Mechanistic model of sodium/proton antiport based on X-ray crystal structures and molecular dynamics simulations

OLIVER BECKSTEIN, DAVID L DOTSON, Arizona State Univ, CHIARA LEE, SHOKO YASHIRO, Imperial College, London, POVILAS UZDAVINYS, CHRISTOPH VON BALLMOOS, DAVID DREW, Stockholm University, Sweden, ALEXANDER D. CAMERON, University of Warwick — Na⁺/H⁺ antiporters are membrane proteins that are vital for cell homeostasis but the mechanistic details of their transport mechanism remain unclear, in particular, how Na⁺ and protons bind to the transporter. We recently solved X-ray crystal structures for two such antiporters (NhaA and NapA) in two different conformations of the transport cycle. All-atom molecular dynamics (MD) simulations (for a total simulated time > 10 μs), indicate that sodium binding is dependent on the charge states of two conserved aspartate residues. A conserved lysine forms a previously unidentified salt bridge with one of the asparates. Under simulated physiological pH the presence of a Na⁺ ion disrupts and breaks the salt bridge in NhaA. To quantify proton binding, we then performed heuristic pKₐ calculations on our ensemble of simulations. The calculations support our novel hypothesis that the conserved lysine in these antiporter binds protons in a sodium-dependent manner and thus acts as part of the transport machinery. In conjunction with simulations of the conformational transition we propose a new mechanistic model of ion binding for the CPA2 class of antiporters within the larger framework of the alternating access mechanism of transmembrane transport.

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Date submitted: 04 Nov 2014