

Interfacial choline-aromatic cation- π interactions can contribute as much to peripheral protein affinity for membranes as aromatics inserted below the phosphates

Nathalie Reuter

^a Department of Chemistry and Computational Biology Unit, University of Bergen, Norway

Nathalie.Reuter@uib.no

Peripheral membrane proteins populate both soluble and membrane-bound forms. Unlike transmembrane proteins, peripheral binders rely on membrane binding interfaces that are restricted to a small part of their exposed surface and the ability to engage in strong selective interactions with membrane lipids at various depths in the interface, both below and above the lipid phosphates, is an advantage. While aromatic amino acids preferentially partition into membrane interfaces driven by their hydrophobicity, enthalpically favorable interactions with the lipid headgroups are likely to further stabilize high interfacial positions. Yet the role of aromatics in the binding of peripheral proteins to membrane has historically been restricted to that of deep hydrophobic anchors.

Using molecular simulations in combination with experimental affinity data, we could show that tyrosine residues of a bacterial phospholipase interact with the headgroups of phosphatidylcholine-containing lipids via cation- π interactions (Figure 1) [1]. We then evaluated the ability of molecular mechanics force fields to represent the structure and energetics of aromatics-choline cation- π interactions, and subsequently proposed modifications of the CHARMM force field [2,3]. More recently we used Free Energy Perturbation to calculate the energetic cost of alanine substitution for 11 interfacial aromatic amino acids from 3 peripheral proteins [4]. We showed that involvement in cation- π interactions with the headgroups (i) increases the $\Delta\Delta G_{\text{transfer}}$ as compared to insertion at the same depth without cation- π stabilization and (ii) can contribute at least as much as deeper insertion below the phosphates, highlighting the multiple roles of aromatics in peripheral membrane protein affinity.

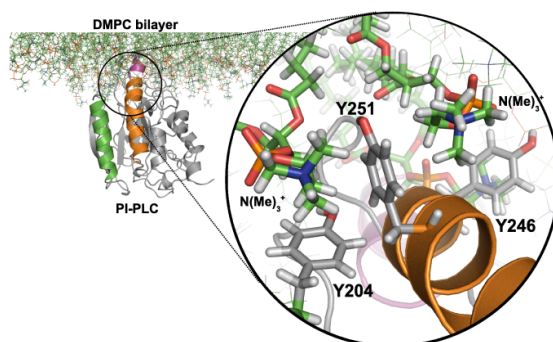


Figure 1: Cation- π interactions between a bacterial phospholipase and a lipid choline [1]

References

1. C. Grauffel, B. Yang, T. He, M.F. Roberts, A. Gershenson and N. Reuter *J. Am. Chem. Soc.* **135** (2013), 5740.
2. H.M. Khan, C. Grauffel, R. Broer, A.D MacKerell, R.W.A. Havenith, N. Reuter *J. Chem. Theory Comput.* **12** (2016), 5585.
3. H.M. Khan, A.D. MacKerell, N. Reuter *J. Chem. Theory Comput.* **15** (2019), 7
4. Q. Waheed, H.M. Khan, T. He, M. Roberts, A. Gershenson and N. Reuter *J. Phys. Chem. Lett.* (2019), in press