Transport ATPases into the year 2008: a brief overview related to types, structures, functions and roles in health and disease

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Abstract Transport ATPases can be lumped into four distinct types, P, F, V, and ABC, with the first three designated 20 years ago (Pedersen, P.L. and Carafoli, E., *Trends Biochem. Sci.* **12,** 146–150, 1987) and the ABC type included more recently. The mini-reviews (>20) that comprise this volume of the Journal of Bioenergetics and Biomembranes describe work presented at the 2007 FASEB Conference (6th) on Transport ATPases (Kathleen Sweadner, Chair; Rajini Rao, Co-Chair). Since these conferences began in 1997, the "transport ATPase field" has seen tremendous progress. Advances include a much better understanding of the structure, mechanism, and regulation of each of the four major ATPase types as well as their physiological and medical relevance. In fact, the transport ATPase field has entered a new era in which work on these enzymes is likely to contribute to new therapies for multiple diseases that affect both people and animals. Among these are cancer and heart disease, mitochondrial diseases, osteoporosis, macromolecular degeneration, immune deficiency, cystic fibrosis, diabetes, ulcers, nephro-toxicity, hearing loss, skin disorders, lupus, and malaria. In addition, as several members of the transport ATPase family include those involved in drug resistance their study may help alleviate this recurring problem in drug development. Finally, the transport ATPase field is also paving the way for nanotechnology focused on nano-motors with work on the F-type ATPases (F_0F_1) leading the way. These ATPases driven in reverse by a proton gradient have the capacity to interconvert electrochemical energy into mechanical energy and finally into chemical energy conserved in the terminal bond of ATP. In mammalian mitochondria these events occur on a larger complex or "nano-machine" called the "ATP synthasome" that consists of the ATP synthase in complex formation with carriers for P_i and ADP/ATP.
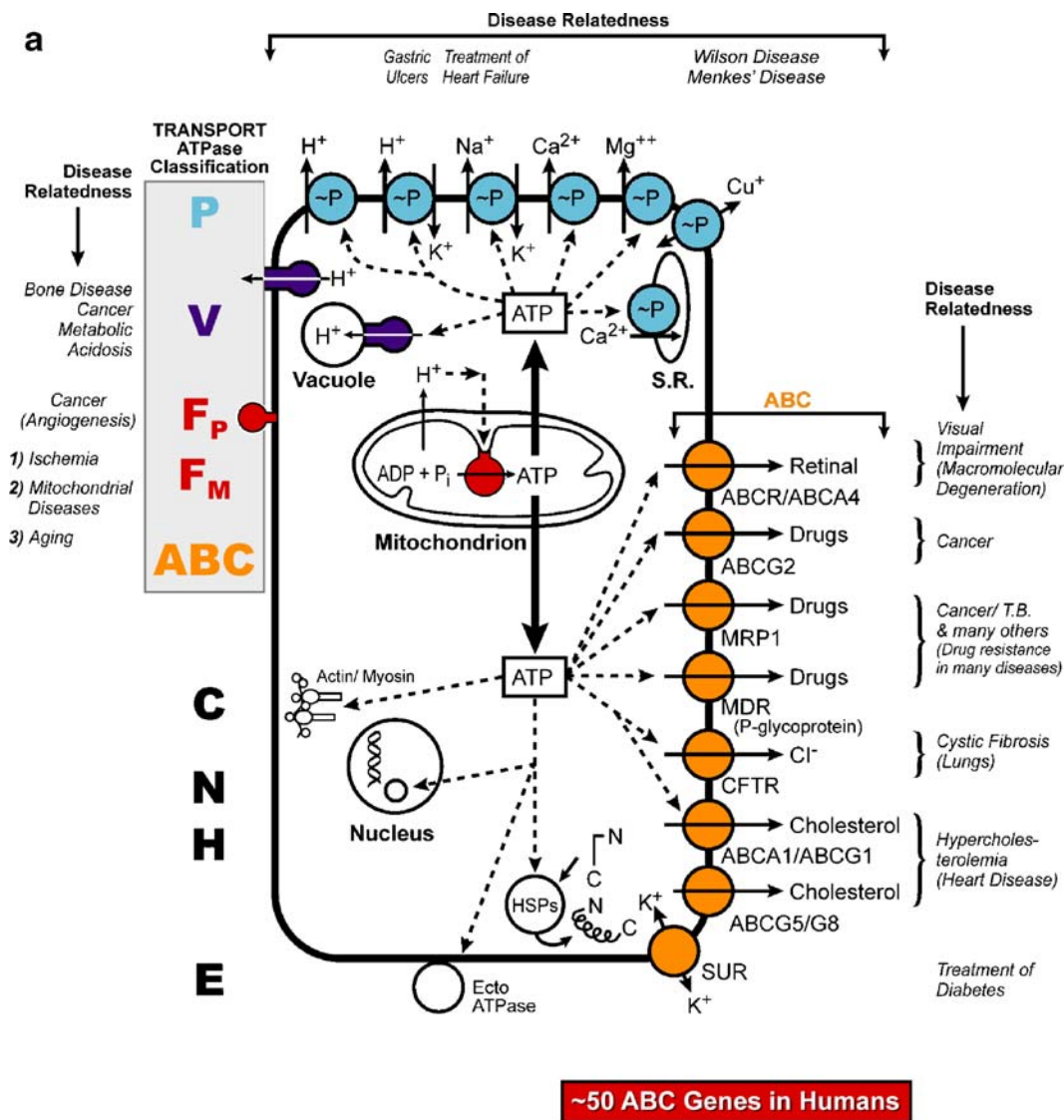
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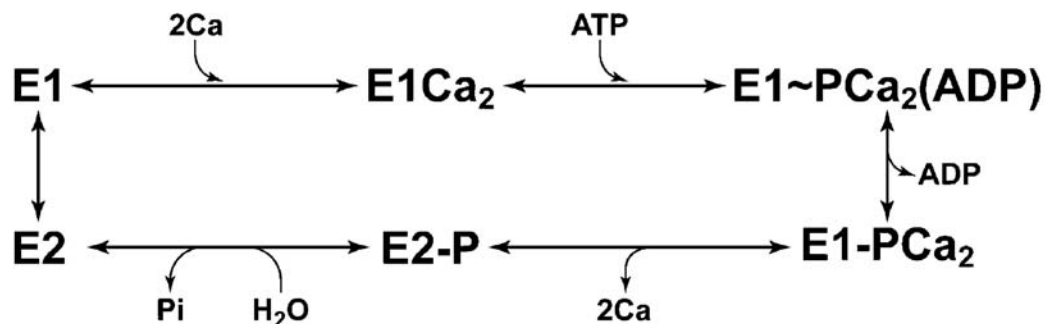e-mail: ppederse@jhmi.edu

