Structure and Activity of PPAR Gamma Ligand Binding Domain Bound with Synthetic Agonists

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The nuclear receptor PPAR (peroxisome proliferator-activated receptor) is a ligand-activated transcription factor that forms heterodimers with the retinoid X receptor (RXR) and transactivate PPAR-responsive elements (PPREs) of target genes involved in insulin signaling, lipid/glucose metabolism, immune response and cell cycle. Three isotypes of human PPAR, called a, ? and ß/d, have been characterized, showing distinct tissue distributions, physiological roles and ligand specificity. Incorrect functions of PPAR a and ? are associated with numerous clinical manifestations including obesity, diabetes and atherosclerosis. PPAR? is localized in fat, large intestine, and macrophages. It plays an important role in adipocyte differentiation and is the receptor for a well-known class of antidiabetic insulin sensitizer compounds, the thiazolidinediones (TZD). Some of the TZDs are commercial drugs such as rosiglitazone and pioglitazone. Despite of their insulin sensitizer function, the clinical use of PPAR? agonists in type 2 diabetes has been plagued by mechanism based side effects including weight gain, edema, increased fat mass and tumor formation in rodents. In this work we solved the crystal structure and mesured the activity of the LBD-PPAR? complexed with synthetic agonists. We found some ligands with high *in vivo* activation that are good candidates a new drugs.

Keywords: Crystallography, Diabetes type 2, Nuclear Receptor, Peroxisome proliferator-activated receptor gamma

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