Lipid-protein interaction governing EGF receptor signaling

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Our interest is focused on allosteric protein-lipid interactions and their impact in modifying protein function and structure.
Such an example of lipid allostery is the regulation of tyrosine kinase receptor activity by gangliosides. Although gangliosides have been reported to affect growth factor receptor function (Miljan and Bremer, 2002), this has received little attention in recent literature on growth factor receptor signaling (Lemmon and Schlessinger, 2010). We took the epidermal growth factor (EGF) receptor as a showcase to find out directly whether gangliosides modulate receptor activity as had been claimed. The receptor was reconstituted into liposomes of different lipid composition. The lipid composition had no effect on the equilibrium ligand-binding properties of the EGFR (Coskun et al., 2011). However, a ganglioside dramatically inhibited kinase domain activation. The effect was very specific and was seen only with the ganglioside GM3, which completely abolished autophosphorylation of the receptor. The inhibitory effect could be demonstrated only in proteoliposomes tuned to phase separate into liquid-ordered (Lo) and -disordered (Ld) domains, mimicking lipid raft properties. These data suggest that GM3 can regulate the allosteric structural transition from an inactive to a signaling EGFR dimer and demonstrate the potential importance of glycosphingolipid-protein interactions, mostly neglected in the cell and structural biology field so far.

Coskun Ü, et al (2011) Regulation of human EGF receptor by lipids. PNAS 108:9044-9048
Lemmon, M.A. and Schlessinger, J. (2010) Cell Signaling by receptor turosine kinases. Cell 141, 1117-1134

Miljan EA, Bremer EG (2002) Regulation of growth factor receptors by gangliosides. Sci STKE 2002:re15.