Unique Features of Different Classes of G-Protein-Coupled Receptors Revealed from Sequence Coevolutionary and Structural Analysis

Hung Do[1], Allan Haldane[2], Ronald M. Levy[2], and Yinglong Miao[1]

[1]University of Kansas College of Liberal Arts and Sciences
[2]Temple University

July 30, 2021

Abstract

G-protein-coupled receptors (GPCRs) are the largest family of human membrane proteins and represent the primary targets of about one third of currently marketed drugs. Despite the critical importance, experimental structures have been determined for only a limited portion of GPCRs and functional mechanisms of GPCRs remain poorly understood. Here, we have constructed novel sequence coevolutionary models of the A and B classes of GPCRs and compared them with residue contact frequency maps generated with available experimental structures. Significant portions of structural residue contacts were successfully detected in the sequence-based covariational models. "Exception" residue contacts predicted from sequence coevolutionary models but not available structures added missing links that were important for GPCR activation and allosteric modulation. Moreover, we identified distinct residue contacts involving different sets of functional motifs for GPCR activation, such as the Na+ pocket, CWxP, DRY, PIF and NPxxY motifs in the class A and the HETx and PxxG motifs in the class B. Finally, we systematically uncovered critical residue contacts tuned by allosteric modulation in the two classes of GPCRs, including those from the activation motifs and particularly the extracellular and intracellular loops in class A GPCRs. These findings provide a promising framework for rational design of ligands to regulate GPCR activation and allosteric modulation.

Hosted file

`GPCR_Coevolution_Structures_Proteins.docx` available at https://authorea.com/users/428408/articles/532264-unique-features-of-different-classes-of-g-protein-coupled-receptors-revealed-from-sequence-coevolutionary-and-structural-analysis