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Multidrug Resistance—A Fascinating, Clinically Relevant Problem in Bioenergetics

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A major medical problem in the treatment of disease by pharmacological intervention is the resistance that develops to the drugs employed. Use of the drug of choice to combat a given disease may result not only in the development of resistance to it, but resistance to a number of structurally unrelated drugs as well. After two decades of research in a number of different laboratories, the mysteries underlying the molecular basis of multidrug resistance is rapidly unfolding. It now seems clear that at least two major classes of proteins are involved, those that pump drugs out of the cell at the expense of ATP hydrolysis, i.e., ATPases, and those that utilize an electrochemical ion gradient rather than ATP as the direct driving force.[1] In the latter category proteins that act as H^+/drug antiporters are currently considered to be major players.[1,2]

In this minireview series the focus is on ATPases involved in drug efflux, the most well studied of which is the protein called MDR-1 or P-glycoprotein (reviewed in Refs. 3–5). Relative to many other cellular ATPases that act as ATP-dependent pumps (Fig. 1), MDR-1 is in a unique family most commonly referred to as "ABC Transporters",[6] but also as "M-type",[7] or "traffic ATPases".[8] In this family, there are over 50 known members including the cystic fibrosis transmembrane conductance regulator (CFTR). Most have no role in drug resistance and are involved in the transport of ions or metabolites. Others are involved in the transport of polysaccharides, peptides, or proteins.

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MDR-1 or MDR-1-related proteins have now been studied in some detail in animals cells,[3–6] yeast,[9] bacteria,[1] and parasitic organisms.[10–13] In animal cells, the open reading frame of the MDR-1 cDNA encodes a 1280 amino acid polypeptide of ~170 kDa consisting of two approximately equal halves that are structurally similar to each other. Each half is predicted to include a hydrophobic domain with six predicted transmembrane segments and a relatively hydrophilic region containing an ATP binding domain (Fig. 2). Both domains include the Walker *A* and *B* consensus motifs. Although it is now clear that MDR-1 is an ATPase capable of extruding structurally unrelated drugs from the cell at the expense of ATP hydrolysis, it is not known whether both halves of the protein function as ATPases, or whether one half functions in this capacity while the other is regulatory in nature.

Significantly, drug efflux catalyzed by MDR-1 is competitively inhibited by verapamil,[14] a known Ca^{++} channel blocker, although there appears to be no relationship among Ca^{++}, Ca^{++} channels, and drug efflux. MDR-1 and certain Ca^{++} channels may simply contain a similar amino acid stretch to which verapamil binds. Verapamil is known also to reverse drug resistance of cancer cells presumably by increasing the accumulation of anticancer drugs.[15]

It is known also that there exists in animal cells a protein highly homologous to MDR-1 called MDR-2 which is not involved in drug resistance.[16] However, MDR-2 can be converted to a drug efflux pump by changing four MDR-2 residues back to MDR-1 residues in a small segment within the first intracytoplasmic loop. There is recent evidence that MDR-2 may be involved in phospholipid transport.[17]

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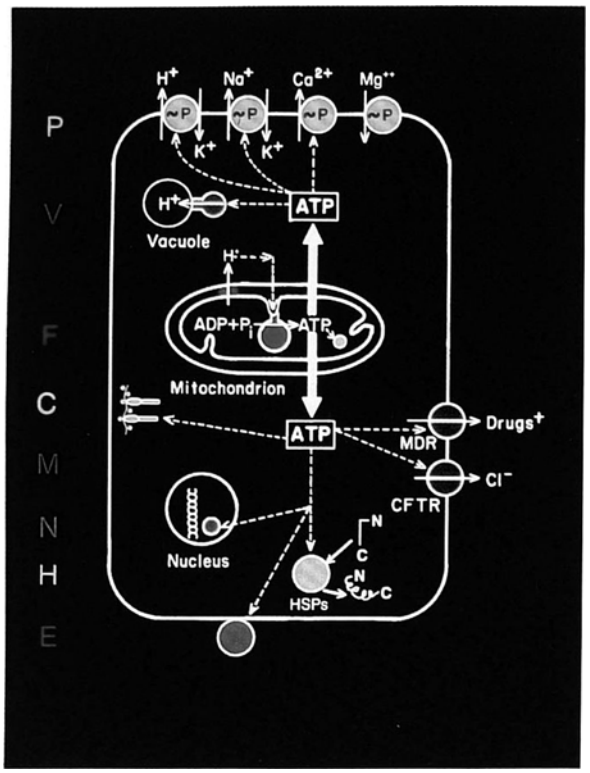

Fig. 1. ATPases in biological systems. There are many different types of cell ATPases with the "Master System" being the *F*-type (F_0F_1 type) or ATP synthase/H^+ ATPase complex. The ATP formed by this unique molecular machine is made available to other cell ATPases which then in tightly "coupled" reactions perform the cellular work. Among these latter ATPases in animals cells are the *P*-type (e.g., Na^+/K^+, Ca^{++}, and Mg^{++}), the *V* or vacuolar type, the *C* or contractile type (e.g., myosin and dynein), the *M* or multidrug resistant-like (e.g., MDR, CFTR, TAP, and many bacterial permeases), the *N* or nucleic acid type (e.g., rec A, the urv_A protein, and the Rho protein), the *H* or heat shock type (e.g., HSP 70 and GroEL), and the *E* or ecto type. Others not shown in the figure include ATP-requiring enzymes essential for biosynthetic reactions, and some ATP-dependent degradative enzymes. (From *J. Biol. Chem.* with permission.) The focus of this minireview series is on ATPases involved in multidrug resistance.

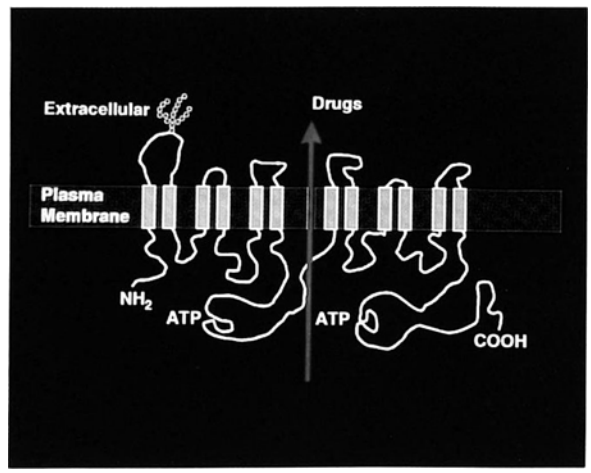

Fig. 2. Predicted membrane topology of the MDR-1 P-glycoprotein. In animal cells, MDR-1 is a ~170-kDa protein consisting of two approximately equal halves that are structurally similar to each other. Each half is predicted to include a hydrophobic domain with six predicted transmembrane segments and a relatively hydrophilic region containing an ATP binding domain. (The reader should consult the recent literature for other views/interpretations of the topology.)

In this minireview series current work on MDR-1 or MDR-1 related proteins are briefly summarized. This includes work on proteins isolated from animal, yeast, and bacterial cells. Work is summarized also on the MDR-1 like proteins recently identified in parasitic protozoa that cause Leshmania.[12,13] An MDR-1-like protein has been recently detected also in parasitic protozoa responsible for African sleeping sickness but does not appear to be responsible for the resistance these organism develop to drugs used to treat the disease.[18]

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