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AN OVERVIEW OF THE EFFLUX PUMP IN MICROBIAL IN THE DIFFERENT STAGES

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INTRODUCTION

Bacterial efflux pumps (EPs) are proteins located and embedded in the bacterial plasma membrane whose function is to penetrate the organism's protective cell wall and reach the periplasm or cytoplasm before reaching its intended target. Recognize and eliminate pollutants.[1]

In addition, EP also recognizes toxic compounds that are bacterial metabolites and are responsible for their excretion function. In other words, EP is a transporter of harmful compounds from within the bacterial cell to the external environment. With the possible exception of an excretory function, EPs utilize energy sources for their function in terms of transporting compounds against concentration gradients. Efflux pumps are generally composed of outer membrane proteins, intermediate periplasmic proteins, inner membrane proteins, and transmembrane tubules.[2]

Transmembrane passages are located in the outer membrane of the cell. The duct also binds to two of her other proteins. Periplasmic membrane proteins and integral membrane transporters. Periplasmic and inner membrane proteins of the system combine to control the opening and closing of ducts. When a toxin binds to this inner membrane protein, it triggers a biochemical cascade that transmits signals to periplasmic and outer membrane proteins to open channels and transport the toxin out of the cell. This mechanism relies on energy-dependent protein-protein interactions generated by toxin translocation to H+ ions via inner membrane transporters.[3]

Fully assembled in vitro and in vivo structures of the AcrAB-TolC pump were resolved by cryoEM and cryo-ET. These ABC transporter proteins are composed of two domains. One is embedded in the plasma membrane and the other is inside the plasma membrane. The domain located inside the plasma membrane has two sites for substrate binding and two sites for ATP binding and hydrolysis. Upon recognition of a contaminant and its binding to an ABC transporter, ATP is hydrolyzed to provide the energy required for the transporter's conformational changes that facilitate the release of the contaminant into the environment.[4]

The exact structural changes that occur, as well as the means by which transporters recognize structurally unrelated compounds, are not yet fully understood. Unlike ABC transporters, members of the Resistance Nodulation Division (RND) family derive their energy from PMFs formed because of cellular metabolism. Protons that do not need to associate with molecular oxygen are transported to the cell surface where they partition and bind to components of the protective lipopolysaccharide layer and basic amino acids of the outer cell wall of Gram-negative and Gram-positive bacteria.[5]

Role of efflux pump in antibiotic resistance

Efflux pumps are bacterial transport proteins involved in the extrusion of substrates from the cell interior into the external environment. These substrates are often antibiotics and confer an antibiotic-resistant phenotype on bacteria expressing efflux pumps. Since the discovery of the first drug-resistant efflux pumps in the 1990s, advances in molecular microbiology have allowed methicillin-resistant Staphylococcus aureus (MRSA), Streptococcus pneumoniae, Clostridium difficile, and Enterococcus spp. Listeria monocytogenes and Gram-negative bacteria (GNB) such as Acinetobacter baumannii, Escherichia coli, Klebsiella pneumoniae, Stenotrophomonas maltophilia, Campylobacter jejuni, Pseudomonas aeruginosa, Neisseria gonorrhoeae, Vibrio cholera, Salmonella.[6]

These efflux pumps are energy dependent as these substrates are transported against concentration gradients. Based on the mechanism by which this energy is dissipated, effluent pumps fall into two broad categories. The primary efflux pump draws energy from the active hydrolysis of ATP, while the secondary efflux pump draws energy from the chemical gradient formed by protons or ions such as sodium. Five major families of efflux pumps have been described in prokaryotes. namely, the major active transporter ATP-binding cassette (ABC), the minor multidrug resistance family, the multidrug and toxin efflux (MATE) family, the major facilitator superfamily (MFS) and resistance nodules.[7]

All members of the mitotic family (RND) are secondarily active transporters. The complexity by which these pump proteins are organized also provides insight into their structure and the molecular mechanisms of substrate transport. Drug resistance of GPB is mediated mainly by efflux transporters located in the cytoplasmic membrane, whereas efflux pumps of GNB are more complex due to the multilayered cell envelope.[8]

The inner or cytoplasmic membrane and the outer membrane, separated by the periplasmic space, together form a tripartite protein channel through which drugs are effluxed. The RND family of efflux pumps is composed of a tripartite structure and is a major contributor to the inherent antibiotic resistance of GNBs, with a wide range of antibiotics and biocides including fluoroquinolones, β-lactams, tetracyclines and linezolid. Eject. However, in GPB, MFS transporters predominate, such as NorA from S. aureus and PmrA from S. aureus. pneumoniae and Eme-A from E. faecalis extrude numerous antibiotics from different classes. Evacuation pumps are often more inherent than most other determinants of resistance.[9]

The genes encoding these transporters are found in both susceptible and resistant bacteria and are often part of operons whose expression is regulated at the transcriptional level. Mutations in regulatory proteins or mutations in promoters cause overexpression of these efflux pumps, leading to drug resistance. Bacterial efflux systems efflux only one or one class of antibiotics, or efflux multiple classes of antibiotics (MexAB-OprM, NorA, and BmrA, including different classes of antibiotics, antiseptics, dyes, etc.)., and detergent) can be specific. It's called an MDR drain pump.[10]

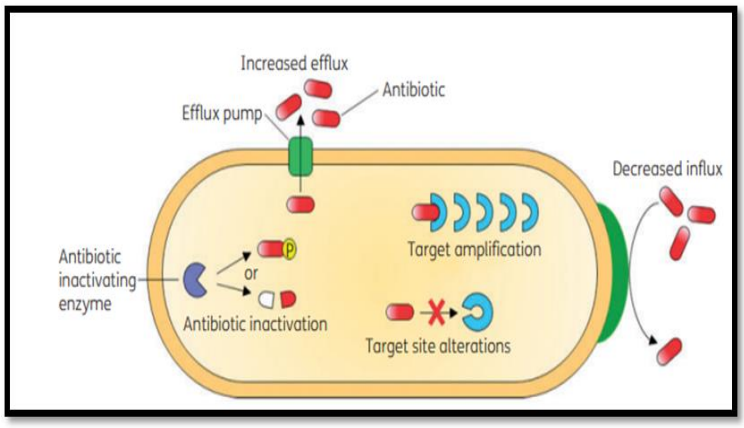

Figure Number 01: Schematic diagram highlighting the antibiotic resistance mechanisms utilized by bacteria. MDR pathogens can employ one or more of these mechanisms to become resistant to a diverse array of antibiotics. This figure appears in colour in the online version of JAC and in black and white in the print version of JAC.

