Ion Pumping by Ca^{2+}-ATPase of Sarcoplasmic Reticulum

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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 transports 2 Ca^{2+} and counter-transports 2~3 H^+ per ATP hydrolysed. SERCA1a consists of 10 transmembrane helices, 3 cytoplasmic domains (A, actuator; N, nucleotide binding; P, phosphorylation) and small lumenal loops [1]. In E1, transmembrane Ca^{2+}-binding sites have high affinity and face the cytoplasm; in E2, the binding sites have low affinity and face the lumen of sarcoplasmic reticulum (extracellular side). Actual transfer of bound Ca^{2+} is thought to take place between E1P and E2P. We have determined the crystal structures of this enzyme in 5 different states [2], namely, Ca^{2+}-bound E1·2Ca^{2+}, Ca^{2+}-unbound but thapsigargin bound E2(TG), Ca^{2+}- and AMPPCP-bound E1·AMPPCP, Ca^{2+}-, ADP- and AlF_x bound E1·AlF_x·ADP, and Ca^{2+}-unbound but MgF_4^{2-} bound E2·MgF_4^{2-}, where MgF_4^{2-} and AlF_x work as stable analogues of phosphate. Detailed comparisons of these structures show that very large rearrangements of cytoplasmic domains and transmembrane helices take place, and that ATP, phosphate, Ca^{2+} and Mg^{2+} are the principal modifiers of the domain interactions.

[1] Toyoshima C., Inesi G., *Ann. Rev. Biochem*., 2004, **73**, 269. [2] Toyoshima C., Nomura H., Tsuda T., *Nature,* 2004, **432**, 361.

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