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THE PUSH AND PULL OF THE ATP-BINDING CASSETTE (ABC) TRANSPORTER SYSTEMS (ANTIBACTERIAL DRUG BLOOMING)

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ABSTRACT ABC transporters are also called Nucleotide binding domains. The structural architecture of ABC transporters consists minimally of two TMDs and two NBDs. Four individual polypeptide chains including two TMD and two NBD subunits, may combine to form a full transporter. There are two types of ABC transporters, In flux ABC Transporters, and Efflux ABC Transporters .Influx carry Maltose, Histidine,Arabinose,and Galactose. Efflux ABC transports antibiotics, Protiases,and toxins. They contains two hydrophobic proteins.The interaction of channel proteins . On receiving the signal, the nucleotide binding protein hydrolyses ATP and sends it inside the cell. Inorganic phosphates are released.Transport protein acts as gates. They function as molecular machines by coupling ATP binding, hydrolysis, and phosphate release to translocation of diverse substrates across membranes. Entry of the molecules (Inorganic molecules,organic molecules,sterols,metal ions,polypeptides,proteins) and exit of molecules from cell membrane is under this control. They are involved in cellular homeostasis.Most efflux transporters belong to the ATP-binding cassette (ABC) superfamily of membrane proteins, which may influence the intracellular concentration of numerous compounds in a variety of cells and tissues. Antibiotic resistance threatens to take us back to a time before penicillin when the majority of deaths were caused by infections.

KEYWORDS : Efflux, Influx, ATP-binding cassette (ABC) transporters, Multidrug resistance (MDR)

INTRODUCTION

The ATP-binding cassette (ABC) transporters are responsible for drug resistance and a low bioavailability of drugs by pumping a variety of drugs out cells (1)

The cell membrane, cytoplasm, and nuclear protein participate in these resistance mechanisms [2].

Multidrug membrane transporters can extrude a wide range of substrates, which cause multidrug resistance and ineffective treatment of diseases.(3)

ATP-binding cassette (ABC) membrane transporters are one of the largest membrane transport superfamilies, and they exist in all living organisms and play highly significant roles in biological functions.(4,5)

The ABC membrane transporters can selectively transport a wide variety of substrates across cellular membranes, even though they share a common modular architecture, two transmembrane domains (TMDs) and two nucleotide-binding domains (NBDs)(6,7)

The multidrug ABC membrane transporters can extrude chemotherapeutic agents out of bacteria or tumor cells, which causes multidrug resistance (MDR) and ineffective treatment of diseases, underscoring the importance of understanding their underlying mechanisms to design more effective therapy (8,9)

Fluoroquinolones (e.g., Oflx, norfloxacin, ciprofloxacin, levofloxacin, and gemifloxacin) are widely used antibiotics to treat a variety of respiratory and urinary tract infections, which include pneumonia, chronic bronchitis, and tuberculosis. (10)

Noble metal nanoparticles (NPs) possess unique physicochemical properties. Their high surface-area-to-volume ratio allows them to serve as effective drug carriers that offer high payloads, high permeability, high local target concentrations, and high binding affinity due to multivalence effects.(11,12)

The involvement of ABC transporters in the development of anthelmintic resistance has also been identified in animal parasitic nematodes (13,14)

Therefore, ABC transporters might be involved in the active efflux of anthelmintic drugs away from their target sites, resulting in decreased drug concentration and increased parasite survival (15)

In addition, it has been suggested that anthelmintics such as ivermectin (IVM), levamisole (LEV) and thiabendazole (TBZ) are substrates of ABC transporters and there is considerable

evidence that exposure to anthelmintics also modulates the expression patterns of different ABC transporters in nematodes (16,17)

ABC transporters can typically be classified into importers, exporters, and extruders (18)

ABC proteins cause cystic fibrosis, hypercholesterolemia, retinal degenerations, lipid trafficking disorders, and sideroblastic anemia with ataxia (19)

Helminths possess a larger number of ABC transporter genes than mammals, which have only a few multidrug resistance (MDR) transporters (20)

History of ABC Transporters

ABC transporters constitute one of the largest families of membrane proteins.(21)

The early 1980's saw the cloning of several genes encoding such transporters, spearheaded by the histidine permease of *Salmonella typhimurium* and maltose permease of *Escherichia coli* [22].