Types of efflux pump inhibitors (Epis) based on their mechanism of action

PPIs in the laboratory show promise as therapeutic adjuncts. Various EPIs with different mechanisms of action have been reported, but these can be broadly divided into two categories: Since efflux pumps depend on cellular energy, the separation of energy dissipation and efflux activity presents an intriguing approach to efflux inhibition.[11]

The proton gradients or the ATPases that power these pumps have been tried as targets for various EPIs. Such inhibition schemes do not require direct interaction of the inhibitor with the efflux pump itself. have become a universal scheme for their inhibition. Carbonyl cyanide-m-chlorophenyl-hydrazone (CCCP) is probably the best-known laboratory EPI. The ionosphere perturbs the proton motive force (PMF) by affecting both its components. This also renders bacterial cells metabolically inactive, leading to debate as to whether the synergistic effects that CCCP exhibits with various antibiotics are in fact the result of cellular efflux pump inactivity or metabolic inactivity.[12]

CCCP has been reported to reduce the activity of Helicobacter pylori and Klebsiella tetracyclines. A synergistic effect between carbapenems and CCCP has also been reported and is independent of CCCP's efflux inhibitory activity, supplanting previous hypotheses that CCCP results in metabolically inactive cells and synergistic effects with antibiotics. I support you. This coupled with its cytotoxicity to mammalian cells, limits CCCP to laboratory use only.[13]

Types of epis based on their origin

Although many molecules have shown potential as EPIs, the mechanism of action for most of them is unknown. Therefore, it becomes difficult to classify such molecules based on their mechanism of action. To account for EPIs without a clear mechanism of action, EPIs can be classified based on their source. This leads to three broad categories including EPIs from plant products, synthetic chemicals, and microorganisms.[14]

Plant-derived EPIs Plant-derived phytochemicals contain a variety of chemical adjuvants that synergistically enhance antibiotic potency many-fold. The major subclasses of plant-derived EPIs are listed below.[15]

Plant alkaloids

Reserpine, an antipsychotic drug extracted from the root of Rauwolfia serpentina, is a promising EPI that targets efflux pumps in the MFS and RND superfamily. Reserpine is reported to enhance the antibacterial activity of antibiotics by directly interacting with amino acid residues of the efflux transporter protein Bmr, which mediates tetracycline efflux in Bacillus subtilis. Furthermore, reserpine has been shown to reverse NorA-mediated resistance in S. aureus by increasing norfloxacin activity up to 4-fold. However, clinical use of reserpine with clinically used antibiotics has not yet been achieved due to its nephrotoxicity.[16,17]

Piperine

Alkaloid known to inhibit human P-glycoprotein ABC transporters via a cytochrome P450-mediated pathway. The efflux pump inhibitory activity of both piperine and its derivative piperidine has also been demonstrated against pathogenic bacteria such as Staphylococcus aureus and mycobacterial species. report. A study done in Staphylococcus aureus showed that piperine promotes the accumulation of ciprofloxacin by inhibiting the Nor A efflux pump. In Mycobacterium tuberculosis H37Rv and some clinical isolates, piperine has been reported to potentiate the activity of rifampicin by inhibiting uncharacterized efflux pumps.[18]

Flavonoids

Baicalein, a 5, 6, 7-tri-hydro-flavone, is a weakly antibacterial flavone isolated from the leaves of thyme (Thymus vulgaris). It improves the susceptibility of clinical MRSA strains to β-lactam antibiotics including ciprofloxacin and oxacillin, cefmetazole, and ampicillin. Baicalein was also reported to enhance the potency of tetracycline in TetK-overexpressing staphylococci by inhibiting [3H]-tetracycline uptake.[19]

Polyphenols

Catechin gallates, a group of phenol metabolites, have been reported to reverse MRSA resistance. Catechin gallates, such as epicatechin gallate and epigallocatechin gallate, are weak inhibitors of the NorA efflux pump, with epicatechin gallate being slightly more potent. Interestingly, both compounds have been reported to increase discharge at low concentrations. These molecules have been suggested to have two distinct binding sites with different affinities on the NorA efflux transporter. At low concentrations, catechins occupy high-affinity binding sites, resulting in increased efflux of NorA substrates. Effects as an EPI are only observed at high concentrations.[20]

Epis of synthetic origin

Apart from natural plant-derived products, screening of novel semi-synthetic or synthetic diverse chemical libraries is a useful method for identifying potential EPIs. Many screening efforts have resulted in varying degrees of success. Such synthetic small molecule EPIs can be further classified as follows.[21]

Arylpiperidines and Aryl piperazine derivatives

Arylpiperidines and their derivatives such as 3-arylpiperidine have been reported to restore susceptibility to linezolid and promote accumulation in E. coli47. Another series of analogues, phenylpiperidines, are selective serotonin reuptake inhibitors and are known to inhibit the function of her MDR efflux pump in Staphylococcus aureus. These compounds also affect the activity of E's AcrAB-TolC pump. E. coli, but does not affect the efflux activity of Pseudomonas aeruginosa RND efflux pumps such as MexABOprM and MexCD-OprJ.[22]

