How Ca^{2+}-ATPase pumps ions across the membrane

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Ca^{2+}-ATPase of skeletal muscle sarcoplasmic reticulum (SERCA1a) is an integral membrane protein of 110K and the best characterised member of the P-type (or E1/E2-type) ion translocating ATPases. It consists of 10 transmembrane helices (M1-M10), 3 cytoplasmic domains (A, actuator; N, nucleotide binding; P, phosphorylation) and small lumenal loops. According to the classical E1/E2 theory, transmembrane Ca^{2+}-binding sites have high affinity and face the cytoplasm in E1; in E2, the binding sites have low affinity and face the lumen of sarcoplasmic reticulum (or extracellular side). Actual transfer of bound Ca^{2+} is thought to take place between two phosphorylated intermediates, E1P and E2P. At the same time, 2 or 3 protons are countertransported from the lumen to the cytoplasm, despite that the sarcoplasmic reticulum membrane is leaky to protons. We have determined the crystal structures of this ATPase in 8 different states that cover nearly the entire reaction cycle, and also carried out all-atom molecular dynamics simulations. These analyses show that ion pumps use large rearrangements of cytoplasmic domains to move transmembrane gates of ion pathway, and that ATP, phosphate, Ca^{2+} and Mg^{2+} are the principal modifiers of the domain interfaces. Large domain motions are needed because ion pumps vigorously fluctuate by thermal energy, yet utilises it effectively for translocating ion.

Movies showing the structural changes in the reaction cycle can be downloaded from my home page (http://www.iam.u-tokyo.ac.jp/StrBiol/resource/res.html).

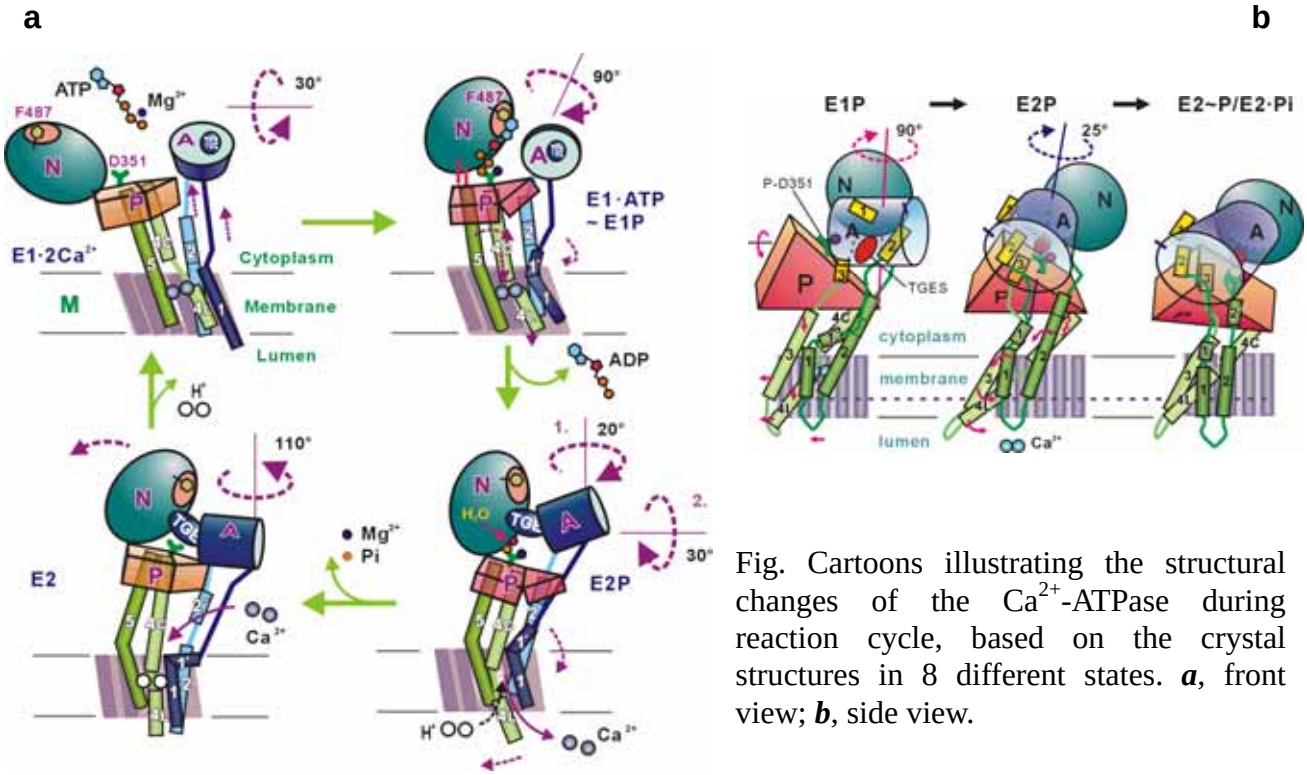

Fig. Cartoons illustrating the structural changes of the Ca^{2+}-ATPase during reaction cycle, based on the crystal structures in 8 different states. ***a***, front view; ***b***, side view.

[1] C. Toyoshima, H. Nomura and T. Tsuda. "Lumenal gating mechanism revealed in calcium crystal structures with phosphate analogues" *Nature* **432**, 361-368 (2004)

[2] C. Toyoshima, Y. Norimatsu, S. Iwasawa, T. Tsuda and H. Ogawa. "How processing of aspartylphosphate is coupled to lumenal gating of the ion pathway in the calcium pump" *Proc. Natl. Acad.Sci.U.S.A.* **104**, 19831-19836 (2007).