Computational analysis of the membrane association of Group IIA secreted phospholipases A2: A differential role for electrostatics
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In Press. Biochemistry.

ABSTRACT
Secreted phospholipases A2 (sPLA2’s) are enzymes that hydrolyze glycerophospholipids at the sn-2 position, which leads to the production of lipid mediators of many cellular processes. These interfacial enzymes are regulated by their lipid specificity at two levels: membrane binding and substrate recognition. Different sPLA2’s utilize different combinations of electrostatic and hydrophobic interactions to adsorb to membrane surfaces, which results in the wide range of membrane binding behaviors observed. Here the finite difference Poisson Boltzmann (FDPB) method is used to quantitatively analyze the contribution of electrostatic interactions to the membrane association of two highly basic group II sPLA2’s: Agkistrodon piscivorus piscivorus (AppD49) sPLA2 and non-pancreatic human group IIA (hGIIA) sPLA2. The calculations predict how membrane binding is affected by ionic strength, membrane composition, substitutions of residues in the enzymes, and the presence of calcium in the active site. In addition, the results provide molecular models for the membrane-associated forms of the enzymes. Furthermore, these models account for 1) changes in orientation and protonation state of both the native and charge reversal forms of the enzymes at the membrane surface, and 2) the effect of protein/vesicle aggregation, as observed for hGIIA sPLA2. Importantly, the modeling quantitatively describes the complex membrane binding behaviors of these interfacial enzymes in terms of simple physical forces and provides structural information that is difficult to obtain experimentally. The computational analysis shows that nonspecific electrostatic interactions not only play a major role in recruiting these enzymes to membrane surfaces but also orient the enzymes for productive catalysis at the membrane interface.