Peptidomimetic compounds

The dipeptide amide compound PAβN was one of the first EPIs discovered through a chemical genetics approach. It has been reported to potentiate the activity of many antibiotics, including fluoroquinolones, macrolides, and chloramphenicol, in GNB by inhibiting the RND efflux pump. However, its toxicity to mammalian cells has limited its clinical potential. Several synthetic derivatives have been evaluated with different basic properties, such as reduced toxicity, improved stability, and improved solubility, but none of the active analogs can significantly alleviate the disadvantages of the parent molecule. I could not do it. Therefore, PAβN and its new derivatives are of limited use in the laboratory as standards for determining inhibitor-sensitive efflux levels of specific antibiotics in various bacterial pathogens.[23]

Pyridopyrimidine and Pyranopyridine derivatives

The pyridopyrimidine analogues D2 and D13-9001 have been described as MexAB-OprM-specific pump inhibitors in MexAB-overexpressing Pseudomonas aeruginosa under both in vitro and in vivo conditions49. It has been suggested that D13-9001 can inhibit antibiotic efflux by binding to specific sites in the efflux pump (AcrB in E. coli and MexB in Pseudomonas aeruginosa). Furthermore, crystallographic data indicate that the hydrophobic tert-butylthiazolylaminocarboxyl moiety of D13-9001 binds tightly to a hydrophobic trap in the deep substrate-binding pocket of the pump, providing the structure required for proper

pump activity. Suggests to prevent change. In addition, it has been reported that the hydrophilic component of D13-9001 also interacts with the substrate-binding channel of the pump, preventing substrate from binding to the pump.[24,25]

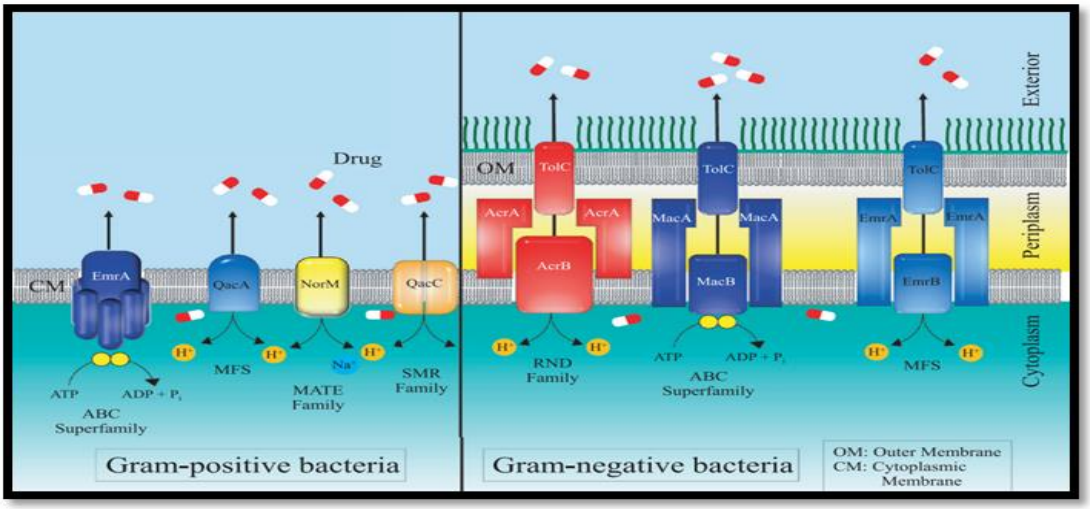

Figure Number 02: The five classes of efflux pumps in bacteria, (i) ATP-binding cassette superfamily, (ii) major facilitator superfamily, (iii) multidrug and toxic compound extrusion family, (iv) small multidrug resistance family, and (v) resistance nodulation division family. The organization of these efflux pumps is different in Gram-positive and Gram-negative bacteria.

Efflux pumps in bacteria

Efflux pumps are membrane proteins that are involved in the export of noxious substances from within the bacterial cell into the external environment. They are found in all species of bacteria, and efflux pump genes can be found in bacterial chromosomes or mobile genetic elements, such as plasmids. Efflux pumps can extrude a wide array of substrates, including antibiotics, detergents, dyes, toxins and waste metabolites. They can be specific for a single substrate or can export a wide range of structurally diverse substrates. Efflux pumps that can export several substrates, including multiple different classes of antibiotics, may be associated with MDR. There are five superfamilies of efflux pumps that are associated with MDR: multidrug and toxin extrusion (MATE).[26]

Small multidrug resistance (SMR), major facilitator superfamily (MFS), ATP-binding cassette (ABC), and resistance-nodulationdivision (RND). To date, RND efflux pumps have only been found in Gram-negative bacteria and are organized as tripartite systems consisting

of a cytoplasmic membrane pump, a periplasmic adaptor protein and an outer membrane protein channel.[27]

All the efflux pump superfamilies utilize energy from the proton/sodium motive force, except for the ABC superfamily, which are primary transporters that utilize energy from ATP hydrolysis to mediate the efflux of substances from within the cell. Efflux pumps are a key component of drug efflux, which is one of the main mechanisms of antibiotic resistance in bacteria. In Gram-positive bacteria, the MFS superfamily of efflux pumps is the most widely studied and includes clinically relevant examples, such as NorA of Staphylococcus aureus, which exports fluoroquinolones and quaternary ammonium compounds.[28]

The most clinically significant efflux pumps in Gram-negative bacteria belong to the RND superfamily, which includes AcrAB-TolC of Escherichia coli and Salmonella enterica, and MexAB-OprM of P. aeruginosa and AdeABC of Acinetobacter baumannii. All species of bacteria can express efflux pumps from more than one superfamily and/or more than one type of efflux pump from the same superfamily.[29]

