic Mismatch: A Re-evaluation Of The Orientation Of Model Transmembrane Peptides From Solid-State NMR

Santi Esteban-Martin[1], Erik Strandberg[2], Gustavo Fuertes[1], Anne S Ulrich[3], Jesus Salgado[1].
[1]University of Valencia, Valencia, Spain, [2]Institute for Biological Interfaces, Forschungszentrum Karlsruhe, Karlsruhe, Germany, [3]Institute for Biological Interfaces, Forschungszentrum Karlsruhe. Institue of Organic Chemistry, University of Karlsruhe, Karlsruhe, Germany.

The basic physical rules underlying the organization of biological membranes can be gathered under the simple, but powerful, concept of hydrophobic mismatch. For example, the mutual adjustment of the lipid and protein hydrophobic lengths can be related with the existence of lipid rafts and explain discrete secretory pathways in the Golgi apparatus. The orientation of membrane protein fragments is predicted to follow the same hydrophobic mismatch principles, as illustrated by some experiments and molecular dynamics simulations. However, this appears to be challenged by results of solid-state 2H NMR experiments on model transmembrane peptides, displaying tilt angle values unexpectedly small and weakly reacting to changes of the lipid bilayer thickness. Here we bridge theory and experiments to show that previous 2H NMR experimental data of model transmembrane peptides in membranes of different thickness can be re-interpreted by using alternative models which consider explicit rigid-body peptide fluctuations. The result is a new set of tilts which follows nicely the hydrophobic mismatch expectations, and is coherent with molecular dynamics simulations as well as with other mismatch studies conducted with natural protein fragments.

822-Pos Board B701

The Structural Plasticity Of Lung Surfactant Peptide KL4 In Lipid Membranes

Joanna R. Long[1], Anil K. Mehta[2], Yilin Meng[1], Adrian Roitberg[1], Vijay Antharam[1], Omjoy Ganesh[1], Suzanne Farver[1].
[1]University of Florida, Gainesville, FL, USA, [2]Emory University, Atlanta, GA, USA.

Surfactant protein B, SP-B, is critical to lung function and is particularly important in the trafficking of lipids within pulmonary surfactant and altering lipid properties at the air-water interface. The N- and C-terminal segments of SP-B have been identified as the most active domains in SP-B and remedial efforts in treating respiratory distress have focused on these domains and synthetic analogs of them. KL_4 is a 21-residue peptide mimetic of the C-terminus of SP-B. The periodicity of the lysine residues in KL_4 should prevent formation of a canonical amphipathic α-helix at lipid interfaces, yet upon partitioning into membranes CD measurements suggest formation of a helix. Using a suite of ssNMR experiments, in concert with circular dichroism spectroscopies, we are developing a molecular level understanding of the varied structure and function of KL_4 and its parent sequence, $SP\text{-}B_{59\text{-}80}$. In particular, our results highlight their lipid-dependent plasticity and unusual amphipathic helical secondary structures. We will present structural data obtained with solid-state NMR measurements which can resolve two helical conformations in KL_4 with backbone torsion angles that deviate from a traditional α-helix and highlight the adaptive structure of amphipathic helices. We will also present phosphorous and deuterium NMR lineshape data which demonstrate the concentration dependent effects of SP-B related peptides on lipid dynamics in POPC/POPG and DPPC/POPG lipid lamellae. Our observations suggest a means for the peptides to penetrate deeply into lipid environments containing a high percentage of saturated lipids and to bind more peripherally to vesicles containing higher levels of unsaturated lipids. The adaptive structure and penetration depth of SP-B related peptides could explain the mechanism of action of SP-B and demonstrate the structural variability possible for amphipathic helices in lipid bilayer environments

823-Pos Board B702

Structure Of Complexes Of Helix-5 From Bax With Lipid Membranes

Gustavo Fuertes[1], Joshua Manor[2], Santi Esteban-Martín[1], Isaiah T. Arkin[2], Jesús Salgado[1].
[1]Instituto de Ciencia Molecular, Universidad de Valencia, Paterna (Valencia), Spain, [2]The Alexander Silberman Institute of Life Sciences, The Hebrew University of Jerusalem, Jerusalem, Israel.

Bax is a proapoptotic protein implicated in the release of cell-death activating factors from the mitochondrial intermembrane space. Although the structure of the membrane-bound forms of Bax is unknown, it has been proposed to form proteolipidic pores. Studies with synthetic lipid vesicles have shown that fragments encompassing helix-5 of Bax retain a membrane permeabilization ability that is similar to that of the full-length protein. Here we report on the structure of peptide-membrane complexes formed by a Bax helix-5 peptide and lipid bilayers. The relative orientation of the peptide and the lipids are determined using site-specific infrared spectroscopy, assisted by isotopic labeling of backbone groups with the $^{13}C{=}^{18}O$ probe. The peptide is highly α-helical in all lipid membranes studied, and its orientation reveals different binding modes that depend on the bilayer phase state. In partially fluid POPC bilayers helix-5 of Bax lies almost parallel with respect to the membrane plane, most likely interacting at the level of the interface. However, in gel phase DMPC bilayers the peptide adopts a tilted orientation, which suggests a deeper insertion in the membrane. In turn infrared spectroscopy and X-ray diffraction data show that in some instances the Bax helix-5 peptide influences the phase transition properties of the lipids by increasing membrane fluidity. Taken together, these effects can be related with the membrane perturbation properties of the Bax helix-5 fragment and with its mechanism of action as a molecule inducing the formation of lipidic pores.

Membrane Physical Chemistry I

824-Pos Board B703

Lateral Stress Profiles In Lipid Monolayers

Svetlana Baoukina[1], Siewert J. Marrink[2], D. Peter Tieleman[1].
[1]University of Calgary, Calgary, AB, Canada, [2]University of Groningen, Groningen, Netherlands.

We have used molecular dynamics simulations to study the lateral stress profiles in lipid monolayers at the air/water interface. From the calculations, we determined the ''surface of tension'' in the complex interfacial layer. We identified the factors for monolayer stability, which allows explaining the maximum surface pressure sustained by a selected lipid mixture (collapse pressure). This is relevant for understanding the function of biological interfaces, such as the surfactant-covered gas exchange interface in the lungs, and designing artificial/replacement surfactant mixtures.

We calculated the stress distributions for lipid monolayers of different composition under varying surface pressure, including both liquid-expanded and liquid-condensed phases. The stress distribution in the hydrocarbon chain region is most affected by the surface pressure. In the liquid-expanded phase, the stress becomes negative at the chain/air interface. In the liquid-condensed phase, the negative stress in the chains is partially compensated by positive pressure due to increased density, and the profile is characterized by multiple peaks originating from chain and head group ordering. The simulations were performed with both atomistic and coarse-grained molecular models, which led to qualitatively similar results. To test the estimated collapse pressures, the coarse-grained model was used to simulate monolayer collapse upon lateral compression. To induce 2D-3D transformations that require long time scales, small defects were introduced, which provided nucleation sites for monolayer folding.