Introduction

As noted in earlier reviews (Pedersen 2002, 2005), the transport ATPase field had its origin at the University of Aarhus in Denmark in the year 1957 when Jens Skou, a physician scientist, reported the discovery of a Na^+, K^+ ATPase in crab nerves while attempting to understand anesthetics that control pain (Skou 1957). Now in the year ending in 2007, exactly half a century later and nearly 10 years after Skou was awarded a Nobel prize, we find that his discovery has blossomed into a vigorous field of energetic investigators working on transport ATPases within every continent on our planet. It is thus fitting that on this 50th anniversary of the publication of his discovery and upon publication of this transport ATPase review series that Skou's Danish colleagues, also at the University of Aarhus, have bestowed upon him and the field of transport ATPases a most wonderful gift in the form of the first crystal structure of the Na^+/K^+ ATPase (Morth et al. 2007).

Significantly, transport ATPases are found in the animal, plant, and bacterial worlds and as shown in Fig. 1a are designated as types P, F, V, and ABC (Pedersen and Carafoli 1987; Pedersen 2002, 2005). They have three features in

Fig. 1 a Summary of transport ATPase types and some of the diseases with which they are associated [Modified from Pedersen 2005]. Transport ATPases fall into four major categories, i.e., types P, V, F, and ABC signifying respectively those that proceed through a reaction path involving a covalent phosphorylated intermediate, those that appear in vacuoles, those that were originally called "F_oF_1", and those that have become known as "ABC transporters". The figure lists also a sampling of the numerous diseases/pathological states that result from problems related to a given transport ATPase. Also shown in this figure are other well known ATPases that fall into other categories and are not discussed in this review. Specifically, *C* stands for ATPases involved in contraction or cellular movement; *N* for those ATPases involved in nuclear events; *H* for heat shock proteins, and *E* for ecto ATPases that appear on the surface of some cell types. **b** The reaction cycle of the P-type Ca^{+2} transporting ATPase found in the sarcoplamic reticulum of muscle [Also see Toyoshima and Inesi (2004)]

common: they exist in biological membranes, hydrolyze ATP, and transport at least one substance across a biological membrane at the expense of ATP hydrolysis. In fact, they are nano-machines (P and ABC type) or double nano-machines (F and V type). For the most part these transport ATPases are involved in performing much of the membrane related "trafficking" work in which all cell types must engage (Fig. 1a). Other transport ATPases, e.g., some in cancer cells (Dean et al. 2001; Gottesman and Ambudkar 2001, Ambudkar et al. 2003) and some in cells associated with other diseases, are involved in drug resistance making the destruction of such cells and therefore the cure of a given disease extremely difficult. In order to (1) understand how these incredibly tiny "workers" help maintain viable almost every living cell in the universe; (2) identify what has gone awry in the many diseases that result from mutations therein; and (3) discover how to treat such diseases by overcoming drug resistance, six FASEB transport ATPase meetings have been held over the past decade to review the rapid progress that has resulted from their study. ["FASEB" designates the Federation of American Societies for Experimental Biology and is located in Bethesda, Maryland (USA)].

This volume (JOBB 39 5/6) of the Journal of Bioenergetics and Biomembranes includes over 20 mini-reviews summarizing work presented at the most recent (June 9–14, 2007) FASEB Conference on Transport ATPases. Specifically, this brief introductory article provides (1) An overview of current knowledge related to the function(s), reaction pathway, and structure of each the four major types of transport ATPases (P, F, V and ABC) and (2) a sampling of diseases with which some are associated.

P-Type ATPases

These membrane-associated ATPases are involved in the transport of cationic forms of calcium, sodium, potassium, copper, and some other metals across biological membranes. As shown by Post and colleagues (Charnock et al. 1963; Post et al. 1965) shortly after the discovery of the Na^+/K^+ ATPase by Skou (1957), these transport ATPases proceed through a reaction cycle that involves a covalent phosphorylated intermediate (Fig. 1b). In fact, the name "P-type ATPase" given these enzymes by Ernesto Carafoli and the author (1987) is based on this key reaction intermediate. The other transport ATPase types, i.e., F, V and ABC *do not* involve a covalent phosphorylated intermediate during their reaction cycle.

The two P-type ATPases that have been studied most extensively are the Na^+/K^+ (reviewed in Andersen and Vilsen 1995; Caplan 2007) and the Ca^{+2} (Toyoshima and Inesi 2004; Toyoshima (2007)) with the former enzyme involved in electrolyte and fluid balance, and the latter involved in muscle relaxation or functions specific to some

other tissues. At the expense of ATP hydrolysis, the Na^+/K^+ ATPase drives the exit of 3 Na^+ ions out of cells and the entry of 2 K^+ ions while the Ca^{+2} ATPase drives the exit of 2 Ca^{+2} ions (Fig. 1b). In each case, the complete reaction process occurs in a cyclic fashion involving several different intermediates, one a covalent phosphorylated intermediate (Fig. 1b). In recent years due to the crystallographic work of Toyoshima and colleagues combined with many excellent biochemical/mutational studies by others [reviewed in Toyoshima and Inesi (2004); Toyoshima (2007)], there has been tremendous progress in obtaining detailed information about the reaction cycle of the muscle Ca^{+2} ATPase found in the sarco-endoplasmic reticulum. Therefore, our current knowledge of how this transport ATPase really works via multiple conformational changes in carrying out its physiological functions in muscle and likely other tissues is quite advanced.

