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Homology modeling of aryl hydrocarbon receptor and its ligand-binding properties investigated by molecular dynamics simulation

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Homology Modeling of Aryl Hydrocarbon Receptor and its Ligand-Binding Properties Investigated by Molecular Dynamics Simulation

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Abstract

The aryl hydrocarbon receptor (AHR) is a ligand-dependent, basic helix-loop-helix Per-Arnt-Sim (PAS) containing transcription factor that can bind and be activated by structurally diverse chemicals, including the toxic environmental contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dixoin (TCDD). Since the crystal structure of the AHR has not yet been determined, little is known about the ligand-binding mechanisms at the molecular level. Thus homology modeling followed by molecular dynamics study is helpful in understanding the ligand-binding process and relevant protein local dynamics. In this thesis, several computational methods including homology modeling, ligand-docking, molecular dynamics simulation, steered molecular dynamics simulation (SMD) and free-energy umbrella sampling are employed to investigate two important biological properties of AHR proteins. One of the properties is the biological activity difference on mouse AHR (mAHR) among various ligands. The results reveal that the hydrogen bond formed between His331 and His285, which might be critical in controlling the opening of ligand-unbinding path, is stronger in the TCDD-bound mAHR complex than those of the other ligand-bound complexes. The "unbinding" path predicted by SMD and umbrella sampling for TCDD is also different from those of the other ligands. Additionally, we predicted that the ligand-binding process is induced by the synergistic interaction among a loop connecting Aβ and Bβ, a loop connecting Hβ and Iβ and the ligand. The other biological property of AHR is that TCDD shows significant biological activity difference between mouse and human. The MD simulation results suggest that a mutation from Alanine-375 to Valine-381 partially contributes to this species difference. The possibility of a compound indigo as endogenous AHR ligand has also been interrogated by computational methods.

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