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RESEARCH ARTICLE

BIO INFORMATCS

ABC DEPENDENT CANCER SUPPRESSION

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ABSTRACT

ATP-binding cassette transporters (ABC-transporter) are members of a protein super family that is one of the largest and most ancient families with representatives in all extant phyla from prokaryotes to humans.ABC transporters are transmembrane proteins that utilize the energy of adenosine triphosphate (ATP) hydrolysis to carry out certain biological processes including translocation of various substrates across membranes and non-transport-related processes such as translation of RNA and DNA repair. They transport a wide variety of substrates across extra- and intracellular membranes, including metabolic products, lipids and sterols, and drugs. They are classified as ABC transporters based on the sequence and organization of their ATP-binding cassette (ABC) domain(s). ABC transporters are involved in tumor resistance, cystic fibrosis, bacterial multidrug resistance, and a range of other inherited human diseases. Human ABC transporters are involved in several diseases that arise from polymorphisms in ABC genes and rarely due to complete loss of function of single ABC proteins. These proteins are characterized by the presence of two nucleotide-binding domains, and present recent study aims at the association and dissociation of these domains is a common basic molecular mechanism of operation that couples ATP binding/hydrolysis to substrate transport across membranes. Using biosoftware tools, the structural prediction for transmembrane glycoproteins targeted cancer cells were also studied.

KEYWORDS

ATP binding cassette transporter, transmembrane proteins, tumor resistance.

I INTRODUCTION

ATP-binding cassette (ABC) transporters are multidomain integral membrane proteins that utilize the energy of ATP hydrolysis to translocate solutes across cellular membranes in all phyla. ABC transporters form one of the largest of all protein families and are central to many important biomedical phenomena, including resistance of cancers and pathogenic microbes to drugs. Elucidation of the structure and mechanism of ABC transporters is essential to the rational design of agents to control their function.

ABC transporters are involved in the transport of molecules such as ions, sugars, amino acids, vitamins, peptides, polysaccharides, hormones, lipids and xenobiotics. They are also involved in diverse cellular processes such as maintenance of osmotic homeostasis, nutrient uptake, resistance to xenotoxins, antigen processing, cell division, bacterial immunity, pathogenesis and sporulation, cholesterol and lipid trafficking and developmental stem cell biology. They employed mainly for maintenance and repair of DNA and for gene regulation. They involved in tumor resistance, cystic fibrosis, bacterial multidrug resistance, and a range of other inherited human diseases.

1 FUNCTIONS

In prokaryotes, importers mediate the uptake of nutrients into the cell. The substrates that can be transported include ions, amino acids, peptides, sugars, and other molecules that are mostly hydrophilic. The membrane-spanning region of the ABC transporter protects hydrophilic substrates from the lipids of the membrane bilayer thus providing a pathway across the cell membrane. Eukaryotes do not possess any importers. Exporters or effluxers, which are both present in prokaryotes and eukaryotes, function as pumps that extrude toxins and drugs out of the cell. In gram-negative bacteria, exporters transport lipids and some polysaccharides from the cytoplasm to the periplasm. The third subgroup of ABC proteins do not function as transporters, but are rather involved in translation and DNA repair processes.

In the cystic fibrosis transmembrane regulator (CFTR) and in the sulfonylurea receptor (SUR), ATP hydrolysis is associated with the regulation of opening and closing of ion channels carried by the ABC protein itself or other proteins.

Human ABC transporters are involved in several diseases that arise from polymorphisms in ABC genes and rarely due to complete loss of function of single ABC proteins. Such diseases include Mendelian diseases and complex genetic disorders such as cystic fibrosis, adrenoleukodystrophy, Stargardt disease, Tangier disease, immune deficiencies, progressive familial intraheptic cholestasis, Pseudoxanthoma elasticum, persistent hyperinsulinemic hypoglycemia of infancy due to focal adenomatous hyperplasia, X-linked sideroblastosis and anemia, age-related macular degeneration, familial hypoapoproteinemia, Fundus flavimaculatis, Retinitis pigmentosum, cone rod dystrophy, and others. The human ABCB (MDR/TAP) family is responsible for multiple drug resistance (MDR) against a variety of structurally unrelated drugs. ABCB1 or MDR1 P-glycoprotein is also involved in other biological processes for which lipid transport is the main function. It is found to mediate the secretion of the steroid aldosterone by the adrenals, and its inhibition blocked the migration of