As indicated above, new information about the details of the mechanism of the Na^+/K^+ ATPase has just been published (Morth et al. 2007). Specifically, the crystal structure at 3.5 Å resolution has been reported for the complete enzyme consisting of the catalytic α. subunit as well as the non-catalytic β and γ subunits. Features of the catalytic α subunit are stated by the authors as follows: "As in the Ca^{2+}-ATPase, the αM4 and αM6 helices of the Na^+, K^+ ATPase are unwound in the middle, thereby making space for the ions, and αM1 shows a characteristic ~90° kink near the cytoplasmic surface of the membrane, where it comes into contact with αM3. This contact point may function as a pivot for movement of αM1 in connection with ion binding."

Also, it is stated that "Significant differences from SERCA are seen in αM7, which is unwound at gly 848, resulting in a kink, and in the cytoplasmic end of αM10. These differences may be a consequence of the interaction of the β-subunit. Moreover, the C terminus may be influential." For further details, the reader is referred also to the mini-review by Einholm et. al. (2007) that comprises one of those included in this volume of the J. Bioenerg and Biomemb.

Structural information has now been obtained also for a P-type ATPase (ATP 7B) involved in regulating copper homeostasis and biosynthesis of copper containing enzymes in human tissues. Specifically, the solution structure of the N-terminal domain of this P-type ATPase in the presence of ATP was solved by using heteronuclear multidimensional NMR spectroscopy (Dmitriev et al. 2006). The structural data obtained indicate that this domain shows higher similarity to the bacterial K^+ translocating ATPase than to the mammalian Ca^{+2} and Na^+/K^+ ATPases. Finally, a bacterial copper transporting ATPase (Cop A) studied recently by Hatori et al. (2007) implicates similarities in mechanism to the muscle Ca^{+2} ATPase. Thus,
