Mechanism of phospholipid scrambling by a G protein-coupled receptor
Anant K. Menon
Department of Biochemistry, Weill Cornell Medical College
1300 York Ave, New York, NY 10065, USA

The G protein-coupled receptor opsin is a phospholipid scramblase that catalyzes the transbilayer translocation of >10,000 phospholipids per second when reconstituted as a monomer into synthetic vesicles. Several other class-A G protein-coupled receptor (GPCR) proteins such as the beta1- and beta2-adrenergic receptors are also able to scramble phospholipids. To address the molecular mechanism by which these proteins facilitate rapid lipid scrambling, we carried out large-scale ensemble atomistic molecular dynamics simulations of the opsin GPCR. We report that, in the process of scrambling, lipid head groups traverse a dynamically revealed hydrophilic pathway in the region between transmembrane helices 6 and 7 of the protein while their hydrophobic tails remain in the bilayer environment. As key residues on the lipid translocation pathway are conserved within the class-A GPCR family, our results illuminate unique aspects of GPCR structure and dynamics while providing a rigorous basis for the design of variants of these proteins with defined scramblase activity.

References: