Molecular Rationale Behind the Differential Substrate Specificity of RND Transporters AcrB And AcrD

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Resistance-Nodulation-Division (RND) transporters AcrB and AcrD in *Escherichia coli*, recognize and expel into the medium a wide range of substrates ranging from lipophilic to amphiphilic molecules, contributing to the onset of bacterial multidrug resistance (MDR). Despite sharing an overall sequence identity of nearly 66% (similarity of nearly 80%), these Acr pumps feature distinct substrate specificity patterns whose underlying basis still remains elusive. In an attempt to understand the molecular basis responsible for this behavior, we performed a comparative analysis of multi-copy μs-long MD simulations of the apo-forms of the two transporters AcrB and AcrD, focusing on substrate binding and transport pathways. Our results illustrate how physicochemical and topographical properties (shape, lipophilicity, electrostatic potential, hydration and distribution of multi-functional sites) within the binding pockets impact the substrate specificities in AcrB and AcrD. Furthermore, we identified dynamic features (not inferable from sequence analysis or static structures) such as different flexibilities of specific loops lining the binding pocket that could potentially influence the substrate recognition profile. Our findings can be valuable for drawing structure (dynamics)-activity relationship of these multifunctional recognition sites to be employed in drug design.