dendritic immune cells, possibly related to the outward transport of the lipid platelet activating factor (PAF). It has also been reported that ABCB1 mediates transport of cortisol and dexamethasone, but not of progesterone in ABCB1 transfected cells. MDR1 can also transport cholesterol, short-chain and long-chain analogs of phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS), sphingomyelin (SM), and glucosylceramide (GlcCer). Multispecific transport of diverse endogenous lipids through the MDR1 transporter can possibly affect the transbilayer distribution of lipids, in particular of species normally predominant on the inner plasma membrane leaflet such as PS and PE.

2 CAUSES

Mutation due to chemical carcinogens

The errors which cause cancer are often *self-amplifying*, eventually compounding at an exponential rate. For example:

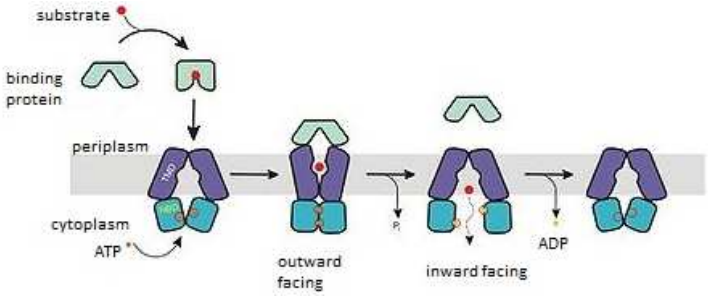
- A mutation in the error-correcting machinery of a cell might cause that cell and its children to accumulate errors more rapidly
- A mutation in signaling (endocrine) machinery of the cell can send error-causing signals to nearby cells
- A mutation might cause cells to become neoplastic, causing them to migrate and disrupt more healthy cells
- A mutation may cause the cell to become immortal (telomeres), causing them to disrupt healthy cells forever

This present study deals with the mechanism of increasing ATP synthesis which was affected during cancerous infection. And it also includes how the ABC dependent glycoprotein suppresses the entry of anticancer drugs for the infected persons. The structural mechanism of ABC transporter and structural depictation are also studied.

II MECHANISM

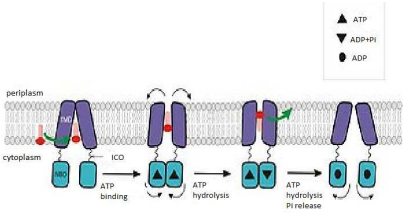
3 Mechanism of transport for importers

The mechanism of transport for importers supports the alternating-access model. The resting state of importers is inward-facing, where the nucleotide binding domain (NBD) dimer interface is held open by the TMDs and facing outward but occluded from the cytoplasm. Upon docking of the closed, substrate-loaded binding protein towards the periplasmic side of the transmembrane domains, ATP binds and the NBD dimer closes. This switches the resting state of transporter into an outward-facing conformation, in which the TMDs have reoriented to receive substrate from the binding protein. After hydrolysis of ATP, the NBD dimer opens and substrate is released into the cytoplasm. Release of ADP and P_i reverts the transporter into its resting state. The only inconsistency of this mechanism to the ATP-switch model is that the conformation in its resting, nucleotide-free state is different from the expected outward-facing conformation. Although that is the case, the key point is that the NBD does not dimerize unless ATP and binding protein is bound to the transporter.



