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Thematic Minireview Series: New Directions in G Protein-coupled Receptor Pharmacology*

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Over the past half-century, The *Journal of Biological Chemistry* has been the venue for many landmark publications on the topic of G protein-coupled receptors (GPCRs, also known as seven-transmembrane receptors). The GPCR superfamily in humans is composed of about 800 members, and is the target of about one-third of all pharmaceuticals. Most of these drugs target a very small subset of GPCRs, and do so by mimicking or competing with endogenous hormones and neurotransmitters. This thematic minireview series examines some emerging trends in GPCR drug discovery. The first article describes efforts to systematically interrogate the human "GPCR-ome," including more than 150 uncharacterized "orphan" receptors. The second article describes recent efforts to target alternative receptor binding sites with drugs that act as allosteric modulators of orthosteric ligands. The third article describes how the recent expansion of GPCR structures is providing new opportunities for computer-guided drug discovery. Collectively, these three articles provide a roadmap for the most important emerging trends in GPCR pharmacology.

A remarkable array of extracellular signals, including photons, single ions, volatile odors, lipids, hormones, neurotransmitters, and proteases, transmit signals via G protein-coupled receptors. Once activated, these receptors engage a G protein heterotrimer, or in some cases accessory proteins such as β-arrestins and protein kinases. The G proteins exchange GDP for GTP, and the dissociated α and β/γ subunits then activate various enzymes and ion channels inside the cell. RGS proteins (regulators of G protein signaling) act to counter the effect of GPCRs[2] by accelerating G protein GTPase activity.

Much of the literature related to GPCR pharmacology has focused on a relatively small number of hormone and neurotransmitter receptors. Prominent among these are the receptors for epinephrine, histamine, adenosine, acetylcholine, dopamine, serotonin, and opioids. There is a growing realization, however, that GPCRs can also be regulated allosterically. Current efforts to systematically match GPCRs with potential drugs, including both allosteric and orthosteric modulators, are described in the first minireview by Bryan L. Roth and Wesley K. Kroeze (1). The potential of allosteric drugs is detailed in the second minireview written by Patrick R. Gentry, Patrick M. Sexton, and Arthur Christopoulos (2). Additional discovery opportunities, arising from newly available GPCR crystal structures, are described in the third minireview by Ali Jazayeri, Joao M. Dias and Fiona H. Marshall (3).

The completion of the human genome sequencing project presented new opportunities, and new challenges, for drug discovery. Prior screening efforts were conducted one receptor at a time, typically with a tailor-made radioligand probe or second messenger assay as a readout. As a consequence, the target space was limited to a very small number of previously characterized receptors. Bryan Roth and his colleagues have been at the forefront of efforts to develop screens that are comprehensive, highly parallel, and very high-throughput. The first minireview by Roth and Kroeze describes how these efforts have required development of new tools such as broad-spectrum functional readouts, sophisticated bioinformatics analysis, and of course high-quality chemical libraries. The infrastructure requirements are beyond those available to most academic and industry laboratories. The resources developed by the Roth laboratory are freely available, and have been used by more than 500 investigators over the past 5 years. These efforts have already yielded a number of novel and candidate drug-like small molecules (1).

Although most GPCR-directed agents mimic or block the binding of some endogenous hormones or neurotransmitters (the so-called orthosteric sites), it is also possible to modulate the activity of GPCRs by targeting topographically distinct (allosteric) binding sites. The second minireview by Gentry, Sexton, and Christopoulos (2) describes some important considerations when pursuing allosteric agents as drugs. As noted by the authors, an allosteric agent might modulate one receptor subtype but not another, despite the ability of both receptors to bind a common orthosteric ligand. Thus allosteric agents have the potential for improved pharmacological selectivity.

It is worth noting that all GPCR signal transduction is intrinsically allosteric as it involves the simultaneous and cooperative binding of an agonist outside and a G protein (or accessory protein) inside. In that light, it seems likely that allosteric binding sites might also exist for endogenous substances such as phospholipids, sterols, and endogenous peptides as well as various receptor-binding proteins. Indeed one recent crystal structure revealed sodium bound to an allosteric site, near the ligand binding pocket of the δ-opioid receptor, responsible for the "sodium effect" that has long been used to differentiate opioid agonists from antagonists (4).

The growing number of crystal structures of GPCRs is likely to reveal other examples of non-canonical binding sites that might serve as potential drug targets, which brings us to the third minireview by Jazayeri, Dias, and Marshall (3). These authors describe technological advances leading to a rapid growth in high-resolution GPCR structures, and how those structures are transforming drug discovery efforts. Computa-

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[2] The abbreviation used is: GPCR, G protein-coupled receptor

tional drug-screening methods in particular have benefitted from the existence of large chemical databases that annotate the biological properties of small molecules. Investigators are docking such molecules with potential binding pockets evident in the crystal structures of various GPCRs. These efforts are also allowing medicinal chemists to convert low-affinity drugs into larger compounds with improved affinity and efficacy. These methods are routine for soluble enzymes but are only now being implemented for GPCRs.

Although structure-based screens hold great potential, the spectrum of available structures remains fairly narrow. An even greater challenge will be to design compounds that specifically recognize an activated receptor conformation. To date, there is only one crystal structure depicting an agonist-bound receptor and G protein complex (5). There are as yet no structures of a receptor bound to any of the known accessory proteins. Such structures would facilitate the design of biased agonists, both orthosteric and allosteric, that selectively promote coupling of receptors to G proteins, β-arrestins, receptor kinases, RGS proteins, and other GPCRs (as receptor oligomers). In the meantime, sophisticated computational techniques, including molecular dynamics simulations (6) and structural informatics analysis (7), are helping us to identify structural signatures and dynamic properties unique to activated receptors (3).

Given the long history of GPCRs as drug targets, there is a strong rationale for pursuing new receptor targets and new binding sites within known targets. It is our hope that this minireview series will provide a guidepost to these efforts in receptor pharmacology, structural biology, and biological chemistry.

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