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COMMENTARY—MOLECULAR PHARMACOLOGY IN CHINA

A Chinese Perspective on Receptors and Receptor Regulation

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ABSTRACT

A receptor is a protein molecule that receives chemical signals from outside a cell, which enables the cell to respond to the signal molecule. Receptors mediate numerous important physiologic effects upon binding extracellular agonists. However, sustained activation of the receptor may lead to pathologic effects. Cells can regulate the number and function of receptors to alter their sensitivity to different molecules by a feedback mechanism, such as change in the receptor conformation, uncoupling of the receptor effector molecules, receptor sequestration, etc. In this special issue, some Chinese scientists were invited to contribute impactful discoveries and insightful reviews in the field of molecular pharmacology, especially receptor and receptor regulation.

Receptors are the largest family of cell-surface molecules involved in signal transmission, which can broadly be classified into the following categories: ionotropic receptors, G protein–coupled receptors, kinase-linked and related receptors, and nuclear receptors. Receptors play key physiologic roles, such as cell signaling, regulation of gene expression, cell cycle and proliferation, cellular growth and differentiation, development, and metabolism. Because receptors are involved in a variety of critical functions, it is not surprising that several major diseases have been related to receptor dysfunctions, including cancer, cardiac diseases, neurodegeneration, and inflammatory diseases. About 50% of currently marketed drugs are targeted to receptors. Receptors have become a frontier area of research, both in basic research and translational medicines.

More than 40 years since the first G protein–coupled receptor (GPCR) was cloned, key questions still remain unanswered in the GPCR field. One of these questions is how a limited number of common transducers of GPCRs (4 subtype arrestins and 16 subtype Gα proteins) allowed translation of the input information from approximately 800 different GPCRs in the human genome to tens of thousands of distinct cellular outcomes. Both different G protein conformations and arrestin conformations can account for this precise and diverse signaling mechanism (Nuber et al., 2016; Wootten et al., 2016). Recently, Dr. Lefkowitz from Duke University and Dr. Tobin from University of Leicester (Leicester, England) presented a "barcode" hypothesis that the activation of receptors can transduce different signaling pathways via distinct barcodes constituted by receptor phosphorylation sites (Yang et al., 2017). However, a principle of this barcode has not been elucidated until recently due to a lack of primary sequence identity of the receptor phosphorylated C tail at first glance (Yang et al., 2017). By using a de novo unnatural amino incorporation method and 19F-NMR technology, Dr. Jinpeng Sun's group identified the mechanism underlying the arrestin-mediated GPCR functions, of which the phosphocoding of the receptor could be, in theory, translated to more than 1000 different combinations through the 10 phosphate-binding pockets lying in the N terminus of arrestin (Yang et al., 2015). This new insight of arrestin-mediated GPCR signaling provides a potential mechanism in the operation of receptor phosphocoding by GPCRs and arrestins, and will greatly help in developing new therapeutic methods by operating arrestin functions downstream of specific GPCRs.

The concept of biased GPCR signaling is a hot research area, and developing biased GPCR ligands sheds light on new pharmacological applications (Maudsley et al., 2012; Reiter et al., 2012; Rominger et al., 2014). However, the mechanism of biased signaling is largely undefined. In China, several studies have revealed that the biased β-adrenergic and cholecystokinin A receptor (CCKAR) signaling regulated distinct islet and brain functions, which not only contributed to the recent increased repertoire of the independent G protein and arrestin

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ABBREVIATIONS: CGP7930, 3,5-bis(1,1-Dimethylethyl)-4-hydroxy-β,β-dimethyl-benzenepropanol; EGFR, epithelial growth factor receptor; GABAB, gamma-aminobutyric acid B; GPCR, G protein–coupled receptor; GRK, GPCR kinase; GS39783, N,N′-Dicyclopentyl-2-(methylthio)-5-nitro-4,6-pyrimidinediamine; IR, insulin receptor; IRS, insulin receptor substrate; PXR, pregnane X receptor.

functions, but also laid out foundations for development of new therapeutic methods for diabetes and neurology diseases (Wang et al., 2014a; Ning et al., 2015; Dong et al., 2017). For example, research conducted by Dr. Jinpeng Sun's group suggested that appropriate management of the antiasthma drug formoterol can effectively improve learning and memory (Dong et al., 2017), whereas the biased ligands of CCKARs that only activate Gs or β-arrestin-1 pathways could be a better antidiabetic therapeutic method (Ning et al., 2015). Moreover, when they used the biased agonist of angiotensin II type 1 receptors to study arrestin-mediated catecholamine secretion from the adrenal glands, they found that different arrestin subtype–biased signaling generated distinct physiologic outputs, which suggested β-arrestin-2 subtype–biased signaling, rather than β-arrestin-1–subtype biased signaling, has better therapeutic potential to treat heart diseases (Liu et al., 2017).

