Supporting Information

The Recognition of 'LXXLL' by Ligand Binding Domain of the Farnesoid X Receptor in Molecular Dynamics Simulation

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Content of Supporting Information:

Docking Result of 6ECDCA, structural comparison between the two crystal structures and conformational change of helix12 in simulation-I

Docking Result of 6ECDCA

SF 1. The Autodock3 result and structural comparison (ligand-binding site) between the two crystal structures (1ot7 and 1osv). 1ot7 (chain B) is colored in orange, and 1osv (chain B) in blue. The ligand-

bind site residues (near the head of the ligands, including H444, Y358, F363, Y366 and I359) were almost identical. The conformation of 6ECDCA (docking output, colored by atom type) is very similar with experimental ones. Only one cluster is found in AUTODOCK 100 LGA runs, and the best prediction docking energy is -16.55 kcal/mol.

Comparison between the Two Crystal Structures

SF 2. The structural comparison (alpha carbon and backbone) between 1osv (chain B, blue) and 1ot7 (chain B, red) are present. The rmsd (alpha carbon, backbone and all atoms) of the structure is only 0.2067, 0.2510, 0.2967 angstroms respectively, indicating that the two structures are almost identical. The only difference between the two structures is the N-terminal residue (240 site). In 1ot7, the N-terminal residue is threonine, and that in 1osv is alanine. This difference is tiny. Refer to Devarakonda et al. *Mol. Cell.* 2003, 11, 1093-1100.

Conformational change of helix12 in simulation-I

SF 3. Comparison among the crystal structure (in cyan), the averaged structure of simulation-II (from 2 to 4 ns, in orange), and the averaged structure of simulation-I (from 21 to 25 ns, in blue). The leucine sidechain (Leu5 in simulation-I, Leu_8 in simulation-II and crystal) that inserts into subpocket2 is represented by VDW model.

The position of coactivator-1 and helix-12 in simulation-II is similar to that in the crystal structure (SF 3, orange and cyan). Because of the opposite direction of coactivator-2, the simulation-II does not reproduce the LBD-coactivator complex completely (SF 3). The rmsd of helix-12 in simulation-I changes a little after the coactivator-2 enters the AF2 site from 1.29 ± 0.30 Å in first 7.5 ns to 3.16 ± 0.34 Å in last 14 ns, bigger than 2.31 ± 0.38 Å in simulation-II. From SF 3, it can be seen that the helix12 in simulation-I moves away from the original position by about one helix turn. Two factors are proposed for this movement. First, the repulsive electrostatic interaction between E464 and ASP7 pushes the helix12 away. Second, the three conserved leucine sidechains (especially Leu5, SF 3) insert more deeply into AF2 site in simulation-I than cases in simulation-II and crystal structure ($C_{\text{LLL-LBD (I)}} = 306 \pm 22$, $C_{\text{LLL-LBD (II)}} = 287 \pm 22$, $C_{\text{X-ray (A)}} = 232$ and $C_{\text{X-ray (B)}} = 234$). So, these three leucine sidechains need larger room, and the helix12 has to move away to expand the AF2 site.