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Editorial

A new era for GPCR research: structures, biology and drug discovery

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Cells in a living organism must communicate with each other through continuously sending and receiving messages. G-protein coupled receptors (GPCRs) are the largest family of communicating molecules at the cell surface. They transmit diverse extracellular signals, ranging from light and small chemical hormones to large peptide and protein hormones, and as such they play crucial roles in numerous physiological and pathological processes. More importantly, GPCRs are the most successful class of drug targets that are relevant to many major diseases, including cancer, heart failure, and inflammatory diseases. Over 50% of currently used drugs are targeted to GPCRs. However, these drugs target only 50–60 GPCRs, leaving the majority of human GPCRs, exceeding 800, unexplored for drug discovery. Given the prominent roles of GPCRs in biology and their successful track records as drug targets, GPCRs have become a hot frontier in basic research of life science and therapeutic discovery of translational medicines.

In this special issue, there are nine exciting reviews that cover a broad scope of GPCR structures, biology, diseases, and drug discovery. Among them, four reviews are dedicated to GPCR structures. Over the last few years, we have witnessed a revolution in Class A GPCR structural biology. Rhodopsin is the founding member of the GPCR family and its signaling mechanism is a paradigm for many other GPCRs. The crystal structure of bovine rhodopsin was first solved in 2000 and since then structures of rhodopsin have been solved in several functional states, including the inactivated dark state, partially active opsin, and the fully active state that is bound with a Gαt peptide. ZHOU, MELCHER, and XU review the signaling mechanisms gained from rhodopsin structures and compare these mechanisms to other members of Class A GPCRs, most notably β2-adrenergic receptor (β2AR)[1]. Class B and C GPCRs distinguished themselves from Class A GPCRs by having a large extracellular domain for binding of ligands. Compared to Class A GPCRs, structure determination for the full-length receptors of other families of GPCRs is lagging behind. However, structures for a half dozen of Class B and C GPCR extracellular domains (ECDs) in complex with their respective ligands have been determined. The structures and ligand binding mechanisms of Class B and Class C GPCRs will be reviewed by the XU and LIU groups, respectively[2, 3]. The rapid explosion of Class A GPCR structures is owed to technology development in various stages of structure determination; including protein expression, purification, crystallization, and X-ray diffraction, for which a thorough review is provided by ZHAO and WU[4].

Following the reviews of GPCR structures, five reviews are focused on GPCR biology, diseases, and drug discovery. β2AR is a prototype of GPCRs, and in parallel to rhodopsin, it has been serving as a model for studying other GPCRs. WOO and XIAO review the signaling mechanisms by β-adrenergic receptor subtypes that provide a basis for developing selective biased β2 agonists for the treatment of heart failure[5]. Moving from heart to immune systems, YE and SUN review the role of GPCRs in inflammation processes from chemotaxisis to transcriptional regulation of inflammation programs[6]. Lappano and Maggiolini provide a systematic review on the relationship of cancers with various subfamilies of GPCRs, which may serve as the basis for developing novel pharmacological interventions for cancers[7]. A large number of GPCRs are orphan

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receptors whose ligand remains unknown. Despite missing cognate ligands, many orphan GPCRs are known to play important physiological functions, mostly from genetic knockout studies. LIU and colleagues provide a thorough review on different class of orphan nuclear receptors, their functions, and possible strategies for identification of endogenous ligands[8]. Finally, as one of the most important drug targets, GPCRs are widely pursued by both academic and industrial research for drug discovery. ZHANG and XIE provide a comprehensive review on methods of GPCR drug discovery, including various ligand binding and cell-based functional assays, many of which are tool kits for basic research as well as drug discovery for GPCRs[9].

Followed the waves of technological advances and interdisciplinary approaches in modern biological research, the field of GPCRs is evolving rapidly into a new phase of exciting progresses. With a rich history of biology and drug discovery, GPCR research is expected to continue to be a dominant source of innovative medicines for the 21st Century. We hope that the collection of these nine exciting reviews will provide a window into this new era of GPCR research and drug discovery.

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