In addition to β-arrestin, increasing nontraditional functions of GPCR kinases (GRKs) have also been discovered beyond their original function for GPCR desensitization. Zhu et al. (2012) found that Gi-biased β_2-adrenergic receptor signaling links GRK2 upregulation to heart failure, and that GRK2/β-arrestin signaling mediates the proliferation of cardiac fibroblast induced by arginine vasopressin (Chen et al., 2017) and cell survival evoked by hypoxia (Zhu et al., 2013). In this special issue, Dr. Weizhong Zhu's laboratory found that GRK2 mediates arginine vasopressin–induced interleukin-6 production via nuclear factor kB p65 signaling in neonatal rat cardiac fibroblasts (Xu et al., 2017). Thus, GRK2 could be a drug target for treatment of various diseases, including heart failure and cardiac inflammation.

Gamma-aminobutyric acid B (GABAB) receptor is a metabotropic GPCR for the main inhibitory neurotransmitter GABA in the central nervous system. Increased expression of GABAB receptor has been detected in various human cancer tissues and cancer cell lines, but the role of GABAB receptor in cancer is controversial, and the underlying mechanism is poorly understood. Dr. Jianfeng Liu's research group reported that GABAB receptor agonist induced transactivation of epithelial growth factor receptor (EGFR) and activation of downstream ERK1/2 signaling in a ligand- and Gi/o protein–dependent pathway, leading to enhanced migration and invasion of human prostate cancer cells (Xia et al., 2017). Positive allosteric modulators of GABAB receptor, such as CGP7930 (3,5-bis (1,1-Dimethylethyl)-4-hydroxy-β,β-dimethyl-benzenepropanol), rac-BHFF, and GS39783 (N,N′-Dicyclopentyl-2-(methylthio)-5-nitro-4,6-pyrimidinediamine), can function as positive allosteric modulator agonists to induce EGFR transactivation and subsequent ERK1/2 activation. Moreover, CGP7930 also promoted cell migration and invasion through EGFR signaling. This study suggests that the neurotransmitter receptor plays an important role in tumor invasion and metastasis and provides new insights into the development of a novel strategy for prostate cancer treatment by targeting neurotransmitter signaling. In addition to EGFR, Dr. Jianfeng Liu's group also revealed several years ago that heterodimeric GABAB receptor transactivated insulin-like growth factor receptor 1 in cerebellar granular neurons, resulting in activation of Akt signaling and protecting neurons from apoptosis (Tu et al., 2010). These studies suggest that a single GPCR has the potential to transactivate multiple receptor tyrosine kinases and induce cellular-specific responses.

Although GPCRs form functional monomers, increasing evidence indicates that GPCR dimerization has a critical role in cell signal integration. Dr. Liu and colleagues also studied the details of the conformational rearrangement of the 7-transmembrane of homodimeric metabotropic glutamate receptors and provided important information for the activation mechanism of metabotropic glutamate receptors, thus improving our understanding of the negative cooperativity of GPCR dimer (Xue et al., 2015).

