Dissecting the sequence and structure determinants of gpcr - gprotein selectivity via structural bioinformatics and machine learning

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GPCRs are crucial in cellular signaling, interacting variably with G-proteins. To elucidate these interactions at the sequence level, we have developed PRECOGx, a novel machine learning framework utilizing ESM1b embeddings from protein language models. It can predict GPCR G protein coupling, enhancing our understanding by encompassing all GPCR classes. We are also able to examine GPCR mutation variants and splice forms. ('Previously published in: Matic M et al. (2022) J Nucleic Acids Research, Volume 50, Issue W1, 5 July 2022, W598–W610). Complementing PRECOGx, our analysis of the GPCRome involved examining 362 GPCR-G-protein 3D structures from the PDB database. This study identified interaction networks for Gs and Gi/o binding, highlighting crucial interaction fingerprints and secondary structure elements. Additionally, we analyzed the conformational differences between Gs and Gi/o by calculating the root-mean-square deviation(RMSD) of G protein part of structures showing more flexible mode of binding of Gi/o. We also compute interface binding energies (Rosetta) and observe a greater stability in Gs vs Gi/o couplings, with class A receptors exhibiting more stability than class B1 for Gs couplings ('Previously published in: Matic M et al. (2023) Nat Commun 14, 4361). Expanding our research, we employed AlphaFold Multimer to predict tetramer complexes of 827 GPCR-G protein structures, including those involving Gq11 and G1213 proteins. This comprehensive study offered new insights into G-protein binding modes across all four families. We also compared these structures to inactive states of GPCRs (predicted by AlphaFold and stored in GPCRDb), investigating the potential of GPCR intramolecular contacts to indicate varying G-protein couplings. Our approach underscores the importance of conformational shifts within the transmembrane (TM) bundle in dictating GPCR-G-protein interactions, shedding light on potential avenues for drug design and therapeutic strategies.

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