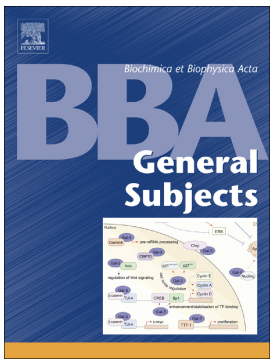

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Water-mediated interactions enable smooth substrate transport in a bacterial efflux pump

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Abstract

Background: Efflux pumps of the Resistance-Nodulation-cell Division superfamily confer multi-drug resistance to Gram-negative bacteria. The most-studied polyspecific transporter belonging to this class is the inner-membrane trimeric antiporter AcrB of *Escherichia coli*. In previous studies, a functional rotation mechanism was proposed for its functioning, according to which the three monomers undergo concerted conformational changes facilitating the extrusion of substrates. However, the molecular determinants and the energetics of this mechanism still remain unknown, so its feasibility must be proven mechanistically.

Methods: A computational protocol to mimic the functional rotation mechanism in AcrB was developed. By using multi-bias molecular dynamics simulations we characterized the translocation of the substrate doxorubicin driven by conformational changes of the protein. In addition, we estimated for the first time the free energy profile associated to this process.

Results: We provided a molecular view of the process in agreement with experimental data. Moreover, we show that the conformational changes occurring in AcrB enable the formation of a layer of structured waters on the internal surface of