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Special issue on transport ATPases

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Transport of solutes across plasma membranes and intracellular organelles is an absolute requirement for cell survival and homeostasis in all organisms, including bacteria, archaea, and eukaryotes. Transport of ions and metabolites against a concentration gradient requires free energy input, which is most commonly supplied by ATP. Enzymes that utilize ATP for transport of specific solutes are referred to as transport ATPases. These enzymes constitute a rather extensive family, subdivided into P, V, and ABC groups, according to their mechanism and the transported species. F-type ATPases that utilize electrochemical energy for formation of ATP are also considered transport ATPases (physiologically working in reverse). An increasing body of knowledge on the essential role of transport ATPases in functions such as signaling, homeostasis, and energy metabolism has developed. We have also learned of their relevance to diseases, including heart, mitochondria, cancer, osteoporosis, retinal degeneration, immune deficiency, cystic fibrosis, diabetes, gastric ulcer, nephrotoxicity, hearing loss, skin, copper-related disorders, lupus, and malaria. Compounds of pharmacological and therapeutic interest, and their interaction with transport ATPases, such as ouabain, thapsigargin, gastric H⁺ pump inhibitors, and the antimalarial artemisinins, have been recognized. Furthermore, the important role of transport ATPases in the establishment of drug resistance has become evident.

Early discoveries of transport ATPases were followed by their physiological roles, cellular localization, pharmacology, definition of catalytic and transport mechanisms, molecular characterization of proteins, cloning and determination of sequences, heterologous expression, mutational analysis, and, more recently, structural resolution at the atomic level. From the conceptual standpoint, utilization of substrate (i.e., ATP) free energy was originally viewed as a requirement for *chemiosmotic work*, in order to overcome transmembrane concentration gradients and electrical charge imbalance. For instance, if we consider the sarcoendoplasmic reticulum (SERCA) Ca²⁺ ATPase, which is currently characterized in great detail, we would define the free energy required for its chemiosmotic work as

$$\Delta G = RT \ln \left(\left[\text{Ca}_{\text{in}}^{2+} \right] / \left[\text{Ca}_{\text{out}}^{2+} \right] \right) + zF\Delta V,$$

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reflecting the transmembrane Ca^{2+} concentration that can be achieved and the transmembrane electrical potential. This is certainly correct, but does not clarify the mechanism of transport. On the other hand, an initial mechanistic view of active transport was provided by Albers [1] and Post [2] or the Na^+/K^+ ATPase and by deMeis [3] for the Ca^{2+} ATPase, suggesting interconversion of these enzymes into two conformational states (E1 and E2) with varying affinities for bound cations. More recently, we learned that the catalytic and transport cycle of transport ATPases entails sequential steps, with defined equilibrium and kinetic constants, and a distinct conformational state of the protein in each sequential state. Large movements of structural domains are essential to the mechanism of transport coupled to substrate utilization. Returning again to the Ca^{2+} ATPase, it is now clear that rotation and bending of headpiece domains, in concomitance with ATP utilization, produce displacements of transmembrane segments including the Ca^{2+} sites. In fact, the conformational transition of the ground state (E1, with Ca^{2+} sites in high affinity and outward orientation) to the phosphorylated state (E2-P, with Ca^{2+} sites in low affinity and inward orientation) can be defined as

and

The energy required for this transition can then be viewed approximately as

$$\Delta G = nRT \ln(10^{-6} \text{M}^2 / 10^{-12} \text{M}^2) = 8 \text{ Kcal per cycle},$$

which is contributed by the ATP γ -phosphate under standard conditions. Analogous considerations, in reverse, can be made regarding the utilization of electrochemical energy by F-type ATPases, where rotatory motion induced by H^+ flux is followed by long-range displacement of protein subunits and conformational transitions, affecting the nucleotide and P_i binding site to favor formation of ATP. These considerations indicate that the free energy of ATP is in fact utilized for *conformational work*, which is central to the mechanism of active transport. Therefore, in addition to their enzymatic function as chemical catalysts, the ATPases protein molecules undergo long-range conformational changes that are essential mechanistic linkages to the coupling of catalysis and active transport. Demonstration of protein conformational changes maybe considered a basic conceptual advance that applies to the mechanism of all transport ATPases. Additional discoveries on specific structural features, binding modalities of transported species and ATP, covalent chemistry, stoichiometry, and charge movements are currently advancing our knowledge on the mechanism of each specific ATPase.

In this special issue of ABB, rather than providing an exhaustive list, we endeavored to collect descriptions of selected ATPases, representative of each group, and most useful for explaining general as well as specific features of the structure and function of these enzymes. We also attempted to expose the main methodological approaches used in the field, such as detailed functional characterization, high-resolution structural studies, recombinant and mutation experiments, microscopic detection of charge movements, theoretical analysis, and demonstration of relevance to diseases. We hope that this issue will be useful to scientists who are interested in transport ATPases, as well as for teaching or pursuing graduate courses in biochemistry, biology, biophysics, pharmacology, physiology, and generally medical sciences.

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