Chemical Biology of Nuclear Receptors

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Nuclear receptors are ligand-inducible transcription factors that regulate the expression of their target genes. There are reported to be 48 members of the nuclear receptor family encoded in the human genome, including several orphan receptors whose specific ligands are unclear. Thus, the synthetic ligands for nuclear receptors have been drawing much attention as the biological probes for chemical biology approach, since they can modify the specific gene expression, and have potential clinical utilities towards various malignant diseases, such as cancer, autoimmune diseases, cardiovascular diseases, and so on.

Retinoids are natural and synthetic analogs of retinoic acid, an active metabolite of vitamin A, and are specific modulators of cell proliferation, differentiation, and morphogenesis in vertebrates. Among various nuclear receptor ligands, retinoids are unique, and there are two classes of retinoid nuclear receptors, RARs and RXRs (α, β, and γ). We developed potent synthtic RAR agonist, Am80, which was approved as drug for acute promyelocytic leukemia in Japan in 2005, and are investigating its utilities in the other clinical fields. Further, we found several unique pharmacophores that can be applied to the development of various nuclear receptor ligands besides retinoids. In this symposium, the chemical biology approach targeting nuclear receptors and the clinical applications of nuclear receptor ligands will be discussed.