Structural Insights Into A Novel Collapsed Confirmation of Human ABCB1 In A Lipid Environment

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ATP-binding cassette subfamily B1 (ABCB1) is a polyspecific membrane transport protein that holds tremendous physiological, pharmacological, and clinical relevance for its role in cellular detoxification, mediation of drug pharmacokinetics, and acquired multidrug resistance. Here, we report cryo-electron microscopy (cryo-EM) structures of nanodisc reconstituted human ABCB1 in a hitherto unseen collapsed conformation with a closed transmembrane pathway and closely spaced but separated NBDs at 3.5 Å resolution. The structures, determined with and without a potent ABCB1 inhibitor, also point to a potential small molecule/lipid-binding site outside the canonical transmembrane drug binding site that has implications for the development of novel allosteric inhibitors of ABCB1. Finally, we map out the underlying conformational transitions that bring about the observed collapsed state, and analyze the influence the scaffold proteins commonly used for nanodisc formation that can influence the conformational dynamics of ABCB1, which may also have implications for other membrane proteins in general.