Doctoral thesis/dissertation Digest Form

Thesis/dissertation Title
Structural study of the ligand-binding specificity of peroxisome proliferator-activated receptors delta (PPAR δ)
核内受容体 PPAR δのリガンド特異性に関する構造研究

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Approved Digest

The peroxisome proliferator-activated receptors (PPARs) belong to the nuclear receptor superfamily of zinc-finger type transcription factors that play key roles in controlling fatty acid metabolism and catabolism for energy homeostasis by inducing the expression of genes involved in biosynthesis, oxidation, storage, and transport of lipid. The PPAR family contains three subtypes: PPARα, PPARγ and PPARδ (PPARβ). PPARα and PPARγ are the molecular targets of a number of marketed drugs for treating hyperlipidemia, insulin resistance, and other diseases.

Several studies demonstrate that PPARδ is an attractive drug target in treating obesity and diabetes, however, no synthetic PPARδ agonists have been approved for human use. Much effort to develop PPARδ agonists have been improved based on early synthetic PPARδ agonists characterized by phenoxyacetic acids such as GW501516. Metformin is the most effective and commonly used for oral therapy in treating type 2 diabetes mellitus by controlling blood sugar levels. Although metformin is widely used, its mechanism of the pharmacological action remains poorly understood.

Recently, PPARδ has been suggested as a direct target of metformin. Curiously, metformin is a biguanide compound, which displays a chemical structure distinct from those of phenoxyacetic acid derivatives. The comprehensive study of PPARδ-metformin interaction in term of three-dimensional structure at atomic resolution is important to understand the exact recognition mechanism of metformin and provides a useful structural information for further drug development.

Here I showed the crystal structures of the ligand binding domain (LBD) of human PPARδ complexed with metformin or phenformin (a metformin derivative) at high resolution (2.00 Å and 2.32 Å, respectively). The structure of PPARδ LBD-metformin complex consists of four shorts stranded β-sheet and a bundle of 12 α helices. I found that both drugs are located inside of the ligand-binding cavity and interact to PPARδ LBD via multiple hydrogen bonds formed by the guanidino group of the drugs with polar residues, together with contacts with nonpolar residues, stabilizing the metformin binding by contacting with both the biguanide moiety and the methyl groups of metformin.

The structural comparison with structures of PPARδ LBD bound to phenoxyacetic acid derivatives clarifies that the hydrogen bonding interaction between the metformin guanidino group and PPARδ LBD exhibit a similar fashion to the carboxylates group of phenoxyacetic acid derivatives, although the chemical structures are dissimilar to each other. This should be a reason why we could not recognize that PPARδ is the direct target of biguanide compounds.

In conclusion, I have provided the first structural evidence for the specific binding of chemical compounds other than phenoxyacetic acid derivatives to PPARδ. This finding leads to a deeper understanding of the specificity of the PPARδ agonists and provides valuable structural information for potential next-generation drug design in treating metabolic syndromes including diabetes mellitus.