Title: Cholesterol fill-in model mechanism for substrate recognition by ABC proteins.
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Abstract: Many of the 48 or 49 human ABC proteins are involved in lipid homeostasis and in defence against hydrophobic substances in food and the environment. Defects in their functions cause various diseases, suggesting that they play very important roles in human health; however, the mechanism of how they handle enormous numbers of hydrophobic compounds with various structures and molecular weights, or phospholipids and cholesterol, major components of cellular membranes, is not known. We compared the functions of drug-transporting and lipidtransporting ABC proteins, and found that (1) ABC proteins, either lipid or drug transporters, have a similar substrate binding site which recognizes PL and cholesterol, or drugs and cholesterol; (2) Cholesterol in membranes binds to various ABC proteins together with PL or drugs, and plays an important role in substrate recognition, especially by ABCB1/MDR1, where cholesterol fills the empty space in the substrate binding site when small drugs bind to it. ABC proteins exert very flexible substrate recognition, i.e., one-tomany interaction rather than the conventional rigid one-to-one interaction. We propose calling the mechanism the cholesterol fill-in model".