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UNLOCKING THE POWER OF ABC TRANSPORTERS: UNVEILING THEIR FUNCTIONS IN CELLULAR HOMEOSTASIS AND POLYPHARMACOLOGICAL

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Abstract

A major class of membrane proteins is ABC transporters, which are employed for various activities like the transportation of substances from the exterior to the intracellular environment and vice versa. These proteins require energy in the form of ATP for the movement of substrate in the direction opposite to substrate asymmetry. These transporters are responsible for transporting materials across the plasma membrane in all organisms, including prokaryotes like bacteria and eukaryotes like humans. They play a vital role in the homeostasis of various cells, nutrient balance, and are also involved in multi-drug resistance. ABC transporters consist of two domains for nucleotide binding and two for the material that crosses the semipermeable barrier, as well as additional components like coupling helices and accessory domains that are necessary to carry out specific functions. There is a different genetic makeup for both prokaryotes and eukaryotes, with eukaryotes having one gene responsible for the expression of partial or complete numbers of transporters. The mechanism of ABC transporters involves altering configurations, as they are involved in conformational changes necessary for substrate transportation. ABC transporters have multiple types and sub-types based on their functions, with each playing an important role in a specific function. For instance, in humans, ABCA to ABCG are linked with the transport of lipids and drug resistance. ABC transporters are clinically significant as they are involved in multi-drug resistance during the treatment of malignancies. Malfunctioning of chloride ion channels due to faults in CFTR can cause cystic fibrosis. It is necessary to understand the structure and functions of ATP transporters so that we can address health problems like cystic fibrosis and multi-drug resistance.

Keywords: *ABC transporters, Concentration gradient, Confirmational domains, Cystic fibrosis, Multi-drug resistance*

INTRODUCTION

ABC (ATP-binding cassette) transporters represent one of the largest and most diverse families of membrane proteins, playing an indispensable role in cellular homeostasis, multidrug resistance, and various physiological processes (1, 2). These transporters utilize energy derived from ATP hydrolysis to actively transport a wide array of substrates across biological membranes, often against their concentration gradient (3). The substrates transported by ABC transporters include ions, sugars, lipids, peptides, bile salts, and a broad spectrum of xenobiotics, including therapeutic drugs. Given their ubiquity and essential functions, ABC transporters are found across all domains of life, from bacteria to humans, with their structural and functional diversity reflecting their evolutionary adaptability (4).

The fundamental structure of ABC transporters consists of two nucleotide-binding domains (NBDs) and two transmembrane domains (TMDs), which together facilitate substrate recognition, binding, and translocation across the membrane. The ATP-binding domains, located in the cytoplasm, exhibit conserved motifs such as the Walker A and Walker B sequences, which are crucial for ATP hydrolysis and energy transduction (5). These structural components orchestrate conformational changes that allow ABC transporters to shift between inward-facing and outward-facing states, thereby enabling the transport process. While bacterial ABC

transporters can function as both importers and exporters, eukaryotic ABC transporters predominantly act as exporters, crucially influencing processes such as lipid transport, immune response, and detoxification (3, 6, 7).

The clinical significance of ABC transporters cannot be overstated, particularly in their role in multidrug resistance (MDR). Over expression of certain ABC transporters, such as P-glycoprotein (MDR1/ABCB1), in cancer cells results in the active efflux of chemotherapeutic agents, rendering treatments less effective and posing a major challenge in oncology (8). Similarly, ABC transporters are implicated in genetic disorders such as cystic fibrosis, where mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) gene disrupt chloride ion transport, leading to severe respiratory and digestive complications. Understanding the mechanisms, structures, and functional diversity of ABC transporters is therefore crucial for devel oping novel therapeutic strategies to counteract drug resistance and treat transporter-related diseases (9).

This review aims to provide a comprehensive overview of ABC transporters, emphasizing their molecular architecture, mechanistic function, and clinical implications. By exploring the evolutionary diversity, physiological roles, and pathological consequences of ABC transporter dysregulation, we seek to highlight their significance in both fundamental biology and translational medicine. Additionally, we discuss emerging strategies to modulate ABC transporter activity, which may offer new avenues for overcoming drug resistance and improving therapeutic outcomes in various diseases.

MOLECULAR STRUCTURE of ABC-TRANSPORTERS

All ATP-transporter members' family consists of:

TWO TRANS-MEMBRANE DOMAINS (TMDS)

Each trans-membrane domain (TMDs) consists of six membrane-spanning alpha helices, but up to ten helices in some cases. Transmembrane domains (TMDs) provide pathway (translocation) and also provide specificity. Responsible for substrate recognition (10, 11).