Enzyme-linked receptors are a second major type of cell-surface receptor. Insulin receptor (IR), together with its downstream insulin receptor substrate (IRS), is the key component of insulin signaling, which plays an important role in the regulation of both glucose and lipid homeostasis (Saltiel and Kahn, 2001). Impairment of insulin signaling leads to insulin resistance, which is a key pathogenic factor of various metabolic disorders, including metabolic syndrome, obesity, and type 2 diabetes (Eckel et al., 2005; Mcmillen and Robinson, 2005). Skeletal muscle accounts for up to 75% of insulin-dependent glucose disposal (DeFronzo et al., 1981; Shulman et al., 1990), but the mechanisms underlying muscle insulin resistance remain poorly understood. The group led by Dr. Rui-Ping Xiao identified that MG53, a striated muscle–specific tripartite motif-containing family member, is the E3 ligase of both IR and IRS-1, and is essentially involved in their degradation under circumstances of insulin resistance (Song et al., 2013). MG53 is upregulated in response to metabolic stress and mediates IR and IRS-1 degradation, the development of skeletal muscle insulin resistance, and subsequent global metabolic disorders (Song et al., 2013). This study not only identified that MG53 plays an essential role in skeletal muscle insulin resistance, but was also the first to demonstrate that the insulin resistance of skeletal muscle, instead of liver or adipose tissues, is the initial and central pathologic process during the development of global metabolic disorders. More importantly, it was first found that MG53 was the E3 ligase of both IR and IRS-1, which negatively regulates the IR signaling system. Thus, targeting the interaction between MG53 and IR/IRS-1 may be a novel approach for the treatment of metabolic diseases.

Nuclear receptors constitute another superfamily of receptors. In contrast to membrane-bound receptors, the nuclear receptors are intracellular and act by controlling the activity of genes directly. Pregnane X receptor (PXR) is a member of the nuclear receptor superfamily and is responsible for the detoxification of xenobiotics. PXR is activated by a large number of endogenous and exogenous chemicals, including steroids (e.g., progesterone, spironolactone, dexamethasone), antibiotics (e.g., rifampicin, rifaximin), antimycotics, bile acids, and many herbal and other compounds (Kliewer et al., 2002). Dr. Nanpin Wang and colleagues found that xenobiotic PXR regulates innate immunity via activation of NOD-like receptor family pyrin domain containing 3 (*NLRP3*) inflammasome in vascular endothelial cells (Wang et al., 2014b). In this special issue, Dr. Wang's group further revealed that statins inhibit NLRP3 inflammasome activation in endothelial cells by oxidized low-density lipoprotein and tumor necrosis factor through a PXR-dependent mechanism. Statins have many cardiovascular benefits beyond their lipid-lowering effects. This finding will provide new insight into the pharmacological actions of statins.

In addition to receptors, ion channels are another important class of membrane protein. In this special issue, Dr. Wang

describes the Ca^{2+}-permeable cation TRPV3 channel as an emerging target for itch and skin diseases. TRPV3 is primarily expressed in keratinocytes of the skin, as well as in sensory neurons, where its activation causes a feeling of warmth. Natural compounds, such as camphor, thymol, carvacrol, and eugenol, can activate or potentiate TRPV3. Spontaneous autosomal dominant mutations in TRPV3 can also cause hairlessness, dermatitis, and inflammatory skin lesions in rodents (Asakawa et al., 2006). In 2012, the laboratories of Yang and Wang identified three genetic gain-of-function mutations of TRPV3 from patients that cause Olmsted syndrome characterized by bilateral mutilating palmoplantar keratoderma and periorificial keratotic plaques with severe itching (Lin et al., 2012). These investigations indicate that TRPV3 mediates an important function in skin physiology, and inhibition of overactive TRPV3 may have therapeutic potential for itch and skin diseases. The Wang laboratory also demonstrated the intracellular proton-mediated activation of TRPV3 channels (Cao et al., 2012). The sensitivity of TRPV3 to intracellular acidosis may explain the cosmetic exfoliation effect of weak acids on keratinocytes in the skin.

Pharmacology has made great strides in China. The successful development of artemisinin, a remarkable breakthrough of antimalarial drugs, is a telling example that represents impressive pharmacology research in China, which was recognized by the 2015 Nobel Prize in Physiology or Medicine to Youyou Tu "for her discoveries concerning a novel therapy against malaria." (http://www.nobelprize.org/nobel_prizes/medicine/laureates/2015/) To recognize broad active researches and accomplishments in the molecular pharmacology field in China, this special issue of *Molecular Pharmacology* invited some leading Chinese researchers to contribute their impactful discoveries and insightful reviews. In addition to the previously mentioned work, the work of many other excellent researchers with important contributions cannot be mentioned because of space constraints, so the author expresses apologies. The author hopes that the collection of articles will provide a window to view the pharmacological development in China.

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