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The formation and electron microscopic characterization of artificial and native lipid-bilayer nanodiscs

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Certain amphiphilic copolymers form lipid-bilayer nanodiscs from artificial and natural membranes, thereby rendering incorporated membrane proteins optimal for structural analysis. Recent studies have shown that the amphiphilicity of a copolymer strongly determines its solubilization efficiency. This is especially true for highly negatively charged membranes, which experience pronounced Coulombic repulsion with polyanionic polymers. Here, we present a systematic study on the solubilization of artificial multicomponent lipid vesicles that mimic inner mitochondrial membranes, which harbor essential membrane-protein complexes. In particular, we compared the lipid-solubilization efficiencies of established anionic with less densely charged or zwitterionic and even cationic copolymers in low- and high-salt concentrations. The nanodiscs formed under these conditions were characterized by dynamic light scattering and negative-stain electron microscopy. Overall, our results show that some recent, zwitterionic copolymers are best suited to solubilize negatively charged membranes at high ionic strengths even at low polymer/lipid ratios [1].
As a proof of principle, we show an efficient recovery of protein-encapsulating nanodiscs from membranes of Chaetomium thermophilum, a thermophilic fungus. We identified ~1100 proteins by mass spectrometry and obtained two 3D reconstructions from cryo-EM for the nanodisc-containing cell extract. With this combined methodological approach, we provide a deeper understanding of eukaryotic membrane proteomes [2].

[1] Janson, K.; Zierath, J.; Kyrilis, F.L.; Semchonok, D.A.; Hamdi, F.; Skalidis, I.; Kopf, A.H.; Das, M.; Kolar, C.; Rasche, M.; Vargas, C.; Keller, S.; Kastritis, P.L.; Meister, A.; Biochim. et Biophys. Acta, Biomembr. 2021, 1863, 183725.
[2] Janson, K.; Kyrilis, F.L.; Tüting, C.; Alfes, M.; Das, M.; Träger, T.K.; Schmidt, C.; Hamdi, F.; Vargas, C.; Keller, S.; Meister, A.; Kastritis, P.L.; Biomacromolecules, 2022, 23, 5084-5094.

Abstract Title

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