

Revisiting the role of electrostatic interactions in the membrane binding of peripheral proteins

Emmanuel E. Moutoussamy^{ac}, Qaiser Waheed^{ac}, Hanif M. Khan^{ac} and Nathalie Reuter^{bc}

^a Department of Biological Sciences, University of Bergen, Bergen.

^b Department of Chemistry, University of Bergen, Bergen.

^c Computational Biology Unit, University of Bergen, Bergen.

emmanuel.moutoussamy@uib.no

Over the last decades, much effort has been dedicated into protein/protein or nucleic-acid/protein interaction mapping. However, the ways peripheral proteins interact with membrane lipids are poorly understood in spite of their crucial importance. The most widespread model of protein/membrane association described a two-steps mechanism: (1) the protein approaches the bilayer and orients under the influence of non-specific electrostatics forces and (2) the insertion of hydrophobic residues into the bilayer core. Former studies have established the importance of nonspecific electrostatic forces as a driving force for peripheral membrane association [1]. Nevertheless there is compelling evidence that some proteins display weak nonspecific electrostatics upon binding to lipid bilayers [2]. Using continuum electrostatics calculations, we identified 5 enzymes from the Orientation of Proteins in Membrane (OPM) database, which present unexpected electrostatics properties: a low electrostatic binding free energy and a negative electrostatic potential at their interfacial binding site. In order to understand which forces drive them to the membrane, we investigate the binding site of one of these enzymes: the phospholipase-D toxin from brown spiders. First, we ran multiple Molecular Dynamics (MD) simulations on phospholipase-D placing it away from different bilayer compositions. In all our MD simulations the protein managed to bind to the membrane, adopted the same binding orientation and stayed stably bound at the surface of the bilayer. The analysis of the MD simulations shows that aromatic amino acids especially tyrosines and tryptophans establish a high number of cation- π interactions with the lipid heads. These cation- π interactions are essential, as we observe no binding when we exclude these interaction terms from the molecular model we use. A low electrostatic interactions and the presence of various numbers of weak interactions, such as the cation- π interaction, can be useful for some enzymes, which need to unbind from the bilayer in order to find new substrates.

References

1. D. Murray, S. McLaughlin, and B. Honig, *J Biol Chem*, **276** (2001)
2. H. M. Khan, T. He, E. Fuglebakk, C. Grauffel, B. Yang, M. F. Roberts, A. Gershenson, and N. Reuter ., *Biophys J*, **110** (2016)