Peroxisome proliferator-activated receptors (PPARs) are transcription factors that belong to nuclear receptor superfamily and have three subtypes (α, β/δ, and γ). Each PPAR is activated upon binding of various physiological lipidic and synthetic ligands, and form a heterodimer with retinoid X receptor (RXR), thereby binding to peroxisome proliferator response elements in target genes and regulating expression of multiple genes involved in metabolism (lipid, carbohydrate, and protein), development, inflammation, tumorigenesis, and cellular proliferation/differentiation of higher organisms. These three subtypes have distinct tissue distributions, physiological roles, and ligand specificity, and are currently the therapeutic targets against various metabolic diseases.

The molecular interaction between PPARγ-ligand-binding domain (LBD) and PPARγ ligands have been best studied because PPARγ has been attracting more attention as a target of thiazolidinedione-class antidiabetic drugs, and perhaps, it was much easier to get its apo form (no ligand bound) that could incorporate various external ligands compared to the other two subtypes; a total of 241 X-ray crystallographic data have been so far deposited in the Protein Data Bank, compared to 56 for PPARα and 44 for PPARδ (as of 6/14/2021). This Current Topics include a review paper and three original articles that investigate the PPAR–ligand interactions and provide new PDB data.

First, Prof. Yusaku Miyamae presents the cutting edge introductory review on structural characteristics of PPARγ-LBD, focusing on dynamic mechanisms of ligand recognition. Second, a research group of Prof. Toshimasa Itoh provides structural basis for human PPARγ R288H loss-of-function mutation that was found in sporadic colon cancer patients. Third, a group of Prof. Takuji Oyama demonstrates the binding modes of two newly synthesized PPARα agonists (phenylpropanoic acid derivatives) to PPARα-LBD using a sophisticated ligand-exchange soaking method. Finally, our group introduces the high-resolution (1.77Å) co-crystal structure of PPARγ-LBD and a PPARα/γ dual agonist saroglitazar, and compares with the structure of PPARα-LBD and saroglitazar that we recently reported.

We believe that all these structural analyses of PPAR-LBD using X-ray crystallography contribute to the better understanding of PPAR–ligand interaction, which may help molecular design of novel PPAR-specific, dual, or pan agonists for therapeutics against globally increasing metabolic disease patients.