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Azide- and diazirine-modified membrane lipids: Physicochemistry and applicability to study peptide/lipid interactions via cross-linking/mass spectrometry

Although the incorporation of photo-activatable lipids into membranes potentially opens new avenues for studying interactions with peptides and proteins, the question of whether azide- or diazirine-modified lipids are suitable for such studies remains controversial. We have recently shown that diazirine-modified lipids can indeed form cross-links to membrane peptides after UV activation and that these cross-links can be precisely determined in their position by mass spectrometry (MS) [1]. However, we also observed an unexpected back-folding of the lipid's diazirine-containing stearyl chain to the membrane interface challenging the potential application of this modified lipid for future cross-linking (XL)-MS studies of protein/lipid interactions.

In this work, we compared an azide- (AzidoPC) [2] and a diazirine-modified (DiazPC) [1] membrane lipid regarding their self-assembly properties, their mixing behavior with saturated bilayer-forming phospholipids, and their reactivity upon UV activation using differential scanning calorimetry (DSC), dynamic light scattering (DLS), small-angle X-ray scattering (SAXS), transmission electron microscopy (TEM), and MS. Mixtures of both modified lipids with DMPC were further used for photo-chemically induced XL experiments with a transmembrane model peptide to elucidate similarities and differences between the azide and the diazirine moiety. We showed that both photoreactive lipids can be used to study lipid/peptide and lipid/protein interactions [3]. The AzidoPC proved easier to handle, whereas the DiazPC had fewer degradation products and a higher cross-linking yield. However, the problem of backfolding occurs in both lipids; thus, it seems to be a general phenomenon.

[1] J. Dorner *et al.*: A Diazirine-Modified Membrane Lipid to Study Peptide/Lipid Interactions – Chances and Challenges. *Chem. Eur. J.* **2021**, *27* (59), 14586-14593.

[2] S. Lindner *et al.*: Azide-modified Membrane Lipids: Synthesis, Properties, and Reactivity. *Langmuir* **2017**, *33* (20), 4960-4973.

[3] P. Korn *et al.*: Azide- and diazirine-modified membrane lipids: Physicochemistry and applicability to study peptide/lipid interactions via cross-linking/mass spectrometry. *Biochim. Biophys. Acta Biomembr.* **2022**, *1864*, 184004.

Session

Interaction lipids/polymers/membrane proteins

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