

A promiscuous conformational switch in the secondary multidrug transporter MdfA

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Multidrug (Mdr) transporters are membrane proteins that actively export structurally dissimilar drugs from the cell, thereby rendering the cell resistant to toxic compounds. Similar to substrate-specific transporters, Mdr transporters also undergo substrate-induced conformational changes. However, the mechanism by which a variety of dissimilar substrates are able to induce similar transport-compatible conformational responses in a single transporter remains unclear. To address this major aspect of Mdr transport, we studied the conformational behavior of the *E. coli* Mdr transporter MdfA. Our results show that indeed, different substrates induce similar conformational changes in the transporter. Intriguingly, in addition, we observed that compounds other than substrates are able to confer similar conformational changes when covalently attached at the putative Mdr recognition pocket of MdfA. Taken together, the results suggest that the Mdr binding pocket of MdfA is conformationally sensitive. We speculate that the same conformational switch that usually drives active transport is triggered promiscuously by merely occupying the Mdr binding site.