In addition, efflux pumps also exhibit different substrate profiles, which vary within and between the superfamilies Although efflux pumps are widely implicated in antibiotic resistance, there is growing evidence from numerous studies to suggest that they may play a role in a range of bacterial behaviour, including biofilm formation, pathogenicity and virulence.[30]

Role of efflux pumps in e. coli

Biofilm formation Escherichia coli is a Gram-negative bacterium that primarily inhabits the gastrointestinal tract of vertebrates. The majority of E. coli strains are non-pathogenic, part of the normal intestinal flora, and benefit the host by preventing colonization by pathogenic bacteria through the production of bacteriocins and other mechanisms. Uropathogenic E. Escherichia coli (UPEC), neonatal meningitis Escherichia coli (NMEC), and enteroaggregative Escherichia coli (EAEC) can cause urinary tract infections (UTIs), neonatal meningitis, and infantile diarrhea, respectively.[31]

Importantly, E. coli biofilms are more resistant to clinically effective antibiotics than planktonic cells and show increased expression of multiple efflux pumps. The first type of study demonstrating an association between efflux pumps and biofilms examined efflux gene

expression and planktonic growth in biofilms. A study examining global gene expression in E. coli biofilms using DNA microarrays found that the expression of several genes encoding putative efflux and transport proteins was upregulated.[32]

The transporter genes mdtF and lsrA, which belong to the superfamilies RND and ABC, respectively, have been reported to be expressed at significantly higher levels during biofilm growth than during exponential and stationary phase growth. In one study, E. coli cells grown under anaerobic conditions expressed 20-fold higher expression of the MdtEF efflux pump compared to controls, and mutants lacking the mdtEF gene had significantly lower survival rates under nitrate anaerobic respiration. was reported.[33]

Furthermore, mutant strains lacking mdtEF were significantly more sensitive to nitrosyl indole derivatives, suggesting that MdtEF may be involved in their efflux. Anaerobic conditions are common in the biofilm core because cells in the outer regions of the biofilm actively respire most of the available oxygen. Escherichia coli switching to anaerobic respiration. Therefore, upregulation of the MdtEF pump may protect cells from damage by nitrosylindole derivatives by promoting cell efflux.[34]

The lsrA gene encodes a component of the Lsr-ABCD complex that mediates the transport of AI-2, a signaling molecule that enables her QS in E. coli. Upregulation of lsrA suggests that efflux pumps may play a role in transporting AI in E. coli biofilms. Another study reported that the expression of yihN, an MFS-encoded efflux gene, was two-fold higher in E. coli K-12 biofilms than in planktonic exponential cultures. However, the biofilm phenotype of yihN mutants has not been determined, so it is unknown whether yihN expression is required for biofilm formation. Another study reported that the mdtQ gene was 14-fold more highly expressed in E. coli biofilms grown on mild steel plates than in planktonic cells.[35]

Reported possible substrates of this efflux protein include acriflavine, puromycin, and tetraphenylarsonium chloride, although other substrates of this pump that have not been tested play a role in biofilm formation. may fulfill Several studies have focused specifically on the expression of efflux pumps in E. coli biofilms. Qvist et al. Reported in comparison with E. Escherichia coli F-18 strain. Of these, we found that the expression of genes in the aaeXAB operon, as well as the mdtL, mdtG, setB and yqgA genes increased the most during biofilm growth. It has been previously shown that treatment of E. coli cells with p-

hydroxybenzoic acid (pHBA), an intermediate in ubiquinone biosynthesis and usually present at low levels, upregulates the expression of the RND pump AaeAB.[36]

Furthermore, the AaeAB pump was reported to have very narrow substrate specificity restricted to several aromatic hydroxylated carboxylic acids, including pHBA. It has therefore been suggested that the AaeAB pump may act as a 'metabolic safety valve' that regulates the concentration of intracellular metabolites by controlling the efflux of excess metabolites such as pHBA. Upregulation of the AaeAB pump during biofilm formation may help prevent toxic accumulation of intracellular metabolites.[37]

The MFS pump SetB was previously shown to be involved in the efflux of glucose, a major component of the extracellular biofilm matrix. Thus, upregulation of setB expression during biofilm growth may serve to export sugars to promote biofilm matrix synthesis, but may be non-metabolic, which may be toxic to biofilm cells. It may also help export sugars. May et al. found that overexpression of the MFS efflux pump TetA(C) contributes to the osmotic stress response.[38]

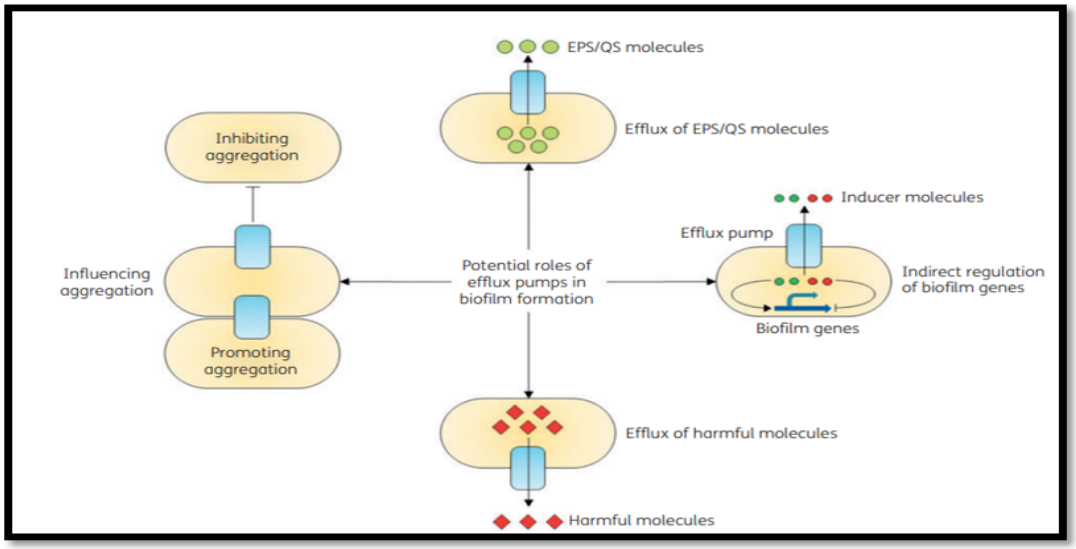

Figure Number 03: Schematic diagram highlighting the four different potential roles of efflux pumps in biofilm formation as suggested from various studies. This figure appears in colour in the online version of JAC and in black and white in the print version of JAC.