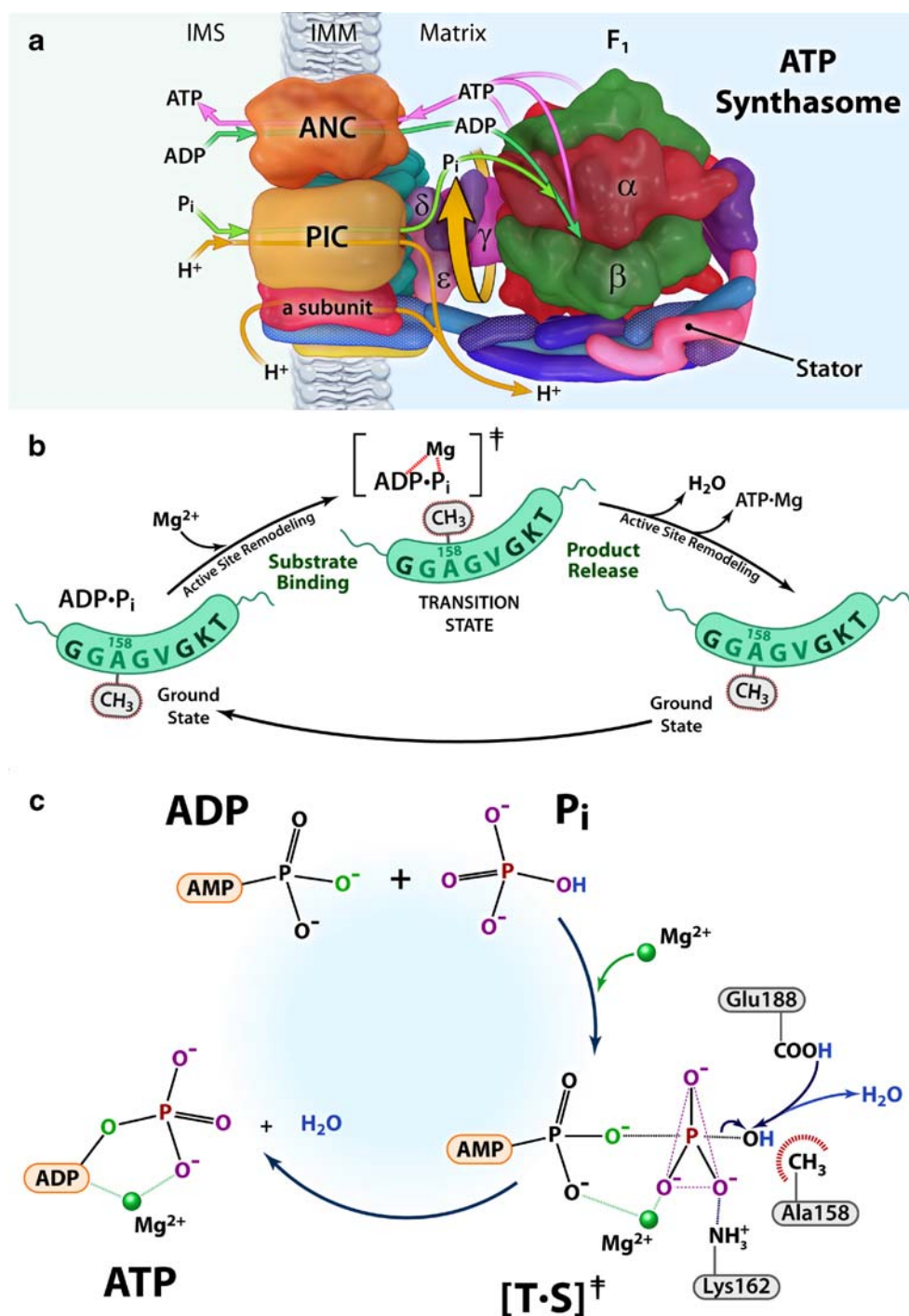
Fig. 2 a Overview of the structure and function of the mitochondrial ATP synthasome (ATP synthase/Phosphate Carrier/Adenine Nucleotide Carrier complex) and how it makes ATP. In the figure the phosphate carrier is designated as "PIC" and the adenine nucleotide carrier as "ANC". Mg^{2+} is not shown here but, as illustrated in "B" and "C", it plays a vital role in the synthesis of ATP from ADP and P_i at the catalytic site of the ATP synthasome. (Catalytic sites on the ATP synthasome are found on the "F_1" headpiece at interfaces between α and β subunits. The catalytic sites are comprised mainly of amino acid residues on β subunits with a minor contribution from the α subunits. **b** Overview of the role in ATP synthesis by the ATP synthasome of Alanine 158 within the P-loop region of the β subunit. Note that alanine 158 moves into the active site region in the transition state as supported by X-ray crystallographic data. Here, it is proposed to lower the local dielectric constant, thus facilitating the dehydration of ADP+ P_i resulting in ATP formation. **c** Details of the chemistry involved in making ATP at the active site of the ATP synthasome. [Note that both **b** and **c** above are based on prior biochemical studies with vanadate (Ko et al. 1997, 1999) and crystal structures of rat liver F_1 in both the ground state (without vanadate, Bianchet et al. 1998) and a transition like-state (with vanadate, Chen et al. 2006)

