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## Molecular dynamics study on cholesteryl ester transfer protein

**Shengli Zhang, Dongsheng Lei, Lei Zhang** and **Gang Ren**
Xi'an Jiaotong University, China

Cholesteryl ester transfer protein (CETP) decreases the level of atheroprotective high-density lipoprotein cholesterol (HDL-C) while elevating the level of atherogenic low-density lipoprotein cholesterol (LDL-C). Several CETP inhibitors have been evaluated in large-scale clinical trials for treating cardiovascular diseases (CVDs) within the last decade. Although the structure of mutated CETP has been revealed through electron microscopy (EM) and the X-ray crystallography, the structure of native CETP in physiological conditions and the detailed mechanism of how CE transfers from HDL to LDL at atomic resolution remains unclear. Here, we employed all-atom molecular dynamics simulations to study the native CETP structure and CE transfer mechanism. We propose the structure of native CETP, which is more different in some aspects with the crystal structure. The simulation results showed that the tunnel is sufficiently large to mediate the transfer of a CE molecule through CETP with a predicted transfer rate comparable to physiological measurements. Analyses of the interactions and energies between the CE and CETP tunnel during transfer indicated several residues that might regulate CETP function during CE transfer. This study provides insight into the CE transfer mechanism for future development of CETP inhibitors.

zhangsl@mail.xjtu.edu.cn

## Protein induced conformational change in ligand: A common theme of bifunctional proteins

**Nandinee Giri**
Indian Institute of Technology Bombay, India

Galactokinase of S. cerevisiae (Gal1p) is a bifunctional protein performing two functions i.e., kinase and signal transducer. The protein uses ATP and galactose as substrates in order to of function kinase while as ligands in order to function as a signal transducer. However, in spite of the available crystal structure, the structural mechanism by which galactokinase exhibits bifunctionality is unclear. One possible way of probing the mechanistic basis of bifunctionality observed in Galactokinase would be to look into the structure of Gal3p which is a paralogous protein of Gal1p and bears a high degree of structure and sequence similarity to galactokinase. It should be noted that Gal3p is a mono-functional protein and can function only as a signal transducer, using ATP and Galactose as ligands. The major significant difference in the crystal structure of both these proteins is the way in which they bind to ATP and Galactose. Gal1p binds to galactose in a canonical way. However it binds to the non-hydrolyzable analog of ATP (AMPPNP) in a non canonical orientation. This orientation of AMPPNP is different from its orientation found in other galactokinases. On the other hand Gal3p binds to ATP in a canonical fashion, but it binds to Galactose in a non-canonical way. Owing to the differences observed in the orientation of bound ligands, the dynamics of the above proteins were studied using Molecular Dynamics (MD) simulation in presence of both ATP and Galactose. The results from the MD simulation studies showed that in case of Gal1p, the bound AMPPNP undergoes a transition from a state where it cannot be phosphorylated (compact) to a state where it can be phosphorylated (extended). This transition of AMPPNP from compact to extended state was coupled to the movement of K266 residue. Mutation of this residue to arginine abolished the kinase activity but retained the signal transduction activity of Gal1p showing the importance of K266 in phosphorylation. On the other hand in case of Gal3p, neither did ATP nor did Galactose undergoes any change in their structure. Also the K258 of Gal3p which is structurally similar to K266 of Gal1p remained immobile and did not show any kind of movement. Therefore based on the above results the following hypothesis was proposed: Gal1p functions as a signal transducer when it binds to ATP in a non-canonical compact conformation. Gal1p functions as a kinase when the bound ATP attains a canonical or extended conformation. The transition of AMPPNP from compact to extended state is coupled to the movement of K266. The major question however which still persists is why Gal3p is unable to catalyze phosphorylation even though it binds to ATP canonically. This aspect of problem is still under investigation.

134300005@iitb.ac.in