The prokaryotic (Bacterial) efflux pumps are divided into six classes

a. Major facilitator superfamily (MFS)
b. ATP-binding cassette (ABC) superfamily

c. Small multidrug resistance (SMR) family
d. Resistance-nodulation cell division (RND) superfamily.
e. Multi-antimicrobial extension (MATE).
f. Drug metabolite transporter (DMT) superfamily

Major facilitator superfamily (MFS)

Basic principles MFS transporters can be divided into three main groups, depending on the transport mode, uniporters transport a single substrate; symporters transport a substrate in association with a coupling ion (typically protons); and antiporters transport a substrate and a co-substrate in opposite directions, such that the binding of one is dependent on the prior release of the other.[39]

Uniporters require no external energy input, but in general, they can only transport their substrates down their concentration gradient, whereas symporters and antiporters can utilize the energy stored in the concentration gradient of their coupling ion or co-substrate to transport substrates against their concentration gradient. However, regardless of the differences in the transport mode, all MFS transporters share the same structural fold. The structural core comprises twelve transmembrane helices (TM1–TM12) that are organized into two structurally similar domains, the N domain (TM1–TM6) and the C domain (TM7–TM12).[40]

These domains can be further subdivided into two inverted repeats of three helices. Various names have been used for these helices, but this article refers to them as the A, B, and C helices. The structural core thus consists of four A-helices (TM1, TM4, TM7, and TM10), four B-helices (TM2, TM5, TM8, and TM11), and four C-helices (TM3, TM6, TM9, and TM12).[41]

The substrate-binding site is located in the center of the protein and consists of residues from both the N and C domains. MFS transporters can adopt inward-open, outward-open or closed conformational states. In the open-in state, there is a cleft between the N and C domains, providing access to the binding site from the cytoplasmic side. In the outwardly open state, there is a gap on the outside of the cell instead. In the trapped conformation, the binding site cannot access the substrate from either side of the membrane.[42]

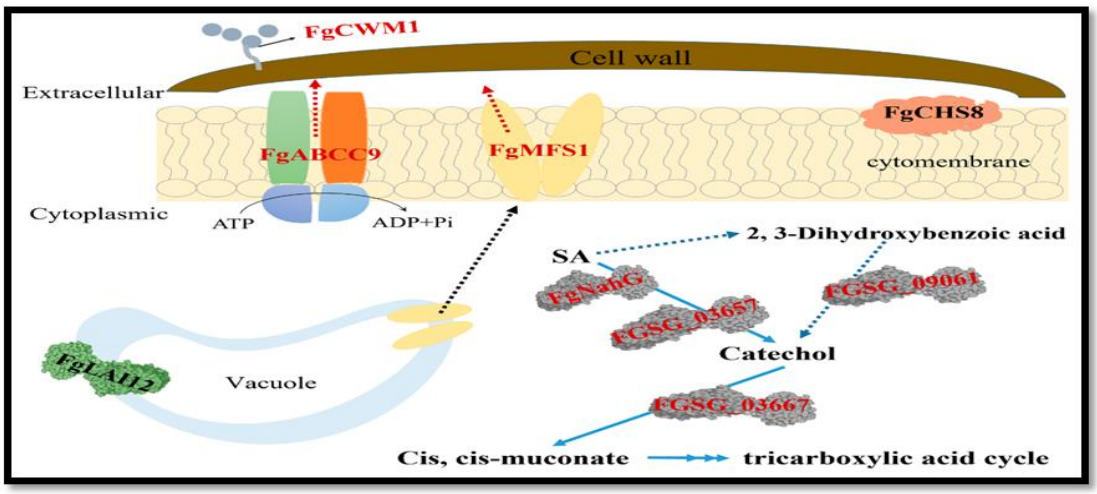

Figure Number 04: Diagrammatic presentation of Major facilitator superfamily (MFS).

ATP-binding cassette (ABC) superfamily

ATP-binding cassette (ABC) genes represent the largest family of transmembrane (TM) proteins. These proteins bind ATP and use energy to facilitate the transport of various molecules across cell membranes. Proteins are classified as ABC transporters based on the sequence and organization of the ATP-binding domain, also known as the nucleotide-binding fold (NBF). NBF contains characteristic motifs separated by approximately 90–120 amino acids found in all ATP-binding proteins.[43]

The ABC gene also contains an additional element, the signature motif (C), located immediately upstream of the Walker B site. Functional proteins typically contain two NBFs and two TM domains. The TM domain contains 6–11 transmembrane α-helices and provides substrate specificity. NBF is located in the cytoplasm and transmits energy to transport substrates across the membrane. ABC pumps are mostly unidirectional. In bacteria, they are primarily responsible for the import of important compounds that cannot be obtained by diffusing into the cell. It travels to the cytoplasm (ER), mitochondria, and peroxisomes.[44]

Most of the known functions of eukaryotic ABC transporters are to transport hydrophobic compounds into the cell as part of a metabolic process, or to transport them extracellularly for transport to other organs or secretion from the body. involves transporting. The ATP-binding cassette (ABC) transporter superfamily includes membrane proteins that transport a variety of substrates across extracellular and intracellular membranes, including metabolites, lipids, sterols, and drugs. Overexpression of specific ABC transporters occurs in multidrug-resistant cancer cell lines and tumors.[45]

Genetic variants in these genes are responsible for a variety of human disorders with Mendelian and complex inheritance, including cystic fibrosis, neurological diseases, retinal degeneration, impaired cholesterol and bile transport, anemia, and drug response phenotypes. Or contribute.