In parallel, medical researchers were tracking down the gene encoding permeability-glycoprotein/P-glycoprotein (P-gp), a large glycosylated membrane protein associated with multi-drug resistance in mammalian cells (23)

P-gp was eventually cloned in 1985 and with increasing availability of cDNA sequences, it became apparent that both the mammalian and the bacterial transporters contained highly conserved nt-binding motifs, hinting at a common evolutionary origin.(24)

In 1986, it was recognized that these ATP-binding subunits defined a large superfamily of transport proteins [25]

Structure of ABC Transporters

The structural architecture of ABC transporters consists minimally of two TMDs and two NBDs. Four individual polypeptide chains including two TMD and two NBD subunits, may combine to form a full transporter.

ABC Transporters and different classes

Entry or exit of molecules are under the control of cell membranes. ABC transporters are directly involved in tumor resistance to chemotherapeutics , drug resistance of parasites , fungal drug resistance , bacterial multidrug resistance, and bacterial virulence and pathogenesis. All ABC transporters share a basic architecture comprising at least two intracellular nucleotide-binding domains (NBDs) and two transmembrane domains (TMDs).(26,27)

The role of ABC Transporters

ABC Transporters are a family of proteins contributing to drug resistance via ATP-dependent drug efflux pumps P-Glycoprotein (P.gp) encoded by the MDR1 gene. ABC Transporter is involved in the excretion of toxins from cells.

The human genome contains 49 *ABC* genes, arranged in eight subfamilies and named via divergent evolution. That *ABC* genes are important is underscored by the fact that mutations in at least I I of these genes are already known to cause severe inherited diseases (eg cystic fibrosis and X-linked adrenoleukodystrophy [X-ALD])

ABC transporters also participate in the movement of most drugs and their metabolites across the cell surface and cellular organelle membranes; thus, defects in these genes can be significant in terms of cancer therapy, pharmacokinetics, and innumerable pharmacokinetic disorders.

What are superbugs?

Bacteria, Fungi, Parasites, and viruses change when exposed to antimicrobial drugs such as antibiotics, antifungal, antimalarial, anthelmintic, and anti-virals. Microorganisms that develop antimicrobial resistance are sometimes referred to as "Superbugs". As a result, the drugs are ineffective and infections persist in the body, increasing the risk of spreading to others.

In bacteria, ABC importers require an additional protein partner: a substrate-binding protein (SBP) that binds the substrate and delivers it to the TMDs.(28)

Types of ABC Transporters

Type I system

This system imports metabolites such as sugars, amino acids, peptides, and compatible solutes (29)

Substrate binding is the first mandatory step in the transport process. For this, both Type I and Type II systems depend on their cognate SBPs (30)

In Gram-negative bacteria, the SBPs are believed to diffuse in the periplasm, although direct evidence for this is still lacking. In Gram-positive bacteria, the SBPs are fused to the membrane via a lipid anchor or are directly fused to the TMDs.(31)

Type II system

Type II systems import trace non-metabolites such as iron–siderophore complexes, hemin, and vitamin B12 (32)

In comparison, the rigid α-helix in Type II systems bars the relative movements of the lobes, resulting in the similarity between the apo and holo conformations of Type II system SBPs (33)

ABC transporters are active transporters, that is, they use energy in the form of adenosine triphosphate (ATP) to translocate substrates across cell membranes. These proteins harness the energy of ATP binding and/or hydrolysis to drive conformational changes in the *transmembrane domain (TMD)* and consequently transport molecules (34)

ABC importers and exporters have a common mechanism for transporting substrates. They are similar in their structures. The model that describes the conformational changes associated with the binding of the substrate is the *alternating-access model*. In this model, the substrate binding site alternates between *outward-* and *inward-facing conformations*. The relative binding affinities of the two conformations for the substrate largely determine the net direction of transport. For importers, since translocation is directed from the periplasm to the cytoplasm, the outward-facing conformation has a higher binding affinity for the substrate. In contrast, the substrate binding affinity in exporters is greater in the inward-facing conformation.