TWO NUCLEOTIDE-BINDING DOMAINS (NBDS)

These 2 cytosolic domains are involve in attachment with the ATP and couple its hydrolysis (provide energy for transport) ATP binds with the (NBDs) nucleotide-binding domains. Located in the Cytosol (12). Each NBD contains characteristic motifs, such as Walker B and Walker A motifs, which participate in ATP binding and hydrolysis as depicted in Fig. 1 (13).

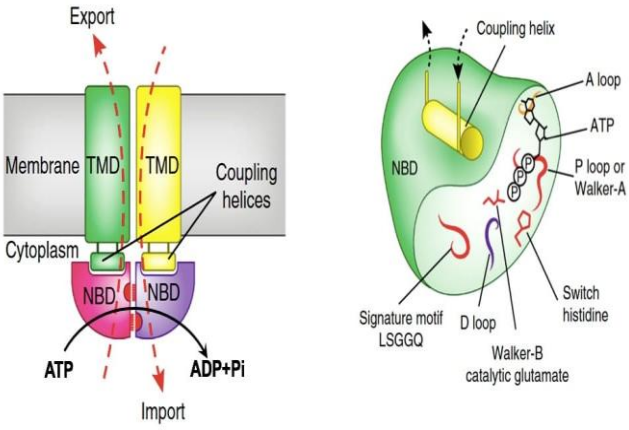

Fig. 1. Conserved NBD architecture

COUPLING HELICES

Coupling helices connect TMD and NBDs, which cause changes in the shape of protein by binding of ATP and ATP hydrolysis. Such changes are important for the transportation system because they allow the transporters to switch between inward and outward facing states (14, 15).

GATE DOMAINS

Some ABC transporters have gate domains that regulate access of substrate to the binding sites. These domains control the opening and closing of the transport pathway, contributing to the specificity and selectivity of substrate transport (16, 17).

ACCESSORY DOMAINS

In addition to the basic TMDs and NBDs, ABC-transporters may also have accessory domains that contribute to their specific functions. These domains can include regulatory elements, sensing domains, or additional structural features that modulate transporter activity (18, 19).

DIMERIZATION INTERFACE

ABC transporters often function as dimers, with the TMDs and NBDs forming a stable interface between the two subunits (18,19). Dimerization is essential for the proper functioning and coordination of the transport cycle.

EXTRACELLULAR BINDING DOMAINS

In specific ABC transporters, primarily in prokaryotes, extracellular binding domains may be present. These domains increase substrate binding specificity and are often involved in initial substrate recognition (20).

GENETIC ARCHITECTURE OF ABC TRANSPORTERS

In bacteria, transporter genes follow a modular approach with four separate genes, each encoding a specific subunit (21). In eukaryotes, on the other hand, typically have a single gene encoding a complete transporter or a half transporter (one TMD and one ABC) (21).

EXPORTER FUNCTIONS

Eukaryotic ABC transporters mainly function as exporters, moving substances out of cells or into compartments (22). Examples include multidrug efflux pumps in humans and TAP (transporter associated with antigen processing) transporters crucial for immune system function (23).

BACTERIAL EXPORTERS

Bacteria also have ABC-type exporters, like LmrA in *Lactococcus lactis,* which play essential roles in multidrug exports and other functions(24, 25).

BACTERIAL IMPORTERS

Importers which are present in bacteria mainly import nutrients with diverse substrates. Bacterial importers typically include two TMDs, two ABC domains (NBD), and a substrate-binding protein (SBP) for substrate delivery as shown in Fig. 2. SBPs play a vital role in determining transporter specificity by binding substrates with high affinity (8, 25, 26).

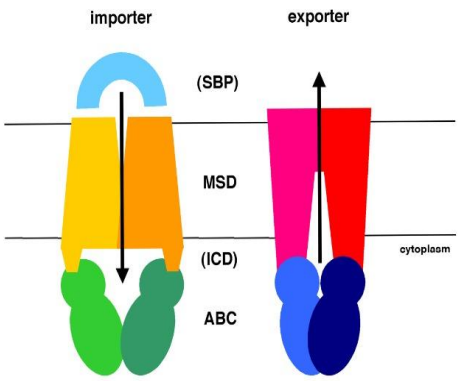

Fig. 2. Molecular architecture of ABC exporters and importers

MECHANISM of ABC-TRANSPORTERS

ALTERNATING-ACCESS MODEL

ABC transporters are like molecular machines in our cells which utilize energy for the transportation of different materials across plasma membrane (27). These proteins use the energy produced by the conversion of ATP to ADP to drive conformational changes within delivery molecules and the transmembrane area. ABC exporters and importers share a common mechanism. They both use ATP energy to undergo shape change (conformational change) in the TMDs (28, 29). This process is described by alternating-access model. This model suggest that the transporter alternate between two shapes, one facing outward and one facing inward. The way the substrate binds to the two distinctive shapes of the protein mainly determines, in which manner the transportation is going (30, 31).