The conservation of the ATP-binding domains of these genes has allowed the identification of new members of the superfamily based on nucleotide and protein sequence homology. Phylogenetic analysis groups the known human ABC transporters into seven distinct protein subfamilies. For each gene, the precise map position on the human chromosome, date of expression and localization within the superfamily were determined.[46]

These data allow predictions about the functional or disease phenotype that may be associated with each protein. A comparison of the human ABC superfamily with that of other sequenced eukaryotes, including Drosophila, shows that the ABC genes are highly specific, with rapid fertility and mortality and most members not conserved in distantly related phyla. indicated that it performs a similar function.[47]

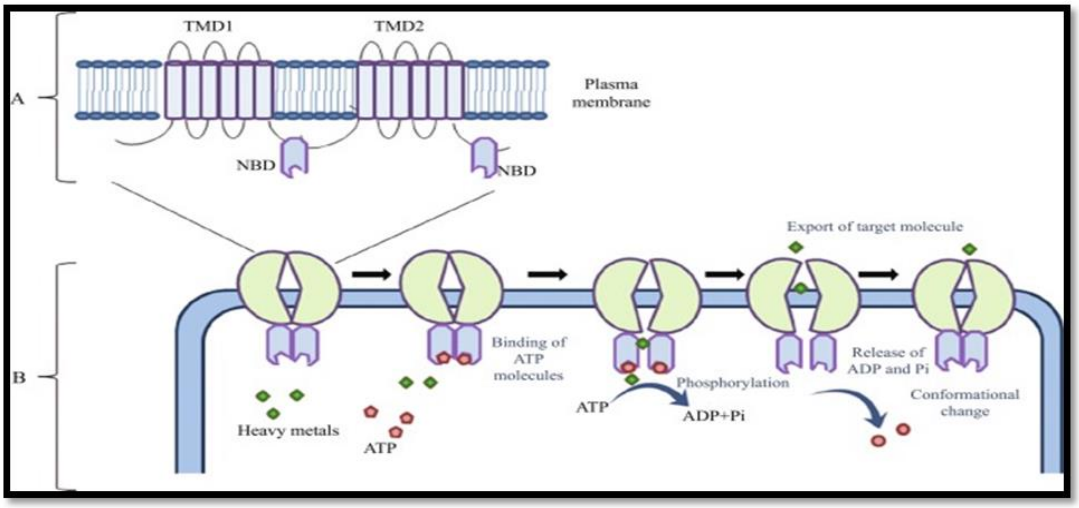

Figure Number 05: Diagrammatic presentation of ATP-binding cassette (ABC) superfamily.

Small multidrug resistance (SMR) family

Members of the Small Multidrug Resistance (SMR) protein family are integral membrane proteins characterized by four α-helical transmembrane strands that confer resistance to a wide range of bacterial preservatives and lipophilic quaternary ammonium compounds (QACs). Grant. Due to their short length and broad substrate profile, SMR proteins are thought to be precursors of larger α-helical transporters such as the major facilitator (MFS)

superfamily and the drug/metabolite transporter (DMT) superfamily. It is To explore its evolutionary relevance to larger multidrug transporters, we performed a comprehensive bioinformatic analysis of SMR sequences (>300 bacterial taxa) to explore previous evolutionary implications of the SMR protein family and their origins. Expanded research.[48]

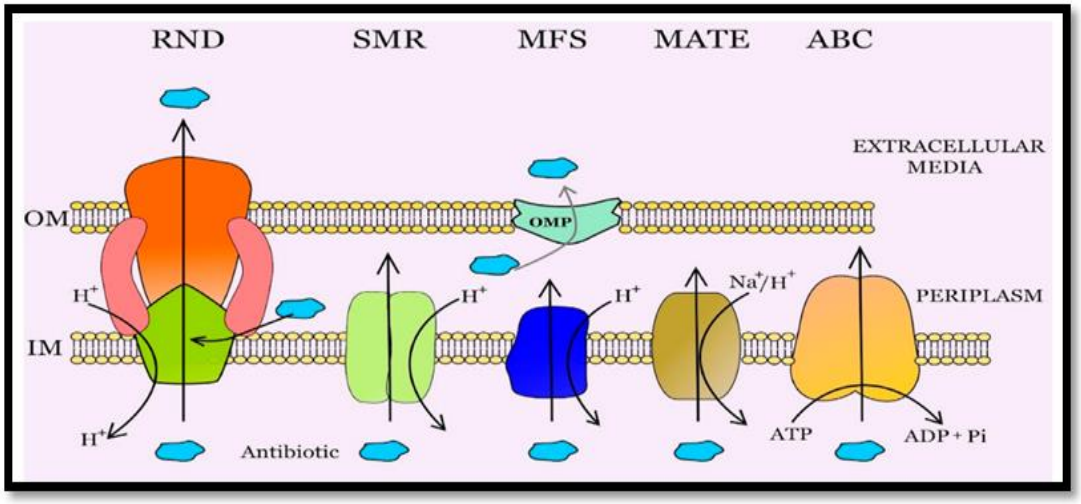

Figure Number 06: Diagrammatic presentation of Small multidrug resistance (SMR) family.

