Structural Insights into Human Peroxisomal ABC Transporters ABCD1 and ABCD3: Mechanisms of Fatty Acid Transport and Disease Pathology

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Human ABC transporters ABCD1 and ABCD3, localized on the peroxisomal membrane, play critical roles in the β-oxidation of fatty acyl-CoAs by transporting these substrates from the cytosol to the peroxisome. Dysfunction in these transporters leads to severe metabolic disorders, including X-linked adrenoleukodystrophy (X-ALD) and hepatosplenomegaly. Here, we report cryogenic electron microscopy (cryo-EM) structures of ABCD1 in three states (apo, substrate-bound, and ATP-bound) and ABCD3 in two states (phytanoyl-CoA-bound and ATP-bound), revealing distinct substrate transport mechanisms.

ABCD1 mediates the transport of very long-chain fatty acids (e.g., C22:0-CoA) with a unique cooperative binding mode, where two symmetric substrate molecules bridge the two transmembrane domains (TMDs). Each molecule's hydrophilic CoA moiety inserts into one TMD, while its hydrophobic fatty acyl chain extends to the opposite TMD. Structural and biochemical analyses elucidate the conformational transitions during ABCD1's transport cycle, advancing our understanding of X-ALD pathology.In contrast, ABCD3 specifically transports branched-chain fatty acids, such as phytanoyl-CoA. Each substrate binds independently to one TMD, and ATP binding induces a conformation open toward the peroxisomal matrix, embedding two CoA molecules in the translocation cavity. This mechanism differs from ABCD1's, emphasizing substrate specificity and structural diversity among ABCD transporters.

These findings provide critical insights into the selective oxidation of fatty acids and the molecular basis of associated diseases, offering a framework for future therapeutic strategies targeting peroxisomal disorders.

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