Importers and Exporters

The transportation is pointed to the cytoplasm from the periplasm, outward-facing structure have more ability to bind with the substrate because of having more affinity with substrate (32). Inward-facing confirmation has excellent binding affinity with the substrate in exporters (33).

ATP-Switch Model

The process begins with the attachment of ATP (adenosine triphosphate) to the cytoplasmic domains of the ABC transporter. This ATP binding causes structural variations in the transporter. The changes in their confirmation are caused by the ATP which bind and act as a switch, altering the structure of the transporter (34, 35). This switch is crucial for the transporter to alternate between different functional states, allowing it to capture the substance at one side of the membrane and expel to the other one. The altered conformation of the ABC transporter facilitates the translocation of the substrate across the membrane (36,37). This active transport process is carried by the conversion of ATP to ADP (adenosine diphosphate) and inorganic phosphate (38).

Transport Cycle

The conformational change in ABC transporters is due to the attachment and breakdown of ATP. At resting state NBDs have arrangements like an open dimer (configuration), which has less ability to bind with ATP(39, 40). In the open arrangement there is a compartment or a chamber which reach to the interior of the transporter. The TMDs have a high-affinity site, the substrate will bind with this site, and the transport initiates, who influence conformational modifications inside the NBDs and give a hike to the affinity of ATP as demonstrated in Fig. 3. Two ATP molecules bind accordingly to create the closed dimer arrangement (configuration) (41, 42).

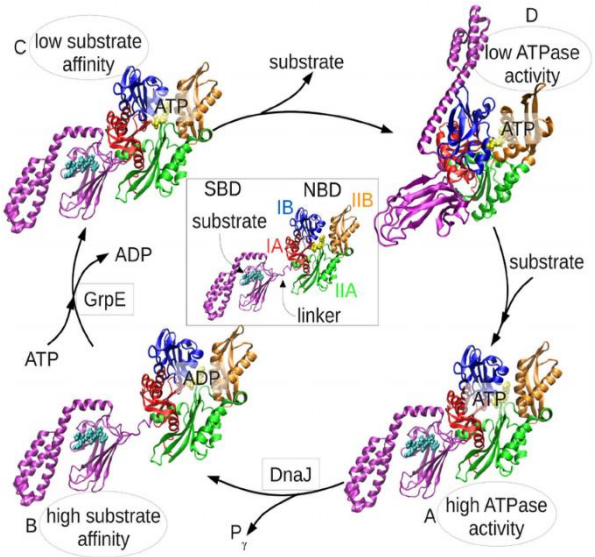

Fig. 3. Mechanism of ABC transporters

The closed NBD dimer involves in the variations which alters the conformation of TMDs, the trans-membrane domain (TMDs) will open and produce a chamber with an opening which is on the other side to the initial state. This modification decreases the affinity of substrate to the TMDs because of this, the substrate will be released and due to the breakdown of ATP, ADP, and inorganic phosphate will be released, which leads to the recovery of transporter proteins (43, 43).

DIVISIONS OF ABC TRANSPORTERS

ABC-transporters are divided into many types and sub-types, which are based on their functions. Table I summarize these transporter along with their functions. In humans, these include ABCA to ABCG. Different subfamilies are specific for different substrates and have different functions. ABCB transporters are often involved in drug resistance. ABCA transporters are associated with lipid transport.

Table I. Example of some selected human ABC proteins

ABC Transporters	Tissue Expression	Function
MDR1	Adrenal, kidney, brain	Export lipophilic drugs
MDR2	Liver	Export phosphatidylcholine into bile salt
CFTR	Exocrine tissue	Transport chloride ions (43)
TAP transporters	ER membrane of nucleated cells	Transport a various number of peptides to the ER lumen from cytosol (44, 67, 68).

ABC transporters play critical roles in many physiological processes. They facilitate the uptake of essential nutrients. They regulate ion concentrations across membranes (44,45). They pump out toxins and xenobiotics. They participate in lipid metabolism and transport. ABC transporters have significant implications in medicine and pharmacology (46).

