Title:	Insights into the molecular basis for substrate binding and specificity of the fungal cystine transporter CgCYN1
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Abstract:	Cystine transporters are a clinically important class of transporters found in bacteria, pathogenic fungi and mammalian cells. Despite their significance, very little is known about the mechanism of substrate recognition and transport. We have carried out studies on the plasma membrane Candida glabrata cystine transporter, CgCYN1 a member of the amino acid-polyamine-organocation (APC) transporter superfamily. A homology model of CgCYN1 was generated by using crystal structures of three known bacterial APC transporters followed by further refinement using molecular dynamics simulations. This revealed a possible translocation channel lined by TMD1, TMD3, TMD6, TMD8 and TMD10 helices. In silico docking studies with cystine along with comparison with other known cystine permeases and closely related lysine permeases allowed prediction of amino acid residues specifically involved in cystine binding. To validate this model a total of 19 predicted residues were subjected to site directed mutagenesis and functionally evaluated by growth on cystine and the analogues cystathionine and seleno-dl-cystine. Biochemical evaluation by radioactive uptake assays confirmed that these mutants showed reduced cystine uptake. Detailed kinetic analysis studies for the transport defective mutants revealed the involvement of residue G255 from the conserved FAYGGTE motif of TMD 6, and T339, S340 and H347 (all from TMD 8) in cystine binding. The implications of these findings on the homologous mammalian cystine transporter, XcT are also discussed.
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