step as well. It therefore appears that the new Glt_{Tk} structure is also highly relevant to the mammalian transporters.

Slotboom and colleagues[5] further suggest that a pocket in the new structure could form a K^+-binding site. The residues participating in this putative site were previously suggested to be crucial for potassium interactions in the mammalian glutamate transporters[11,14]. However, transport by Glt_{Ph} does not require potassium, and this cation is also not observed in the substrate-free Glt_{Tk} structure. Why potassium is required in mammalian but not in archaeal glutamate transporters will have to be resolved by future studies including elucidation of the crystal structures of the mammalian transporters.

COMPETING FINANCIAL INTERESTS
The author declares no competing financial interests.

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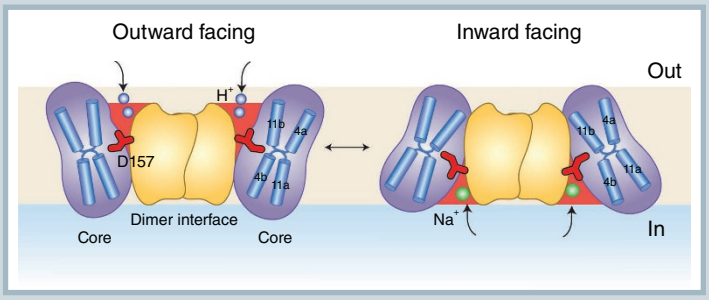
An express elevator for Na^+/H^+

Na^+/H^+ antiporters are found in the plasma membrane of every cell and are essential for maintaining pH and sodium levels within the cell as well as cell volume. Similarly to other secondary active transporters, Na^+/H^+ antiporters are believed to operate through an alternating-access mechanism of transport. Many Na^+/H^+ antiporters are pH regulated, and the structure of *Escherichia coli* NhaA antiporter in a low-pH, inactivated state is the only snapshot of these antiporters currently available. NhaA comprises two domains—a core ion-translocation domain and a dimerization (interface) domain—and the ion-binding site is located in the funnel-like cavity between these two domains, accessible from the inward-facing side of the protein (right panel).



In an effort to gain more information about the conformational cycle of Na^+/H^+ antiporters, Cameron, Drew and colleagues (*Nature* doi:10.1038/nature12484, 1 September 2013) have solved the active-state structure of NapA from *Thermus thermophilus* to 3-Å resolution, obtained from crystals grown at pH 7.8. Overall, the structures of NapA and NhaA are quite similar, but NapA comprises 13 transmembrane (TM) helices, whereas NhaA has only 12. The first six TM helices (TM-1–TM5) of NapA are topologically inverted repeats of the last six helices (TM7–TM12), and these are linked together by TM6. Like other Na^+/H^+ antiporters, NapA exists as a dimer, and a dimer with crystallographic two-fold symmetry is observed in the crystal structure. The dimer interface is formed by tight packing interactions between dimerization domains, primarily between TM-1 of one protomer and TM7 of its partner.

The major difference with the NhaA structure lies in the relative position of the core domain relative to the dimerization domain. In NapA, this change in position creates a negatively charged cavity between domains that now faces outward (left panel). Interactions between TM2, TM4 and TM5 close the cavity off from the cytoplasmic side of the membrane. At the bottom of the cavity, on TM5, are two highly conserved aspartate residues, Asp156 and Asp157, equivalent to Asp163 and Asp164 of NhaA. These residues had previously been shown to be needed for transport activity in NhaA and are probably directly involved in ion binding, depending on their protonation state. Indeed, in the NapA structure, Asp157 (likely to be charged at pH 7.8) points into the center of the cavity, in contrast to the corresponding Asp164 of NhaA, which hydrogen-bonds with the backbone of TM4. Molecular-dynamic simulations of NapA, performed with varying protonation states of the conserved aspartates, indicate binding of Na^+ ions near Asp157 when both residues are charged but only weak binding when Asp156 is uncharged and no binding when Asp157 is protonated. Similar simulations performed on the inward-facing NhaA show Na^+ binding to Asp164 (right).

On the basis of the new and existing structural and simulation data, the authors propose a straightforward model for transport. Comparison between the outward-facing NapA and inward-facing NhaA structures suggests that the dimerization interface remains stable during transport but that the core domain makes a large 21° rotation relative to the dimerization domain. This rotation closes the cavity seen in NapA (left) and opens the cytoplasmic funnel seen in NhaA (right). As this occurs, the ion-binding aspartates are also shifted to the cytoplasmic side of the protein in a single ion-translocation–site mechanism.

This elevator-like movement of the core domain is reminiscent of the large movements of the substrate-binding domain in the glutamate transporter GltPh that occur around a central trimerization-domain scaffold. Interestingly, despite these large conformational changes, Na^+/H^+ antiporters are able to transport up to 1,500 ions per second, a result suggesting that for secondary active transporters in general, there is no direct correlation between the rate of transport and the extent of conformational change needed to achieve it.

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