

Keiko YAMAMOTO

Showa Pharmaceutical University

Nuclear receptors are important proteins involved in gene transcription related to life support such as development and metabolism, and there are 48 species in humans. Together with the progress of molecular biology, recently nuclear receptor research has advanced rapidly and has become one of the cutting-edge research fields among interdisciplinary research beyond the fields of chemistry, biology and medicine. Nuclear receptors, which are transcription factors, are activated by binding with specific ligands such as hormones and express the action by regulating the transcription of target genes. Nuclear receptors are therefore an attractive target for drug discovery research. Indeed, 13% of medicines approved by the US Food and Drug Administration (FDA) are nuclear receptor ligands.

Active vitamin D and long-chain fatty acid metabolites bind to vitamin D receptor and peroxisome proliferator-activated receptor (PPAR), respectively, which are members of nuclear receptors, and exert their action through gene transcription. We designed and synthesized vitamin D derivatives and long chain fatty acid derivatives and studied the interaction between the ligand and the receptors. As a result, we discovered agonists, partial agonists and antagonists, and elucidated their mechanism of action structural biologically.

Active vitamin D is a hormone that regulates calcium metabolism. In addition, it shows various physiological actions such as cell differentiation induction/proliferation suppression, immune regulation. Therefore, development of analogues separating the actions has been continued. Long chain fatty acids have been expected as drugs for lifestyle diseases because they have lipid improvement and hypoglycemic action, and therefore PPAR ligands have been actively developed. Clarification of interaction with receptors is important for reasonably promoting drug discovery research. We have analyzed the X-ray crystal structure of the receptor/ligand complex, clarified the interaction between the ligand and the receptor, and elucidated the mechanism of action.<sup>1,2)</sup> Especially, we showed that partial agonistic action can be explained by the abundance ratio (equilibrium) of agonist binding and antagonist binding structure.<sup>3,4)</sup> Recently, the small angle X-ray scattering (SAXS) which is a structural analysis method of protein in solution is combined with molecular dynamics calculation to clarify the antagonist binding structure. Furthermore, we also revealed an apo-structure not bound by a ligand.<sup>5)</sup> In addition, the difference in fluctuation of the receptor due to agonist and antagonist binding was clarified using hydrogen-deuterium exchange mass spectrometry (HDX-MS) which is a method of analyzing protein fluctuation in solution.<sup>6)</sup> Based on the above results, the mechanism of action of agonists, partial agonists, and antagonists was explained by changes (differences) in structure of receptor proteins. Since nuclear receptors express their actions by a common mechanism, the structural changes revealed in this study are thought to be applicable to other nuclear receptors.

#### References

- 1) *PNAS*, **2000**, *97*, 1467-1472. *J. Med. Chem.*, **2009**, *52*, 1438-1449; **2010**, *53*, 5813-5826; **2012**, *55*, 4373-4381.
- 2) *BMCL*, **2005**, *15*, 517-522. *BMC*, **2006**, *14*, 98-108. 3) *J. Med. Chem.*, **2014**, *57*, 4351-4367. 4) *Bioconjugate Chem.*, **2015**, *26*, 690-698. *ACS Chem. Biol.*, **2016**, *11*, 2447-2455. 5) *J. Med. Chem.*, **2016**, *59*, 7888-7900. 6) *Bioconjugate Chem.*, **2016**, *27*, 1750-1761.