Title:	In silico characterization of residues essential for substrate binding of human cystine transporter, xCT
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Abstract:	xCT is a sodium-independent amino acid antiporter that imports L-cystine and exports L-glutamate in a 1:1 ratio. It is a component of heterodimeric amino acid transporter system Xc- working at the cross-roads of maintaining neurological processes and regulating antioxidant defense. The transporter has 12 transmembrane domains with intracellular N- and C-termini, and like other transporter proteins can undergo various conformational changes while switching the ligand accessibilities from intracellular to extracellular site. In the present study, we generated two homology models of human xCT in two distinct conformations: inward-facing occluded state and outward-facing open state. Our results indicated the substrate translocation channel composed of transmembrane helices TMs 1, 3, 6, 8, and 10. We docked anionic L-cystine and L-glutamate within the cavities to assess the two distinct binding scenarios for xCT as antiporter. We also assessed the interactions between the ligands and transporter and observed that ligands bind to similar residues within the channel. Using MM-PBSA/MM-GBSA approach, we computed the binding energies of these ligands to different conformational states. Cystine and glutamate bind xCT with favorable binding energies, with more favorable binding observed in inward occluded state than in outward open state. We further computed the residue-wise decomposition of these binding energies and identified the residues as essential for substrate binding/permeation. Filtering the residues that form favorable energetic contributions to the ligand binding in both the states, our studies suggest T56, A60, R135, A138, V141, Y244, A247, F250, S330, L392, and R396 as critical residues for ligand binding as well as ligand transport for any conformational state adopted by xCT during its transport cycle.
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