### Measuring Membrane Protein-Lipid Interactions in Nanodiscs with Native Mass Spectrometry

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**Abstract:** Membrane proteins are involved in many essential biochemical functions and make up the majority of drug targets. However, membrane proteins are difficult to study due to their localization in heterogeneous lipid environments, where both the bulk physical properties of the bilayer and specific protein-lipid interactions can influence their structure and activity. Furthermore, detergents, which are frequently used for membrane protein solubilization, may distort the native-like structure and function of membrane proteins. Here, we developed an approach to measure protein-lipid interactions and understand how membrane proteins remodel their local lipid environment. We used native mass spectrometry (MS), which uses nondenaturing conditions to preserve noncovalent complexes for mass analysis, to ionize membrane proteins in lipoprotein nanodiscs containing a binary mixture of lipids. Membrane proteins with bound lipids were ejected from nanodiscs and revealed enrichment of specific lipids surrounding the membrane protein. This approach showed that the *E. coli* ammonium transporter AmtB prefers mostly phosphatidylglycerol lipids but has a minor affinity for phosphatidylcholine lipids. Ultimately, we expect this novel method will provide unique insights into the mechanisms of membrane protein-lipid interactions and help discover new approaches for drug development.