Molecular rationale behind the differential substrate specificity of RND transporters AcrB and AcrD

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Antimicrobial resistance has increasingly become a major public health concern in the recent years especially due to the reduced pace of discovering new potent antibiotics in contrary to the ever-increasing number of multidrug-resistant (MDR) or even pan-resistant Gram-negative pathogenic bacteria. Resistance-Nodulation-Division (RND) transporters like the Acr pumps in *E. coli* recognize and expel into the medium a wide range of substrates ranging from lipophilic to amphiphilic molecules, contributing to the onset of MDR in these bacteria. AcrB and AcrD are two such major RND transporters in *E. coli,* which in spite of sharing an overall sequence identity of nearly 66% (similarity of nearly 80%), feature distinct substrate specificity patterns. In an attempt to understand the molecular basis responsible for this behavior, we report here the first exhaustive study comparing in a systematic way the physicochemical nature of the main putative substrate binding pockets (Access and Deep Pockets) between AcrB and AcrD. The analyses were performed on the trajectories of extensive molecular dynamics simulations of the apo-forms of the two transporters. Our results would be informative to new drug design attempts to correlate the different specificity patterns of these two transporters to the physicochemical as well as topographical properties calculated on (or projected onto) the molecular surface of their multifunctional recognition sites.