CANCER

ABC transporters have significant implications in medicine and pharmacology, particularly in cancer treatment (47). A prominent example is the multidrug resistance protein 1 (MDR1/P-glycoprotein), encoded by the ABCB1 gene, which plays a crucial role in the development of chemoresistance in cancer cells (48). MDR1 actively effluxes chemotherapeutic drugs, such as doxorubicin and vinblastine, from cancer cells, reducing their intracellular concentrations and rendering treatments less effective (49). This efflux mechanism is a major obstacle in chemotherapy, as it enables cancer cells to survive despite drug administration (50).

Moreover, other ABC transporters, such as ABCG2 (breast cancer resistance protein, BCRP), have been implicated in the resistance to various anticancer drugs, including mitoxantrone and topotecan. The overexpression of these transporters in tumor cells is associated with poor prognosis and treatment failure in several cancers, including breast cancer, lung cancer, and leukemia (51,52).

DRUG RESISTANCE

Gene amplification of specific ABC transporters in cancer cells contributes to multidrug resistance by expelling therapeutic agents (53).

DRUG ABSORPTION AND DISTRIBUTION

ABC transporters in the gut and blood-brain barrier influence the intake and distribution of drugs in the body (54).

MULTIDRUG RESISTANCE TRANSPORT PROTEINS (MDR)

MDR1 (now known as ABCB1) was the 1st eukaryotic ABC protein to be recognized in tumor (cancer) cells. These cells express elevated levels of MDR1 and exhibit resistance to a variety of chemically unrelated cytotoxic drugs (Adriamycin, doxorubicin, and vinblastine) that are widely used in cancer

chemotherapy. MDR1 uses the energy which is produce by the hydrolysis of ATP to transport a vast majority of drugs from the interior to the exterior of cell (55).

MECHANISM

MDR1 recognizes substrate and binds to it MDR1 has two domains for nucleotide binding that attach and causes the breakdown of ATP. ATP breakdown results in conformational changes in MDR1. These configurational changes are directed to the transmembrane domains, affecting the substrate-binding sites. The conformational changes in MDR1 facilitate the transport of substrate from the inside of the cell to the outside of the cell. The substrate is actively transported against its concentration gradient. After substrate transportation, ADP and inorganic phosphate are released (56,57).

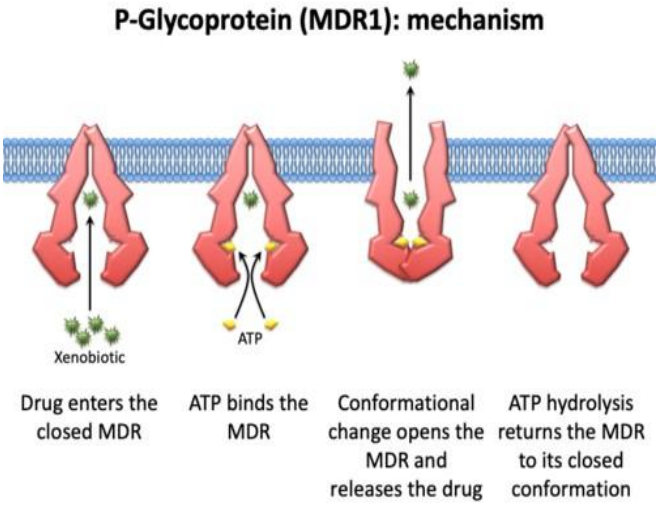

Fig. 4. Mechanism of MDR1

CYSTIC FIBROSIS TRANSMEMBRANE CONDUCTANCE REGULATOR (CFTR)

CFTR is a gene which is expressed in the plasma membrane of epithelial cells of lung cell, pancreas, sweat glands, and other tissues. CFTR function is a chloride ion channel and allows chloride ions to move out of the cell. A vital role in the reuptake of chlorides is also done by CFTR in cells of the sweat glands "lost by sweating"(58,59).

CFTR has 4 domains two are trans-membrane domains and 2 for Nucleotide-binding; in addition, the protein also contains a great cytoplasmic regulatory (R) domain, which has several serine residues, which are the site of phosphorylation catalyzed by cAMP-dependent-protein kinase. Channel opening is trigger by phosphorylation of Regulatory domain and then attachment of two ATP molecules with the2 NBDs domains. Defects in CFTR cause life-threatening conditions known as cystic fibrosis (60,61).

CONCLUSION

ABC transporters have a vital role in the cellular processes by facilitating the active transport of a various range of substrates across cell-membranes. Their involvement in nutrient uptake, drug resistance, and cellular detoxification underscores their significance in maintaining cellular homeostasis. The structural diversity and functional versatility of ABC transporters highlight their adaptability to different cellular environments and their impact on various physiological and pathological conditions. Understanding the mechanisms and classifications of ABC transporters is vital for developing targeted therapeutic interventions and overcoming challenges such as multidrug resistance in medical treatments.

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