Analysis of the effects of ligand-binding on conformational change for lactose repressor using molecular dynamics method

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1. Introduction

Lactose repressor (LacR) controls the transcriptional mechanism of gene information from DNA to mRNA in a ligand-dependent manner. Although the ligand-binding to LacR is found to change the mechanism drastically, the effect of ligand-binding on the conformation of LacR-DNA complex has not been clarified at atomic and electronic levels. In our previous study [1], molecular simulations combined with classical molecular mechanics (MM) and *ab initio* fragment molecular orbital (FMO) methods were performed to elucidate the specific interactions between LacR monomer, DNA and ligand. In the present study, we investigated the change in conformation of LacR-DNA complex induced by the ligand-binding by molecular dynamics (MD) simulations.

2. Details of molecular simulations

The initial structure of the complex with LacR dimer, DNA and anti-inducer ONPF, which is defined as LacR-DNA-ONPF, was constructed based on the PDB structure (PDB code: 1EFA). The structures of LacR-DNA without ligand was constructed by deleting ONPF, while that of LacR-DNA-IPTG with inducer IPTG was constructed by replacing ONPF by IPTG. It is noted that the structure of LacR-DNA-IPTG can not be determined by experiments, because the inducer IPTG weakens the interaction between LacR and DNA. These structures were optimized in water by the MM method based on AMBER99SB-ILDN and TIP3P force fields, and 30 ns MD simulations were performed at 300 K under periodic boundary conditions to elucidate the conformational change.

3. Results and discussion

Fig. 1 shows the structures of DNA-binding domain of LacR-DNA-IPTG and LacR-DNA-ONPF obtained by the MD simulations. The α-helix domain composed of the LacR residues (30–45) comes closer to DNA in LacR-DNA-ONPF than that in LacR-DNA-IPTG. This conformational change is caused from the extension of the domain of the 5–26 residues in the direction perpendicular to DNA, as shown in Fig. 1. As a result, the domain of 30–45 residues is pulled toward DNA, leading to the stronger interaction between LacR and DNA. The specific interactions between LacR, DNA and ligand obtained by FMO calculations are also shown at the symposium. This work was partially supported by THE HORI SCIENCES AND ARTS FOUNDATION.

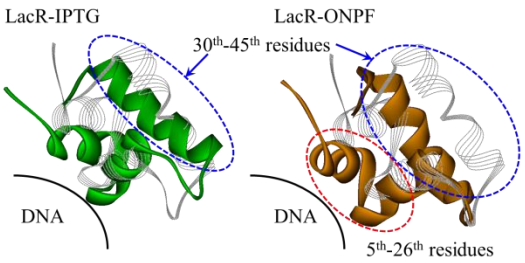

Fig. 1 DNA binding domain of LacR

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