Specific interactions between aryl hydrocarbon receptor and co-factor protein: Molecular simulations combined with MD and *ab initio* FMO methods

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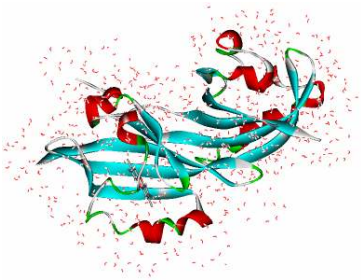
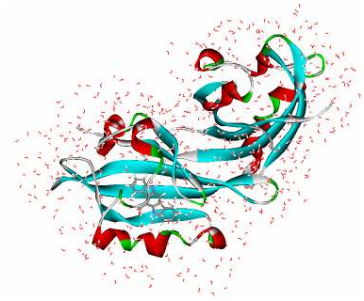
Aryl hydrocarbon receptor (AhR) binds specifically a diverse spectrum of chemicals as a ligand and regulates the expression of genes in a ligand-dependent manner. The co-factor protein ARNT (AhR nuclear translocator) plays an important role in the regulation mechanism by AhR. However, the structure of AhR-ARNT complex as well as the recognition mechanism between AhR and ARNT have not been clarified yet by experiment. In the present study, we obtained stable structures of the solvated AhR-ARNT complex with ligand by classical molecular dynamics (MD) simulations and investigated the specific interactions between AhR and ARNT by *ab initio* fragment molecular orbital (FMO) method.

We first constructed several model structures for the AhR-ARNT complex including a ligand by the homology modeling and the protein-ligand docking programs. Solvating water molecules were added around the complex, and their positions were fully optimized by a classical MM method. In addition, to search for various conformations of the solvated complex, classical MD simulations were performed by MM/MD program GROMACS. For the most stable conformation determined by *ab initio* FMO calculations, the specific interactions between AhR and ligand and between AhR and ARNT were investigated to reveal the effect of ligand on the specific interaction between AhR and ARNT.

Figure 1 shows the optimized structures of the solvated AhR-ARNT-TCDD and AhR-ARNT-FICZ complexes. The positions of the ligands differ considerably, and the relative position between AhR and ARNT is changed by the ligand binding. To elucidate the effect of ligand binding on the specific interactions between AhR and ARNT were investigated in an electronic level by the *ab initio* MP2/6-31G(d) calculations in the FMO method. The results will be shown at the poster. This work was partially supported by the Japan Society for the Promotion of Science.



(a) AhR-ARNT-TCDD



(b) AhR-ARNT-FICZ

Fig. 1 Optimized structures of AhR-ARNT-ligand complex

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