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Editorial

Family reunion of nuclear hormone receptors: structures, diseases, and drug discovery

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Hormones comprise one of the most effective classes of messengers that transmit cell to cell communication in eukaryotic systems. Cells receive messages of hormones through protein receptors, and then translate the hormone signals into concrete action of physiological responses. Homeostasis of hormone systems is essential for human health, and aberrant regulation of hormone signaling has been associated with many diseases, including cancer, diabetes, and inflammation diseases. As such, targeting hormone signaling pathways has become a major venue of pharmacological intervention of many health abnormalities. There are two major classes of hormone receptors: G-protein coupled receptors and nuclear hormone receptors, both of which consist of the top two classes of the most successful drug targets. Two years ago, we published a special issue on structures, biology and drug discovery of G-protein coupled receptors, which has been well received by drug discovery research communities. This year marked the 30th anniversary of the cloning of the first member of the nuclear receptor family and 25th year of the discovery of orphan nuclear receptors, for which no cognate ligands were known at the time of their cloning. Since then we have witnessed a tremendous expansion of our knowledge of this family of receptors. In this special issue, we collected eleven exciting review articles, highlighting our current understanding of structure, function, disease relevance, and drug discovery of nuclear receptors.

Hormones androgen and estrogen have long been known to play key roles in development, growth, and homeostasis of reproductive systems and their dysregulation is the major cause of prostate cancer and breast cancer. The first article by Tan and coworkers will provide comprehensive review on structures, diseases relevance and drug discovery of androgen receptor, the oncogenic driver of prostate cancer[1]. The second review article by Ikeda and coworkers covers the roles of estrogen-responsive genes in breast cancer[2]. Beside androgen receptor and estrogen receptor, the two of classical steroid hormone receptors in cancers, orphan nuclear receptors COUP-TFs also known to play important role in tumorigenesis, and they are respectively reviewed by Xu and coworkers[3]. In addition, the roles of bile acid receptor FXR in liver cancer will be reviewed by Huang and coworkers[4].

Nuclear hormone receptors are also well known for their central roles in metabolic regulation. Classic examples are peroxisome proliferator activated receptors (PPARs) and receptors for glucocorticoids and thyroid hormone, for which roles have been well reviewed in the literatures. In this special issue, we will focus on the emerging roles of orphan nuclear receptors in metabolism. Jiao and coworkers review the regulatory role of FXR in homeostasis of hepatic triglyceride[5]. Audet-wash and Giguère review the roles of estrogen-related receptor α and γ in metabolic control and related diseases[6]. Yan and Xie review the role of constitutive androstane receptor in energy metabolism[7]. The subfamily of ROR orphan nuclear receptors have emerged as important regulators of metabolism and immune system. The structures, biology and related drug discovery targeting RORs have been intensively studied by academic and industrial groups, and are viewed by Zhang and coworkers[8]. Together, these articles provide an overall view on the converging roles of orphan nuclear receptors in metabolic regulation and their potential as drug targets for metabolic diseases.

In addition to endogenous hormones, various environmental compounds can target members of the nuclear receptor family and cause physiological consequences such as disruption of endocrine regulation. William Bourguet's group provides a comprehensive review on structural aspects of nuclear receptors as targets of environmental compounds[9]. Nuclear

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receptors are known to have canonical functions as DNA-binding and ligand regulated transcription factors. In addition to their functions in transcription control, nuclear receptors are also involved in nongenomic actions of cell response to hormones and they are also targeted by regulation of signaling from cell surface receptors. Zhang and coworkers provide a detail review of regulation of nongenomic actions of retinoid X receptor-α by targeting the coregulator-binding sites[10]. Li and coworkers review the signaling cascade from cell surface receptors to nuclear receptors in the pathways of bile acid metabolism[11].

The root of nuclear receptors started with studying the classical endocrine hormones such as steroid hormones and thyroid hormone, which are the keystone of the modern pharmacology. The revolution of molecular biology has given the birth of the nuclear receptor family and established their roles in hormone recognition and signaling transduction. Following the recent technological advances in system biology, high-through-put sequencing, proteomics, and RNA biology, the field of GPCRs is posited for a new phase of exciting progresses. With a rich history of drug discovery and deep tradition of cutting edge science, nuclear receptors will continue to be an exciting field of innovative research and drug discovery for the 21st century. We hope that the collection of these eleven reviews will provide distinct insight into this new era of nuclear receptor research and drug discovery.

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