SL07 **Mechanism of ion transport by P-type ATPases and its regulation**

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I have been working on structural studies on two P-type ATPases, namely, Ca^{2+}-ATPase of muscle sarcoplasmic reticulum (SERCA) and Na^+,K^+-ATPase (NKA), which is expressed all animal cells, for more than 25 years (1). They are ion pumps that establish ion concentration gradients across the membrane, and are implicated in many diseases. Since the success of the first crystallisation of SERCA1a in 2000 (2), more than 10 reaction intermediates that roughly cover the entire reaction cycle have been crystallised (Fig. 1) and allowed us to understand the mechanism of ion pumping. Nevertheless, what we are aiming at is a *complete* understanding of the mechanism or to understand "Why the structure has to be so". Therefore, we are still developing technologies and trying to go deeper. For instance, using recombinant proteins produced with an adenovirus-mammalian cell expression system, we can now address the structures of mutants (3) and other SERCA isoforms and the regulatory mechanism by phospholamban/sarcolipin (4). Furthermore, by developing a technology for visualising lipid bilayers in the crystals, we now begin to understand how Ca^{2+}-ATPase interacts with phospholipids as an integral component of the pumping mechanism (5).

High affinity inhibitors of SERCA and NKA, such as thapsigargin for SERCA and ouabain for NKA, are well known. It may be surprising to know that there are compounds that can increase V_{max} of SERCA (6) and an antibody that works similarly with NKA (7), although the mechanism of activation is still totally obscure. In this lecture, I would like to overview our current understanding of the mechanism of ion pumping by SERCA and its regulation based on the atomic structures.

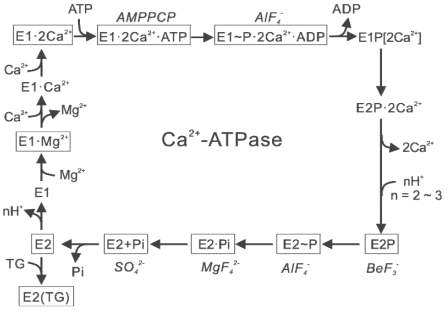

Fig 1. A simplified reaction digaram of SR Ca^{2+}-ATPase (SERCA1a). Boxes show that the crystal structures of the intermediates have been already published.

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