A model that describes the conformational changes in the *nucleotide-binding domain (NBD)* as a result of ATP binding and hydrolysis is the *ATP-switch model*

Weapons of Bacterial Destruction

Bacteria can be quite aggressive. Armed with an impressive array of mechanical and biochemical weapons, they don't mess around when it comes to combating their foes. Notable among these armaments is the Type VI Secretion System (T6SS), a membrane-embedded nanomachine found in many gram-negative bacteria. The needle-like system helps bacteria antagonize prokaryotic and eukaryotic cells by injecting them with harmful proteins (effectors), such as pore-forming toxins and nucleases. T6SSs also promote bacterial survival in other ways, including facilitating acquisition of

resources (e.g., metals).(35)

Don't just sense a presence, detect a threat.

Here leading experts discuss the global strategy of preparedness against antimicrobial resistance, diversity in preclinical science, health benefits for antibiotics. Antibiotic resistance threatens to take us back to a time before penicillin when the majority of deaths were caused by infections.

Scientists have isolated an extremely harmful strain of *Klebsiella pneumoniae* that is resistant to a class of antibiotic agents and presents a severe threat. Antibiotic resistance is becoming increasingly alarming and multidrug resistance makes it worse.

Enzyme Inhibitors Might Combat Antimicrobial Resistance

A new study conducted in Ghent, Belgium has shown that intravenous administration of the metallo-beta-lactamase inhibitor MK-3402 (enzyme inhibitors) can be effective in combating antibiotic resistance. The results will be presented at the American Society for Microbiology Annual Meeting, ASM Microbe 2023.

Public health is seriously endangered by antibiotic resistance. Some bacteria are resistant to therapy due to the production of the metallo beta-lactamase enzyme, which renders a particular class of antibacterial drugs known as beta-lactams ineffective. When used in conjunction with an antibacterial drug (and another blocking medication against other types of beta-lactamase enzymes produced by bacteria), MK-3402 is made to inhibit metallo-beta-lactamase enzymes, ensuring that the antibacterial drug will still be effective against otherwise resistant bacteria.(36)

Use of Antibiotics Can Help Combat Superbugs

According to a study published in the journal Frontiers of Chemistry, researchers from RMIT University have developed a novel antibiotic that can be quickly modified to avoid becoming resistant to harmful superbugs. The antibiotic was developed by Ms. Priscila Cardoso, a PhD student at RMITs School of Health and Biosciences, and Dr. Celine Valery, who served as Cardosos primary advisor.

At present, the need for new antibiotics is greater than ever, as the World Health Organization lists antimicrobial resistance as "one of the top 10 global public health concerns facing humanity." The antibiotic, known as Priscilicidin, has tiny amino acid building blocks that allow it to be customised to combat various forms of antimicrobial resistance. Priscilicidin is a type of antimicrobial peptide.(37)

Antimicrobial resistance: A key priority in national health policy

At the third Global High-Level Ministerial Conference on Antimicrobial Resistance (AMR) in Muscat, Oman, Union Minister Bharati Pawar on Friday, stated that the government has identified antimicrobial resistance (AMR) as a top priority in its national health policy and several initiatives have been taken to tackle the concerning situation.

She stressed that the National Action Plans goal was to coordinate several sectors at the state, national, and international levels, emphasizing an integrated "One Health" approach.(38)

Biofilm and Drug Resistance

Drug resistance is a growing challenge for mankind and poses a new threat to modern healthcare especially in the management of infections and infectious diseases.

Bacteria developed biofilm as one of the most important advantages in finding resistance against antimicrobials and antibiotic agents. It was reported that microbes capable in biofilm formation develop drug resistance to several hundredfold more than non-biofilm-forming microbes (39,40)

Biofilm restricts the entry of antibiotic diffusion through the matrix. It was also reported that a large number of clinically approved antimicrobial agents are unable to enter the biofilm surface and move inside the environment. Antibiotics such as aminoglycosides enter more slowly through the matrix of biofilm than β-lactams. Quorum sensing is an evolved mechanism of cross-talk among microbes and works more efficiently in the biofilm. Hence it provides an ideal environment to microbes residing inside biofilm for the transmission of gene/s responsible for drug resistance. Many genetic mobile elements such as plasmids, transposons, and others can easily transfer among microbial cells inside the biofilm and are well communicated via quorum sensing. Biofilm not only restricts the entry of antimicrobials and antibiotics but also enables several mechanisms to pump out such antimicrobial agents from the matrix to enable an ideal growth environment (41,42).

