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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 pK_a 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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