characteristic digestion patterns obtained for different analog intermediates show that CopA undergoes domain rearrangements very similar to those of the muscle Ca^{+2} ATPase.

F-Type ATPases

In most aerobic cell types F-type ATPases (also called F_0F_1 ATPases or ATP synthases) function not as ATPases but as ATP synthases (Pedersen 2005; Stock et. al. 2000). That is, they make ATP from ADP and P_i in the presence of Mg^{++} (Fig. 2a) in response to an electrochemical gradient of protons generated by an electron transport chain. ATP synthases are located in the inner membrane of mitochondria and bacteria and in the thylakoid membrane of plant chloroplasts. They have been reported to be located also on the surface of endothelial cells (Moser et al. 1999; Kenan and Wahl 2005). These remarkable enzymes consist of two major components, a catalytic headpiece called F_1 and a basepiece/stalk component called F_0. Recently, biochemical and structural efforts spearheaded by Young Ko in the author's laboratory (Ko et al. 2003; Chen et al. 2004) resulted in the discovery that in mammalian mitochondria the ATP synthase is attached also to both the phosphate carrier (PIC) and the adenine nucleotide carrier (ANC) (Fig. 2a). Ko named this ATP synthase/PIC/ANC complex the "ATP synthasome" (Ko et al. 2003). In terms of mitochondrial function this complex makes good physiological sense as to make ATP on the ATP synthase both P_i and ADP must be transported in and directed to the active sites (Fig. 2a) Then, once ATP is made it must exit the mitochondria. To this end, ANC translocates ADP into the mitochondria in exchange for an ATP that leaves on this same transporter (Fig. 2a).