4 *Mechanism of transport of exporters*

ABC exporters have a transport mechanism that is consistent with both the alternating-access model and ATP-switch model. In the apo states of exporters, the conformation is inward-facing and the TMDs and NBDs are relatively far apart to accommodate amphiphilic or hydrophobic substrates. For MsbA, in particular, the size of the chamber is large enough to accommodate the sugar groups from lipopolysaccharides (LPS). As has been suggested by several groups, binding of substrate initiates the transport cycle. The "power stroke", that is, ATP binding that induces NBD dimerization and formation of the ATP sandwich, drives the conformational changes in the TMDs. In MsbA, the sugar head groups are sequestered within the chamber during the "power stroke". The cavity is lined with charged and polar residues that are likely solvated creating an energetically unfavorable environment for hydrophobic substrates and energetically favorable for polar moieties in amphiphilic compounds or sugar groups from LPS. Since the lipid cannot be stable for a long time in the chamber environment, lipid A and other hydrophobic molecules may "flip" into an energetically more favorable position within the outer membrane leaflet. The "flipping" may also be driven by the rigid-body shearing of the TMDs while the hydrophobic tails of the LPS are dragged through the lipid bilayer. Repacking of the helices switches the conformation into an outward-facing state. ATP hydrolysis may widen the periplasmic opening and push the substrate towards the outer leaflet of the lipid bilayer. Hydrolysis of the second ATP molecule and release of P_i separates the NBDs followed by restoration of the resting state, opening the chamber towards the cytoplasm for another cycle.



5 *Role in multi drug resistance*

ABC transporters are known to play a crucial role in the development of multidrug resistance (MDR). In MDR, patients that are on medication eventually develop resistance not only to the drug they are taking but also to several different types of drugs. This is caused by several factors, one of which is increased excretion of the drug from the cell by ABC transporters. For example, the ABCB1 protein (P-glycoprotein) functions in pumping tumor suppression drugs out of the cell. Pgp also called MDR1, ABCB1, is the prototype of ABC transporters and also the most extensively-studied gene. Pgp is known to transport organic cationic or neutral compounds. A few ABCC family members, also known as MRP, have also been demonstrated to confer MDR to organic anion compounds. The most-studied member in ABCG family is ABCG2, also known as BCRP (breast cancer resistance protein) confer resistance to most of Topoisomerase I or II inhibitors such as topotecan, irinotecan, and doxorubicin.

It is unclear exactly how these proteins can translocate such a wide variety of drugs; however one model (the hydrophobic vacuum cleaner model) states that, in P-glycoprotein, the drugs are bound indiscriminately from the lipid phase based on their hydrophobicity.

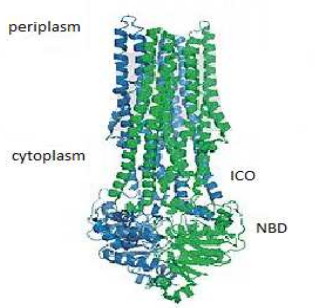
6 *Reversal of multi drug resistance*

Drug resistance is a common clinical problem that occurs in patients suffering from infectious diseases and in patients suffering from cancer. Prokaryotic and

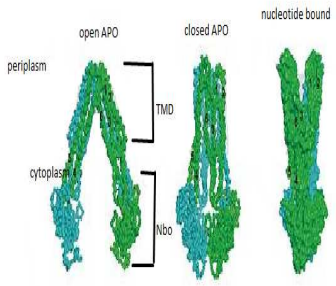
eukaryotic microorganisms as well as neoplastic cells are often found to be resistant to drugs. MDR is frequently associated with over expression of ABC transporters. Inhibition of ABC transporters by low-molecular weight compounds has been extensively investigated in cancer patients; however, the clinical results have been disappointing. Recently various RNAi strategies have been applied to reverse MDR in different tumor models and this technology is effective in reversing ABC-transporter-mediated MDR in cancer cells and is therefore a promising strategy for overcoming MDR by gene therapeutic applications. RNAi technology could also be considered for overcoming MDR in infectious diseases caused by microbial pathogens.

III RESULT

Software predicted structures
1 Structure of ABC exporter



2 Structure of MsbA



CONCLUSION

This paper concludes that the need of ATP only will allow the multi or anticancer drugs to enter into our body. But the cancerous person has no ATP required to activate the entry of the drug which suppress the cancer infection. By changing the switching signals, we can make the drug to enter and that will provide the way to suppress the cancer infection.

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