CALIFORNIA STATE SCIENCE FAIR
2016 PROJECT SUMMARY

Name(s)

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Project Number

36728

Project Title

Quantifying the Complexity of Conformational Transitions in the Partial and Biased Activations of GPCRs

Abstract

Objectives/Goals

G-protein-coupled receptors (GPCRs) are the targets of more than 40% of all marketed drugs. However, in many existing drugs, significant side effects arise as a result of their non-selective inhibition of receptors and signaling pathways. Partial agonists, which inhibit some functions while preserving the core functions of the receptor, and biased agonists, which deactivate one pathway while maintaining the function of the other, may be the next key step towards targeted drugs with fewer side effects. Therefore, I developed a quantitative analysis tool to measure the extent of the conformational transition in the activation process and statistically distinguish between full, partial, and biased activated states.

Methods/Materials

I wrote a tool in Python to take 25 PDB files from the online RCSB protein data bank as input and systematically calculate four different structural metrics among all receptor structures before and after activation. My tool then generates an interactive PyMOL simulation that maps the most significant features to the receptors, allowing me to visualize the most important changes during activation. Using the quantitative data, I was able to detect changes that point towards partial activation and biased activation.

Results

By analyzing these measurements across four receptors, my tool was shown to detect previously-uncharacterized subtle yet significant changes at the binding site, including the non-uniform change in the shape of the binding site during activation as well as the differences between G-protein-peptide-bound rhodopsin and the beta-arrestin-bound rhodopsin.

Conclusions/Discussion

My quantitative tool detects well-known changes that concur with other published results in the field, while detecting subtle yet significant changes that can be used to determine the extent of GPCR activation, showing promise as a means of detection for future partial and biased agonists.

Summary Statement

By analyzing structural protein data, my computational tool detects subtle yet significant patterns that indicate full, partial, or biased activation of GPCRs, showing potential for the development of targeted drugs with fewer side effects.

Help Received

Received help from Dr. Lei Shi and Dr. Mayako Michino with equipment from Shi Lab in the National Institute on Drug Abuse.