KP216 The constructions of 3D-QSAR models for the PPARs agonists in consideration of membrane transport

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1. Introduction

Peroxisome proliferator-activated receptors (PPARs) as ligand-activated nuclear receptors involve in the transcriptional regulation of lipid metabolism, energy balance, inflammation, and atherosclerosis and are key proteins in the pathogenesis of diabetes and cardiovascular disease [1]. To date, three PPAR subtypes, PPARα, PPARγ and PPARδ have been recognized. Some complex structures of the PPARs LBD (ligand-binding domains) with agonists have been determined by X-ray crystallography and their three dimensional (3D) coordinates are available from the protein data bank.

Several QSAR studies of PPARs agonists have been published. In most studies, QSAR models were constructed using either CoMFA fields or 2D-descriptors for IC_{50} which is binding affinity of a PPAR agonist to its receptor measured *in vitro* or EC_{50} which is transactivation activity of an agonist obtained from a cell-based assay. There is no clear correlation between the PPARs binding affinity and the PPARs transactivation activity. Transactivation include three steps, 1) diffusion or transport of the ligand through membranes into the cell and into the nucleus, 2) ligand binding to the receptor 3) conformational change of the receptor induced by ligand binding [2].

In this study, we developed 3D-QSAR models of transactivation of PPARα, PPARγ and PPARδ based on the strategy in which the process of ligand binding to the receptor is represented using CoMFA fields and the process of diffusion or transport of the ligand through membranes are described using physicochemically significant molecular descriptors.

2. Method

First, the 3D structures of PPARs LBDs were classified using root mean square deviations of the amino acids within 3Å around ligand binding site and the representative structures were selected as a target protein for the following computational ligand-docking. Next, the flexible docking of the PPARs agonists whose EC_{50} and IC_{50} are known were carried out to the representative structures of PPARs LBDs using Glide 4.0 (Schrödinger, L.L.C.). The docking poses of each

PPARs agonist were evaluated by the scoring function, Glide Score. The top 1 pose of Glide Score was selected as the binding pose of the agonist. This condition was confirmed with PPARs agonists whose binding conformations to PPARs LBD were known. The alignments of PPARs agonists used in CoMFA were generated by superposing the PPARs LBD-agonist complex structures and deleting the structures of the PPARs LBD. Atomic charges of ligands were calculated with MNDO/ESP method in MOPAC2002 V1 (Fujitsu Limited). The binding conformations of PPARs agonists were used to calculate molecular descriptors by QikProp 2.5 (Schrödinger, L.L.C.) as well as CoMFA fields (SYBYL 7.3, Tripos, Inc.). Finally, 3D-QSAR models were constructed combining the CoMFA fields with QikProp descriptors for transactivation of PPARα, PPARδ and PPARγ.

3. Results and Discussion

After the X-ray structures of PPARs LBDs were classified, five PPARδ (1GWX, 1Y0S, 2AWH, 2B50, 2J14), six PPARγ (1FM6, 1FM9, 1K74, 1KNU, 1WMO, 2ATH) and four PPARα (1I7G, 1K7L, 2NPA, 2P54) were selected as the representative structures.

At first we tried to construct two 3D-QSAR models of PPARδ agonists, one of which correlates the binding affinity (IC_{50}) with CoMFA fields and the other of which correlates the transactivation activity (EC_{50}) with CoMFA fields and QikProp descriptors. 29 PPARδ agonists were docked to five PPARδ LBDs and the binding conformations and molecular alignments of them were generated. From CoMFA for the binding affinity (IC_{50}) using CoMFA field, the good 3D-QSAR model was obtained (r^2 : 0.994, q^2 : 0.424, 6 components). Next we tried to make the 3D-QSAR model for transactivation by combination of CoMFA field and two, three or four descriptors among 21 QikProp descriptors. In result, a good 3D-QSAR model for transactivation were obtained using CoMFA field and four descriptors (hydrophilic component of the SASA(FISA), carbon and attached hydrogen component of the SASA (PISA), predicted octanol/water partition coefficient (QPlogPOW), predicted aqueous solubility (QPlogS)) (r^2 : 0.941, q^2 : 0.554, 6 components). Those descriptors which are based on the molecular surface and the partition coefficients are considered to represent the transport of the ligand through membranes.

In the same way, we are creating 3D-QSAR models for PPARα and PPARγ which will be reported at the symposium.

References

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