Computational Studies of the Structure and Function of Two Lipid-Activated G Protein-Coupled Receptors

Thesis by

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Acknowledgments

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Abstract

Phospholipids are pleiotropic intercellular signaling molecules that have been implicated in various pathologies, including tumorigenesis. Both lysophosphatidic acid (LPA) and sphingosine-1-phosphate (S1P), among other phospholipids, use G protein coupled receptors (GPCRs) to transduce extracellular signals. Other families of GPCRs have successfully been utilized by the pharmaceutical industry, and further understanding of the phospholipid-receptor interaction can highlight potential therapeutic targets in these signaling pathways.

This thesis presents research into the interaction between specific G protein-coupled receptors, lysophosphatidic acid receptor-2 (LPA_2) and sphingosine-1-phosphate receptor-1 ($S1P_1$), and their ligands, in an attempt to further validate our method of GPCR structure prediction and to understand subtype specificity within this family of lipid receptors. Although the first principles method of GPCR structure prediction has quite successfully predicted the protein structure of small molecule receptors, lipid receptors create a unique challenge. The surface area on the inside of a small molecule receptor contains a large percentage of polar groups, easily differentiating the inner surface from the highly hydrophobic outer surface. Lipid receptors do not show as dramatic a distinction, as the inner surface is significantly hydrophobic to bind the lipid ligand.

Herein we propose and test a new method of orienting the seven transmembrane helices of a GPCR relative to one another through an analysis of the lipid solubility of each residue in conjunction with an optimization of the inter-helical hydrogen bonding associations. We predict structures for LPA_2 and $S1P_1$ that replicate the relative binding of different lipids

within the LPA and S1P lipid families. The interaction energies between the receptors and the tested ligands correlates well with ligand efficacy, and qualitative analysis of functional group-residue interactions further validates our model for both LPA_2 an $S1P_1$.

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