Although an atomic resolution structure has not been obtained for the complete ATP synthasome, structures at atomic resolution in the "ground state" have been obtained for its catalytic F_1 component (Abrahams et al. 1994; Bianchet et al. 1998). In addition, a transition state structure in the presence of vanadate has been obtained recently for rat liver F_1 (Chen et al. 2006) in a project also led by Young Ko in the author's laboratory. Significantly, this latter structure confirmed earlier biochemical studies with vanadate by Ko et al. (1997, 1999) that had implicated movement of alanine 158 of the P-loop into the catalytic site. Significantly, as shown in Figs. 2b and c the methyl group of alanine is believed to lower the local dielectric constant within the active site facilitating the release of water and the formation of MgATP from MgADP and P_i (Chen et al. 2006).

In addition to these studies, are the stunning experimental demonstrations of "rotation" in the laboratories headed by Yoshida (Noji et al. 1997) and Futai (Omote et al. 1999),

both in Japan. These studies taken together with the earlier x-ray crystallographic studies (Abrahams et al. 1994) obtained by Walker's team at Cambridge (MRC) implicated involvement of the central F_1 subunits $\gamma\delta\varepsilon$ connected to a ring of "c" subunits in the basepiece as being involved in rotor formation. In fact, these findings helped confirm the earlier suggestion of Vik and Antonio (1994) based on an independent set of data that entry of protons, most likely through subunit "a" in the basepiece, cause via charge interactions with subunit c the entire c-subunit ring to rotate. Rotation of the "γ" subunit part of this rotor through the center of F_1 is now believed to induce conformational changes in the β subunits favorable for MgATP formation from ADP, P_i and Mg^{++} (Fig. 2b, c) in the transition state (Ko et al. 1997, 1999; Chen et al. 2006).

Aside from the above accomplishments, there remains controversy as it relates to how the stator operates in stabilizing the F_1 motor. Although workers in the field are now in general agreement that the stator extends from the basepiece of the ATP synthase to near the very top of F_1 as shown experimentally by the earlier work of Wilkens and Capaldi (1998) and the laboratory of the author (Golden and Pedersen 1998; Ko et al. 2000), there remains controversy as to whether the stator is flexible or rigid. Earlier studies employing mutational analysis were interpreted to imply that the stator is flexible (Cain 2000) whereas recent x-ray crystallographic studies have been interpreted to implicate that the stator is rigid (Dickson et al. 2006). Although further studies will be necessary to resolve this issue, it should be noted that if the stator is rigid, then at that single location in which it positions itself at the top of F_1, stator- $\alpha\beta$ pair interactions will be different for each of the 3 $\alpha\beta$ pairs. Thus, each $\alpha\beta$ pair will not have an identical structure to the other two pairs when ATP is made. A flexible stator would resolve this problem as it would allow for slight changes in position at the top of F_1. Alternative positions of the stator have been discussed earlier by Blum et al. (2001) and should be re-visited with the objective of subjecting them to experimental tests.

V-Type ATPases

In contrast to the P and F type ATPases that play important but limited roles, the V-type ATPases are emerging as a key player in many different physiological processes. They are found in intracellular vacuoles (hence the name "V-type") in eukaryotic cells and also in the plasma membranes of both specialize eukaryotic cells and in prokaryotes. As indicated in a recent review by Wilkens et al. (2005) such ATPases are involved in a variety of vital intra-and intercellular processes including receptor mediated endocytosis, protein trafficking, active transport of metabolites, homeostasis and neurotransmitter release. Although such ATPases

are reversible, i.e, they can either hydrolyze ATP or synthesize ATP, they function exclusively in terms of their physiological function as ATPases (reviewed in Drory and Nelson 2006). In terms of their overall structural features and catalytic capacity to hydrolyze ATP, V-type ATPases bear significant similarity to the F-type ATPases. Also, just as F-type ATPases (ATP synthases) in animal cells that have a complex sub-structure consisting of as many as 17 subunit types (Ko et al. 2003), vacuolar ATPases are just as complex and in some animal cell types are even more complex consisting of > 20 subunit types (Xu et al. 2007). Finally, a central feature of the overall mechanism of V-type ATPases in catalyzing ATP hydrolysis and translocating protons is their apparent requirement for rotation of specific subunits (Imamura et al. 2005).

