

Identifying the hot-spot residues of cationic amino acid transporters during arginine transport by the MM-PBSA approach

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ABSTRACT

Arginine (L-Arginine) is a semiessential amino acid in most mammals including human beings. In order to meet metabolic and signaling requirements, every cell needs to transport arginine across the plasma membrane through cationic amino acid transporter (CAT) proteins, which are overexpressed in the different types of cancers such as acute lymphoblastic leukemia (ALL). This study is aimed at identifying the crucial amino acids in binding of arginine to prokaryotic and eukaryotic CAT proteins. The initial structure for prokaryotic CAT was downloaded from protein data bank (PDB ID: 6F34). Since eukaryotic CAT does not have any crystal structure, we modeled its structure using the MODELLER software base on prokaryotic CAT structure. Being membrane proteins, the lipid bilayer membranes were to be generated to complete the systems by using CHARMM-GUI web server. Subsequently, MD simulations were carried out for 300 ns for each CAT-Arg complex using the GROMACS package. The molecular mechanics Poisson-Boltzmann surface area (MM-PBSA) approach was utilized for calculation of the binding free energy of the complexes. To understand the contribution of individual residues to the binding energy, per residue energy decomposition studies were performed. Consequently, in prokaryotic CAT, Thr43, Asp111, Glu115, Lys191, Phe231, Ile234 and Asp237 were contributing more towards arginine binding energy. The residues Ser44, Ala130, Tyr264, Val267, Asp270, Gly353, Ser354 and Arg360 were found to be the hot spot residues in eukaryotic CAT. The findings at molecular level might shed light on better understanding of mechanism(s) by which the cationic amino acids interact with the corresponding transporters.

Keywords: Cationic amino acid transporter; Molecular dynamics simulation; MM-PBSA calculation