Many antibiotics and antimicrobial agents require an organic and inorganic element or cofactor for their activation. Here, biofilm acts as a reservoir for various metal ions and chemicals altering pH to disable the activity of antimicrobial agents. Further studies also showed that drastic changes in pH and concentration of metal ions antagonize the activity of antimicrobial agents. Microbial biofilm also enriches metabolically inactive cells called persister cells. These cells are present in high percentages inside the biofilm and developed resistance to various hearse environmental stress. These cells remain in the periphery of the biofilm and actually neutralize the effect of antimicrobial agents and offer protection to cells present in the core of the biofilm. Further, studied such cells are highly tolerant to antibiotics forming a reservoir of surviving cells able to rebuild the biofilm population

The ATP-Binding Cassette (ABC) Transport Systems in *Mycobacterium tuberculosis*:

Mycobacterium tuberculosis is a bacterium of great medical importance because it causes tuberculosis, a disease that affects millions of people worldwide. Two important features are related to this bacterium: its ability to infect and survive inside the host, minimizing the immune response, and the burden of clinical isolates that are highly resistant to antibiotics treatment. These two phenomena are directly affected by cell envelope proteins, such as proteins from the ATP-Binding Cassette (ABC transporters) superfamily. (43)

ABC transporters play an important role in bacteria, importing various nutrients required for survival in different niches and exporting substances toxic to the cell. Not surprisingly, disrupting the function of ABC transporters through mutagenesis demonstrates the roles in bacterial virulence that many ABC transporters play. In addition, the membrane location and surface exposure of many of the proteins forming ABC transporters raise the likelihood that these proteins may be immunogenic. Thus, the studies described in this review indicate that ABC transporter proteins may be suitable targets for the development of antibacterial vaccines, either through the development of live attenuated bacteria or through the development of protein- and DNA-based subunit vaccines (44)

An update on ABC transporters of filamentous fungi

Each fungal species has ABC transporters. Despite the lack of functional characterization of many members, current knowledge clearly suggests that upon ATP hydrolysis, ABC proteins either transport a variety of substrates involved in different metabolic pathways and xenobiotics that provide tolerance, even resistance, against antifungal compounds, or participate in processes essential for cell viability, such as ribosome biogenesis. The role of ABC transporters in

antifungal resistance in filamentous fungus *Aspergillus fumigatus*, functional characterization of groups, such as ABCC5, the members of which might be transporters involved in secondary metabolite production.(45)

ABC transporters of human pathogenic yeast *Candida glabrata*: Phylogenetic and expression analysis

ABC superfamily members came to prominence due to their ability to extrude broad spectrum of substrates and to confer multi drug resistance (MDR). Overexpression of some ABC transporters in clinical isolates of *Candida* species was attributed to the development of MDR phenotypes. Among *Candida* species, *Candida glabrata* is an emerging drug resistant species in human fungal infections. (46)

Importance of ABC Transporters in the Survival of Parasitic Nematodes

Nematodes possess a great diversity of ABC transporters; however, only P-glycoproteins have been well-characterized compared to other classes. (47)

Antibiotic Resistance

Almost all countries are suffering from antibiotic resistance.

Increased risk and worse clinical outcomes and death in drug resistant bacteria than patients infected with non -resistant strains of the same bacteria.

Enterobacteriaceae---Colistin is the last resort of treatment for life threatening infections caused by Enterobacteriaceae which are resistant carbapenems

Staphylococcus aureus-- MRSA, estimated to be 64% more likely to die than people with a non-resistant form of infection.

Escherichia coli----Fluoroquinolone is one of the widely used antibiotic for UTI. This is ineffective in more than half of the patients in many countries.