Also in contrast to P and F-type ATPases where many three-dimensional structures at atomic resolution have been obtained, thus allowing for cyclic reaction pathways to be depicted and details of reaction mechanism to be presented, this is not yet possible for the V-type ATPases. Nevertheless, significant progress is being made toward these goals. Specifically, as it relates to structural advances these are summarized in detail in a recent review by Drory and Nelson (2006). Suffice it to say here, a low resolution structural model for a vacuolar ATPase purified from animal cells has been reported recently by Wilkens et al. (2004, 2005). In addition, it would appear that work that may eventually lead to a crystal structure has its origin in the recent report of Gerle et. al. (2006). These workers have obtained two-dimensional crystals and projection images of the intact *Thermus thermophilus* V-type ATPase.

ABC-Type ATPases

ABC-type ATPases are more commonly referred to as ABC transporters (Higgins 2001; Davidson and Chen 2004; Dean and Annilo 2005; Hollenstein et al. 2007). These represent by far the largest class of transport ATPases. They are ubiquitous in biological systems from bacteria to people and clearly of great importance to numerous cellular functions in that they transport an essential nutrient either into or out of a given cell type. In humans there are about 50 ABC-type ATPases/transporters (Gottesman and Ambudkar 2001; Ambdukar et al. 2003; Dean and Annilo 2005), and it seems likely they all play essential roles in those tissues in which they are found. Several of these are depicted in Fig. 1a and most consists of single polypeptide chains that contain two nucleotide binding sites (domains), both of which on inspection might be predicted to catalyze ATP hydrolysis. Most of these nucleotide binding domains (NBDs) have what has been referred to in the literature as the "Walker A and B" binding sequences suggesting that they are highly likely to participate in the binding of

nucleotides (in particular ATP and ADP), and in the presence of ATP and a divalent cation (e.g., Mg^{+2}), to catalyze the hydrolysis of ATP. Although it has not been common practice for investigators working on these ABC-type ATPases (transporters) to write reaction cycles as has been done for those working on P-type ATPases (Fig. 1b), it is certainly possible to do so.

Recently structures of several of these ABC-like ATPases have been obtained at or near atomic resolution (Reviewed in Davidson and Chen 2004; Moody and Thomas 2005, Hollenstein et al. 2007). This information together with mutational/biochemical studies have provided insights into how this class of transport ATPases may work. One of the key features of such transporters is that, although there are commonalities among them as it relates to the structural architecture of their ATP binding domains, the structural architecture of those transmembrane domains that bind and transport the physiological substance of interest are quite different. Moreover, these latter domains must undergo conformational or positional changes upon the binding/hydrolysis of ATP in order to move the agent to be transported from one side of the membrane to the other and then release it.

Some of the substances normally transported by the ABC transporters in humans and animals are shown in Fig. 1 together with the specific transporter involved. Among these are Cl^- (CFTR), cholesterol (ABCA1/ABCG1, ABCG5/G8) and retinal (ABCR/ABCA4). In other cases, such transporters called "multidrug resistant transporters" ("MDRs") may not be normally expressed but induced when one or more foreign substances, e.g., pathogens, drugs or other medications, enter(s) the human or animal system. Among these are MDR (MDR1), MRP1 and a number of others tabulated in earlier reviews noted above.

Roles of transport ATPases in disease or disease treatment

Examples of diseases that have been associated with transport ATPases, either in their cause, treatment, or in some other way are summarized in Fig. 1. Among these are heart disease, liver disease (bile transport), cancer, cystic fibrosis, adrenoleukodystrophy, diabetes, gastric ulcers, eye disease, kidney disease, bone disease, and many others. As it relates to the causes of such diseases, these are due mostly to mutations within the gene (or genes) that encode(s) the transport ATPase. The vast majority involve mutations in the ABC type ATPases (ABC transporters) as nearly 50 different types are now known to exist in humans (Dean and Annilo 2005). As noted above, in addition to those ABC type ATPases involved in the cause of a given disease are those (MDRs) that are involved in opposing the treatment of these and other diseases (Gottesman and Ambudkar 2001; Ambdukar et al. 2003; Lou and Dean 2007).

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