1P10

A Molecular Dynamics Approach to Study the Behavior of Cytochromes

○Shah Md. Abdur Rauf[1], Mohamed Ismael[1], Hideyuki Tsuboi[1], Michihisa Koyama[1], Nozomu Hatakeyama[1], Akira Endou[1], Hiromitsu Takaba[1], Momoji Kubo[1], Carlos A. Del Carpio[1], Akira Miyamoto[1,2]

[1]Grad. Sch. Eng., Tohoku Univ. (6-6-11-1302 Aoba, Aramaki, Aoba-ku, Sendai 980-8579)

[2] NICHe, Tohoku Univ. (6-6-10 Aoba, Aramaki, Aoba-ku, Sendai 980-8579)

【Introduction】

Cytochrome CYP1A2 is a member of CYP1 family that accounts for about 10 to 15% of the total CYP content of human liver and is the major enzyme involved in the metabolism of imipramine, propranolol, clozapine, theophylline, and caffeine. In order to improve insight on the interaction mechanisms of CYP1A2 with substrates, it would be useful to have topological information about the enzyme, including data on its tertiary structure. We use CYP2C5 as a template for the homology modeling of CYP1A2. The aim of this work is to make a detailed structural characterization of CYP1A2 and CYP2C5.

【Method】

Molecular dynamics program, NEW-RYUDO, and MIAX program were used to explore the crystal structure of CYP2C5 and newly build homology models of CYP1A2. We have studied the superimposition images of CYP2C5 and CYP1A2 using Super Pose Version 1.0, hydrophobic patches using MIAX and structural flexibility by molecular dynamics simulation.

【Results and Discussion】

Superposing of the CYP2C5 and CYP1A2 shows high similarity as shown in Fig. 1 due to the secondary structure comparability as well as both belonging to same classified group (Oxidoreductase) with the monooxygenase molecular functionality. We have carried out molecular dynamics simulation in order to provide structural relaxation. Our results revealed that all the geometrical properties of the cytochromes were converged because the total energy did not change significantly after 35 ps. According to our results the model of CYP1A2 showed some changes in the loop areas which is flexible part of the protein, while the helices did not change significantly under the simulation condition as seen in Fig. 2. Changes in the loops surrounding the active pocket elucidate the way, how active hem can interact with the substrate. Hydrophobic residues are less in CYP1A2 than that of CYP2C5. More results will be explained in the presentation.

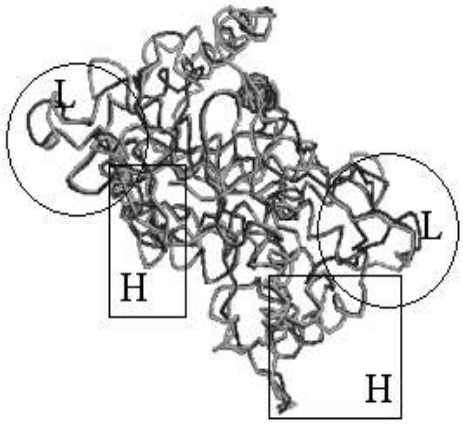

Figure 1: Superimposition image. Gray color indicates CYP2C5 and black color indicates CYP1A2. L in the circle indicates loops and H in the rectangles indicate helices.

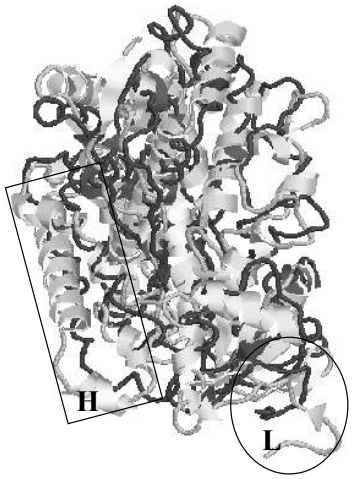

Figure 2: Superimposition image. Gray color indicates the original model and black color indicates the final model of CYP1A2 after 150 ps MD simulation. L in the circle indicates loops and H in the rectangles indicates helices.