Resistance-nodulation cell division (RND) superfamily

Familial transporters are a category of bacterial efflux pumps, particularly identified in Gram-negative bacteria, localized to the cytoplasmic membrane and actively transport substrates. The RND Superfamily includes her seven families-heavy metal efflux (HME), hydrophobic/ amphipathic efflux-1 (Gram-negative bacteria), nodular factor exporter family (NFE), SecDF protein secretory accessory protein family, hydrophobic/amphipathic efflux-2 family, eukaryotic The sterol homeostasis family and the hydrophobic/amphipathic reflux-3 family of organisms.[49]

These RND systems are involved in maintaining homeostasis of the cell, removal of toxic compounds, and export of virulence determinants. They have a broad substrate spectrum and can lead to the diminished activity of unrelated drug classes if over-expressed. The first reports of drug resistant bacterial infections were reported in the 1940s after the first mass production of antibiotics. Most of the RND superfamily transport systems are made of large polypeptide chains. RND proteins exist primarily in gram-negative bacteria but can also be found in gram-positive bacteria, archaea, and eukaryotes.[50]

RND proteins are large and can include more than 1000 amino acid residues. They are generally composed of two homologous subunits (suggesting they arose as a result of an intragenic tandem duplication event that occurred in the primordial system prior to divergence of the family members) each containing a periplasmic loop adjacent to 12 transmembrane helices. Of the twelve helices there is a single transmembrane spanner (TMS) at the N-terminus followed by a large extracytoplasmic domain, then six additional TMSs, a second large extracytoplasmic domain, and five final C-terminal TMSs. TM4 governs the specificity for a particular substrate in a given RND protein. Therefore, TM4 can be an indicator for RND specificity without explicit knowledge of the remainder of the protein.[51]

RND pumps are the cytoplasmic residing portion of a complete tripartite complex that spreads across the outer membrane and the inner membrane of gram-negative bacteria, commonly referred to as the CBA efflux system. The RND protein is associated with an outer membrane channel and a periplasmic adaptor protein, and the association of all three proteins allows the system to export substrates into the external medium, providing a huge advantage for the bacteria.[52]

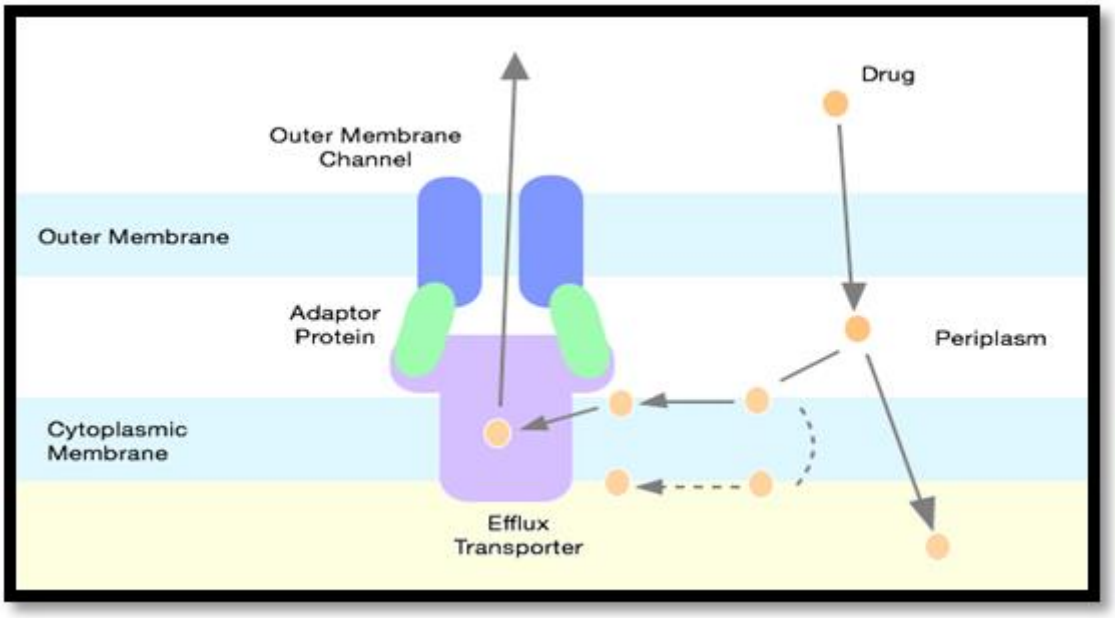

Figure Number 07: Resistance-nodulation cell division (RND) superfamily.

The multi-antimicrobial extension (MATE)

Multi-antimicrobial extrusion proteins (MATEs), also called multi-drug-and-toxin extrusion or multi-drug-and-toxin compound extrusion, are a family of proteins that function as drug/sodium or proton antiporters. These proteins are predicted to have 12 α-helical

transmembrane regions, and some animal proteins may have additional C-terminal helices. The X-ray structure of NorM was determined to be 3.65 Å, and unlike other known multidrug resistance transporters, it has two portals and a unique 12-transmembrane helix predicted to open in the outer sheet of the membrane. revealed an outward conformation with a clear topology.[53]

The multidrug efflux transporter NorM from Vibrio parahaemolyticus, which confers resistance to several antibacterial agents (norfloxacin, kanamycin, ethidium bromide, etc.), and its homolog from E. coli was identified in 1998 as the first Na+-binding multidrug. became an example of Discovered the effluent transporter. NorM is the prototype of his family of new transporters, Brown et al. It is called an extrusion family of several drugs and toxic compounds. NorM is called 'the last of the multidrug transporters' because it was functionally and structurally the last to be discovered.[54]

Drug metabolite transporter (DMT) superfamily

Multidrug and drug-specific efflux systems are responsible for clinically significant resistance to chemotherapeutic agents in pathogenic bacteria, fungi, parasites and human cancer cells. More than 90% of efforts to understand multidrug resistance (MDR) involve members of the major facilitator (MF) and ATP-binding cassette (ABC) superfamily. The ABC superfamily includes ATP-dependent multidrug efflux proteins such as P-glycoprotein and MRP, which are implicated in resistance of human tumor cells to anticancer chemotherapy drugs, and PfMDR1, which is associated with chloroquine resistance in Plasmodium falciparum. It is included. Twenty-nine such ABC transporters can be found in the fully sequenced genome of Saccharomyces cerevisiae. Several functional and structural homologues of ABC-type MDR pumps have been identified in bacteria.[55]

