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Interfacial lipids as modulator of membrane protein oligomerisation

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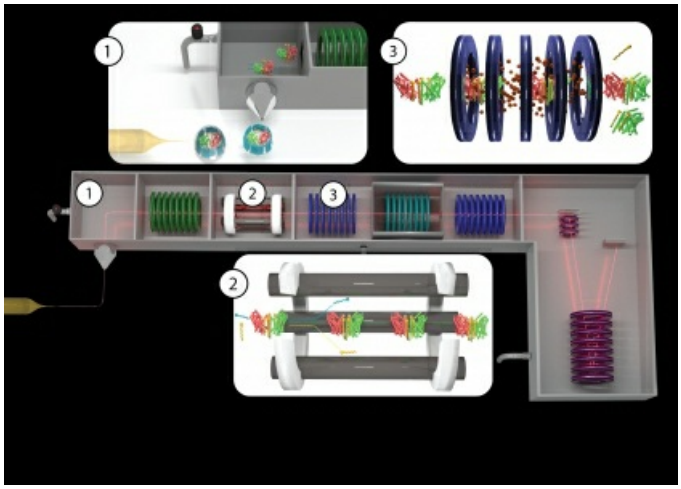
Oligomerisation of membrane proteins in response to lipid binding plays a critical role in many cell-signaling pathways but is often difficult to define or predict. Lack of any experimental technique that can identify endogenous bound lipids directly poses a significant challenge. To overcome this, we developed a novel high-energy mass spectrometric platform to enable tandem MS of membrane protein-lipid complexes. This novel platform allows simultaneous identification of endogenous lipids while bound to membrane protein oligomers and can determine how lipids act as key regulators of membrane protein association.1 Evaluation of oligomeric strength for a dataset of 125 α-helical oligomeric membrane proteins revealed a remarkable correspondence with absence of interfacial lipids in membrane proteins with high oligomeric stability. Whereas a precise cohort of lipid plug within the dimer interface were observed for the bacterial homologue of the eukaryotic biogenic transporters (LeuT), one of the proteins with the lowest oligomeric stability. Further, we show that in sugar transporter SemiSWEET, another protein with low oligomeric stability, lipids act modulator of the equilibrium between the monomer and the functional dimeric form. We then searched for pairs of homologous proteins in our dataset differing in oligomeric stability. We hypothesised that lipids would be essential for dimerisation of the Na+/H+ antiporter NhaA from E. coli, which has the lowest oligomeric strength, but not for substantially more stable, homologous NapA from Thermus thermophilus. Indeed, we found that lipid binding is obligatory for dimerisation of NhaA, whereas NapA has adapted to form an interface that is stable without lipids. Overall, by correlating interfacial strength with the presence of interfacial lipids we provide a rationale for understanding the role of lipids as molecular glues in both transient and stable interactions within a range of α-helical membrane proteins, including the GPCRs

[1] Gupta K et al (2017). Nature, 541,421–424



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