Anchoring of a monotopic membrane protein : the binding of prostaglandin H2 synthase-1 to the surface of a phospholipid bilayer

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Prostaglandin H2 synthases (PGHS-1 and -2) are monotopic peripheral membrane proteins that catalyse the synthesis of prostaglandins in the arachidonate cascade. Picot et al. (1994) proposed that the enzyme is anchored to one leaflet of the bilayer by a membrane anchoring domain consisting of a right-handed spiral of amphipathic helices (residues 73-116) forming a planar motif. Two different computational approaches are used to examine the association of the PGHS-1 membrane anchoring domain with a membrane via the proposed mechanism. The electrostatic contribution to the free energy of solvation is obtained by solving numerically the finite-difference Poisson equation for the protein attached to a membrane represented as a planar slab of low dielectric. The nonpolar cavity formation and van der Waals contributions to the solvation free energy are assumed to be proportional to the water accessible surface area. Based on the optimum position determined from the continuum solvent model, two atomic models of the PGHS-1 anchoring domain associated with an explicit dimyristoylphosphatidylcholine (DMPC) bilayer differing by the thickness of the membrane bilayer were constructed. A total of 2 ns molecular dynamics simulation were performed to study the details of lipid-protein interactions at the microscopic level. In the simulations the lipid hydrocarbon chains interacting with the anchoring domain assume various shapes, suggesting that the plasticity of the membrane is significant. The hydrophobic residues in the membrane side of the helices interact with the hydrophobic membrane core, while the positively charged residues interact with the lipid polar headgroups to stabilize the anchoring of the membrane domain to the upper half of the bilayer. The phosphate headgroup of one DMPC molecule disposed at the center of the spiral formed by helices A, B, C and D interacts strongly with Arg120, a residue on helix D that has previously been identified as being important in the activity of PGHS-1. In the full enzyme structure, this position corresponds to the entrance of a long hydrophobic channel leading to the cyclooxygenase active site. These observations provide insights into the association of the arachidonic acid substrate to the cyclooxygenase active site of PGHS-1.

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