The MF superfamily includes proton force-dependent secondary drug efflux pumps of pathogenic microorganisms such as QacA and NorA from Staphylococcus aureus and CaMDR1 from Candida albicans. Over 20 members of each of the MF and ABC superfamilies have been functionally characterized as his MDR pumps. The remaining three recognized families of MDR bacterial efflux pumps are the Resistance-Nodulation-Division (RND), Small Multidrug Resistance (SMR), and Multi-Antimicrob Extrusion (MATE) families.[56]

Some of these MDR pumps have been specifically evolved to efflux endogenously synthesized or exogenously induced toxic substances (e.g., transporters associated with the antibiotic biosynthetic operons of actinomycetes). Other drugs may be opportunistically delivered (e.g., B. subtilis Blt, which also excretes polyamines). Therefore, there may be overlap between drug efflux and metabolite efflux pumps. Nonetheless, each of the aforementioned superfamilies is composed of members that share structural and mechanistic features not shared by members of other superfamilies.[57-60]

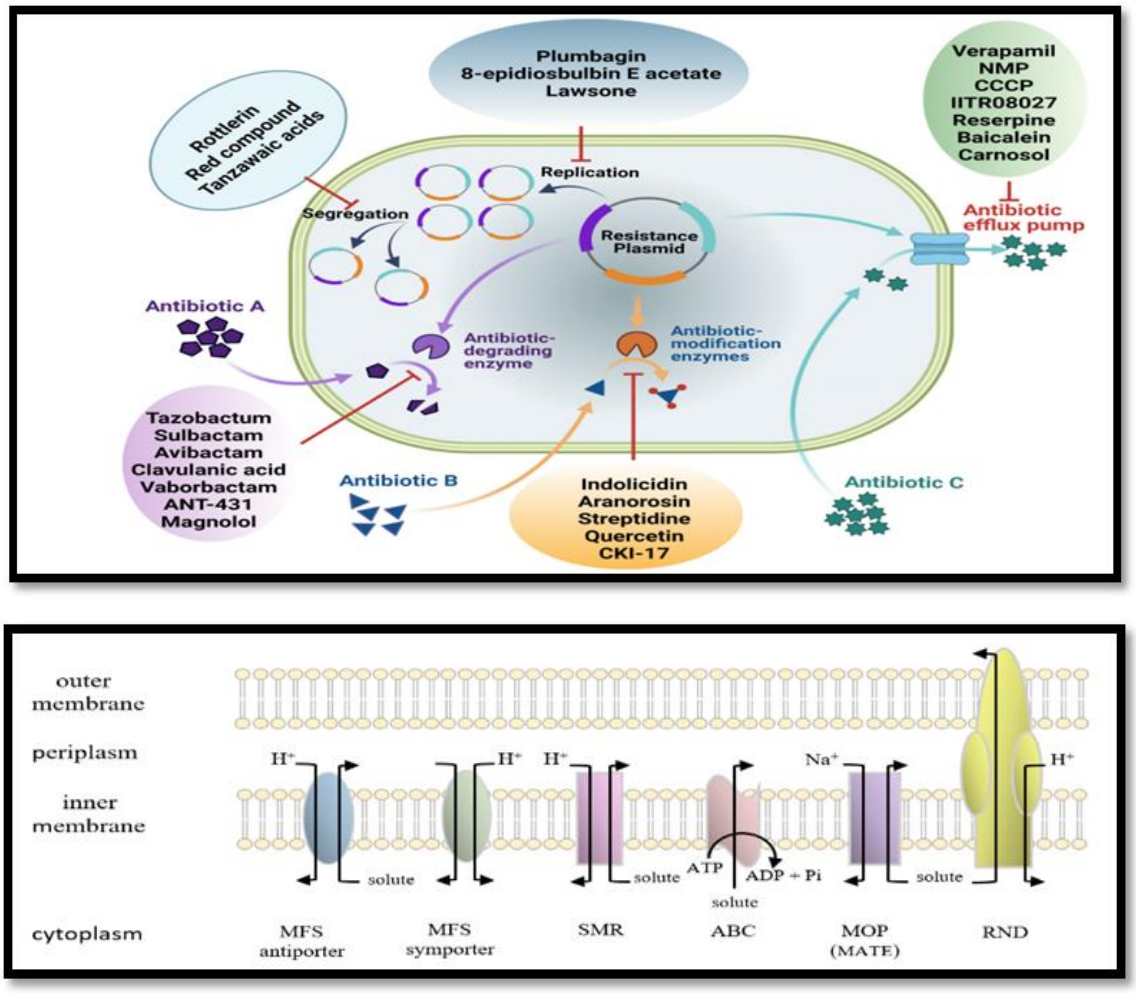

Figure Number 08: Super-families and families of solute transporters mechanism.

CONCLUSION

EPIs can be categorized in accordance with their origin to account for those that lack a distinct mechanism of action. As a result, three major categories include EPI derived from plant products, man-made chemicals, and microorganisms. It is unclear exactly what conformational changes take place or how transporters identify substances with different structures. Members of the resistance node family (RND) get their energy from PMFs created

by cellular metabolism, in contrast to ABC transporters. Small Multidrug Resistance (SMR) protein family members are integral membrane proteins that confer resistance to a variety of bacterial preservatives and lipophilic quaternary ammonium compounds (QACs). SMR proteins are believed to be the ancestors of larger -helical transporters like the drug/metabolite transporter (DMT) superfamily and the major facilitator (MFS) superfamily because of their short length and wide range of substrates. I am here, we conducted an extensive bioinformatics analysis of SMR sequences (>300 bacterial taxa) to learn more about the history and evolutionary significance of the SMR protein family. We also explored its evolutionary relevance to larger multidrug transporters. I verified modern research.

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