Comparative Genomics of GPCRs: ET-Guided Annotation and Re-design of Aminergic Receptors

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G protein coupled receptors (GPCRs) let cells sense and respond to their environment by binding extracellular molecules to trigger intracellular signaling *via* G protein and β-arrestin/ERK pathways. Most drugs today either mimic or interfere with the initial ligand binding event, but the diversity of ligands combined with a lack of structural information (outside of the lone case of the visual receptor rhodopsin) prevent the systematic elucidation of the residues involved in binding and in the subsequent response. Here a comparative genomics approach is used to identify many key amino acids responsible for binding specificity, and their role is demonstrated through the functional re-design of rhodopsin, dopamine, and adrenergic receptors. The computational approach ranks the evolutionary importance of each residue in the sequence and exploits differences among the many branches of the GPCR superfamily to identify ligand specific binding residues as well as generic mediators of the conformational switch. As a test, targeted mutations then predictably interfere with ligand binding, cause constitutive activity, or, strikingly, uncouple G protein signaling from the β-arrestin/ERK pathway. In one example, a dopamine receptor is made responsive to serotonin. These results illustrate the relevance of computational genomics to dissect protein mechanisms at the molecular level with three consequences of therapeutic interest: the rational re-design of protein function through minimal mutations, the rational dissection of cellular pathways by selective modification of individual signaling branches, and the elucidation of ligand binding determinants in GPCRs.