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Exploring the molecular basis and pharmacological consequences of ligand-biased signaling at G protein-coupled receptors using biosensors.

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In recent years, it has become clear that G protein-coupled receptors (GPCRs) are not uni-dimensional switches that turn 'on' or 'off' a single signaling pathway. Instead, each receptor can engage multiple signaling partners to form dynamic complexes that can engage various downstream effector systems that may or may not involve G protein activation. Individual ligands can have differential efficacies toward specific subsets of the signaling effector repertoire that can be engaged by a given receptor. This phenomenon, known as ligand-biased signaling or functional selectivity, opens new opportunities for the development of new drugs with increased selectivity profiles and less undesirable effects. In an effort to better understand the structural and molecular basis of GPCR functional selectivity, we developed a diversity of biosensors based on bioluminescence resonance energy transfer (BRET) that allow real-time monitoring of the interactions between GPCRs and multiple effectors as well as their downstream signaling events. To date we generated more than 30 BRET-based sensors that monitor various aspects of signaling. Their use revealed unexpected new signaling complexes and provide a new tool-set to monitor signal transduction from the membrane to the nucleus and open new avenues for the screening and profiling of drug candidates with favorable functional selectivity. Both orthosteric and allosteric ligands of receptors were found to have a high level of functional selectivity. Examples for the β-adrenergic, angiotensin, opioids and chemokine receptors will be discussed. At the molecular level, site-directed mutagenesis revealed that specific domains of receptors paly crucial role for the activation of selective pathways. Mutant form of receptor can change the relative signaling selectivity of both balanced and biased ligands thus providing insights into the rational design of biased ligands with desired signaling properties.

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