Specificity and Promiscuity of Phosphoinositide Lipid Interactions with GPCRs

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G protein-coupled receptors (GPCRs) are lipid-dependent membrane receptors that serve as important cell signaling hubs. Phosphoinositide (PIP) lipids represent an important class of anionic lipids that play vital roles in cellular function and signaling. PIPs have been reported to modulate GPCR function, although specificity and molecular details of the interactions are still not clear. In this work, we analyzed the specificity of the PIP lipid interactions with two GPCRs using coarse-grain molecular dynamics simulations. Due to the importance of PIP lipids in receptor activation, we have considered the active state of the receptor, bound to its cognate G-protein (Gs or Gi). Our results show that four anionic lipid sites are present at the receptor surface, although the relative populations are dependent on the lipid type. In the case of the serotonin$_{1A}$ receptor, a neuronal GPCR, phosphatidylinositol 4 monophosphate (PIP1) lipids exhibit highest interaction that is located at a charged cleft formed by transmembrane helices VI and VII. We observed electrostatic interactions at a cluster of charged residues (Arg341, Lys342, Lys345) and hydrophobic and aromatic interactions at residue Ile349 and Tyr402. In contrast, phosphatidylinositol 4,5-bisphosphate (PIP2) and phosphatidylinositol 3,4,5-trisphosphate (PIP3) lipids interact less. A reviser trend is observed in the case of the glucagon-like peptide-1 receptor (GLP-1R), an immune-metabolatory receptor, where PIP2 and PIP3 interactions dominate. Our work constitutes an important step to analyze molecular signatures of phosphoinositide lipid-GPCR interactions in the overall context of diverse roles of phosphoinositides in cellular function and signaling.