Klebsiella pneumoniae---It is the major cause of Hospital acquired infections like blood stream infections, pneumonia,, infections in newborns, and ICU patients. Carbapenem antibiotics do not work because of resistance.

Mycobacterium tuberculosis---MDR-TB is resistant to the two most powerful anti-TB drugs'-TB requires treatment courses that are much longer than those of non-resistant TB.Extensively drug resistant tuberculosis (XDR-TB),a kind of TB that is resistant to atleast 4 of the core anti-TB drugs.

Plasmodium falciparum--It is resistant to almost all anti-malarial drugs. There is a risk of MDR will soon emerge in several other parts of world.It is a public health challenge in malaria control.

HIV--In 2010, an estimated 7% of patients starting anti-retroviral therapy (ART) in developing countries had drug-resistant HIV.Greater use of ART is expected to further increase ART resistance in all regions of the world.

Drug efflux Pumps—ATP Driven membrane pumps.

Acquired resistance has different mechanisms such as a) limiting the amount of drug uptake (innate resistance), b) target area of drug modification, c) inactivation of drugs, d) drug efflux. Bacterial genes code for efflux pumps. (48)

Families of efflux proteins mainly seen are

a) ATP binding cassette{ABC},they use energy from ATP hydrolysis. One specific pump in vibrio cholera(VcaM) it transports fluoroquinolones and tetracycline (49)

b) MATE{multi drug and toxic compound extrusion} transporter family. These transporters use Na^+ gradients and efflux fluoroquinolones. Mainly found in gram negative bacteria. The identified NorM pump specific in this family is present in *Vibrio parahaemolyticus , Neisseria gonorrhoeae and Neisseria meningitides (50)*

c) SMR transporter family{small multidrug resistance}. These pumps are hydrophobic and transport lipophilic cations. Uses proton motive force (H^+) to efflux drugs. They provide resistance to beta lactam antibiotics. Found in staphylococcus epidermidis transports ampicillin, erythromycin and tetracycline. Present in *Escherichia coli* transports vancomycin, erythromycin and tetracycline (51)

d) MFS transporter family{major facilitator superfamily}. They carry out efflux via solute/cation symport(H^+ or Na^+) or solute/H^+ antiport. *Acinetobacter baumannii* have separate MFS(SmvA) for erythromycin and (CraA), (CmlA) for chloramphenicol. *Escherichia coli* have (MefB) for macrolides, (QepA) for f;uoroquinolones and (Fsr) for trimethoprim. In *Staph aureus* (LmrS) pumps transport linezolid, erythromycin, chloramphenicol, and trimethoprim. Almost 50% of efflux pumps are MFS pumps in *E.coli* (52)

e) RND transport family is a multi drug transporter that effluxes antibiotics with other substrates. For example, the MexAB-OprM pump in *Pseudomonas aeruginosa* that effluxes beta lactams, chloramphenicol, tetracycline, trimethoprim, sulfamethoxazole. The AcrAB-TolC pump in *E.coli* provides resistance against penicillins, chloramphenicol, macrolides, fluoroquinolones and tetracycline. These pumps work via substrate/H^+ antiport (53)

Hypothesis

We hypothesize that monoclonal antibodies developed against these specific pumps targeting respective bacteria may prevent the working efficiency/inhibition of those pumps and reverse resistance to antimicrobials.

CONCLUSION

Depending upon the characteristics of cell wall and polarity they possess resistance. Some bacteria such as *pseudomonas aeruginosa* form colonization with the help of biofilms. Drugs face difficulty to penetrate these biofilms. Biofilms have matrices made up of proteins, polysaccharides and DNA from resistance bacteria. Public health is seriously endangered by antibiotic resistance. ABC transporters use energy in the form of adenosine triphosphate (ATP) to translocate substrates across cell membranes. ABC transporters are membrane bound proteins. These transporters act like pumps and push the substances into the cells (Influx) and pull the unwanted substances out of cells.(Efflux) Drug transporters play an important role in carrying substrates across different barriers, thus contributing to drug bioavailability. They are called ABC Transporters, because organization of their ATP binding cassette (ABC)domains. They are helpful in the movement of substances (import and export) into and out of cytoplasm.

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