REVIEW ARTICLE

Role of Efflux Pumps in Multidrug Resistance

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Abstract

Introduction: Multidrug resistance (MDR) in infections and cancer has been considered one of the biggest public health threats and usually renders current treatments useless. Efflux pumps or transmembrane proteins ubiquitous across organic domains actively extrude therapeutic markers and reduce intracellular drug concentrations. This evaluation affords a dialogue of the type, mechanisms, and scientific significance of efflux pumps in microbial and oncological resistance and modern-day and emerging strategies for his or her inhibition. Efflux pumps cause MDR by way of eliminating diverse drugs from microbial and cancer cells, which ultimately results in treatment failure. In the case of pathogens, for example, contamination with AcrA (Periplasmic adaptor protein), AcrB (Resistance-nodulation-division [RND]-type inner membrane protein), TolC (outer membrane channel), and MexA (periplasmic adaptor protein), MexA (RND-type transporter), and OprM (outer membrane channel) protein pumps lowers the effectiveness of antibiotics. The different example is a tumor wherein chemotherapy becomes controlled using an overproduction of drug transport ATP-binding cassette (ABCs) like P-glycoprotein, which reduces drug accessibility. **Methods**: A thorough literature review was conducted focusing on the molecular mechanisms, law, and healing concentrated on of efflux pumps in the course of MDR in each instance, together with microbes and cancer models. **Results**: Several efflux structures, inclusive of ABC, resistance-nodulation-cell division, major facilitator superfamily, small MDR, and multidrug and toxic compound extrusion families, paint significantly in opposition to MDR. Their expression is regulated by way of strain-responsive genes, exceptional signaling pathways, and epigenetic changes. Some high strategies are efflux pump inhibitors (EPIs), nanocarriers, and gene-modifying techniques. **Discussion**: Although efflux pumps are often responsible for MDR, the mechanisms display a few overlaps in microbes and most cancers. Clinical translation, however, is hampered by multifactorial demanding situations consisting of pump redundancy, toxicities of EPIs, and interindividual variability. Moving forward, customized remedies and selective EPIs look promising. **Conclusion**: Hence, the relation of efflux pumps to MDR is clear. Strategies to overcome their challenges have an impact on the need to, with the aid of necessity, be particular, low-toxicity interventions, and use personalized remedies to maximize healing and treatment efficacy against resistant infections and cancers.

Key words: ATP-binding cassette transporters, antibiotic resistance, chemotherapy resistance, FLOX pump, FLOX pump inhibitor, multi-drug resistance, P-glycoprotein

INTRODUCTION

Multidrug resistance (MDR) infection and cancer have created a significant challenge for public health management across the globe as a result of increasing morbidity, mortality, and healthcare costs. In general, MDR indicates such cells, whether microbial or neoplastic, which can resist most therapeutically relevant compounds-not because of the structural and functional specificity of drug classes.[1] This inherent capability has made common antibiotics, antifungals, and antivirals ineffective against typical chemotherapeutic agents, rendering infections and cancers much harder to treat, and it often leads to poor outcomes for patients.[2] One important way in which resistance mechanisms against medications operate is the activation of efflux pumps, which confer resistance to MDR. A wide variety of active substrates, including

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medicinal substances, are exported from the cell through membrane-associated transport proteins. These pumps lower intracellular drug concentrations below the effective levels, thereby rendering the treatment useless and leading to a therapeutic failure.[3] The above efflux pumps are distributed into all biological domains – bacteria, fungi, parasites, and human cells; indeed, evolutionarily conserved and biologically important. The ability of these pumps to expel many unrelated compounds further complicates targeting. In pathogenic bacteria and fungi, efflux pumps contribute to antibiotic resistance by extruding drugs that would otherwise interfere with the growth or death of the organism.[3] High expression of certain efflux pumps, including P-glycoprotein (P-gp), in cancer cells results in resistance to several chemotherapeutic drugs, which renders treatment regimens inefficient and increases the risk of disease recurrence. Because efflux pumps play a key role in mediating resistance, more work is required to comprehend their molecular biology, regulation, and function.[4] This review aims to cover the important efflux pump families responsible for MDR, their mechanism of action, clinical implications, and new strategies under investigation to nullify their effects in infectious and oncologic diseases. MDR has become the most important barrier to therapy in infectious disease and cancer, giving rise to increased morbidity, mortality, and costs to the health care system worldwide." In its broader sense, MDR means the ability of cells-whether microbial or neoplastic resist a large number of therapeutic agents, independent of the structure or function of the drug classes.[5] It has rendered typical antibiotics, antifungals, and antivirals ineffective against most chemotherapeutic agents, making infection and cancer much harder to treat, and these sometimes translate into poor outcomes for patients. The action of efflux pumps is one such mechanism concerning MDR [Table 1], and this is a major mechanism that has not yet been established as the mechanism by which interference can manifest toward drugs.[6] Membrane-bound transport proteins called efflux pumps actively export a variety of substrates, such as chemotherapeutic drugs, antibiotics, antifungals, and antivirals, from the cell. Treatment becomes ineffective as a result of the intracellular concentrations falling below the therapeutic threshold.[7] This is a true example of evolutionary conservation and biological significance in that it occurs across domains of life: Bacteria, fungi, parasites, and humans themselves. Moreover, because many of these pumps are substrate-promiscuous, this poses an additional hurdle to their therapeutic targeting. In pathogenic bacteria and fungi, the efflux pumps confer antibiotic resistance through the extrusion of drugs that would otherwise inhibit the organism's growth or kill it.[8] In cancer cells, increased production of certain efflux pumps like P-gp renders them resistant to many chemotherapeutic agents and thus makes the regimens less effective and contributes to the disease recurrence. Treatment failure and disease recurrence are thus both caused by efflux pumps enabling survival under adverse conditions posed by drugs and treatment failure.[9]

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CLASSIFICATION OF EFFLUX PUMPS

Cell-based defense mechanisms against antibiotics and MDR heavily rely on efflux pumps. The active efflux of a broad range of structurally different toxicants, including antibiotics and chemotherapeutics, from the intracellular compartments is made possible by this family of proteins found on cell membranes.[10] Thus, they have the overall effect of lowering the effective intracellular concentrations of these agents, which are crucial factors in determining how infectious and malignant illnesses turn out. Generally speaking, efflux systems may be divided into two primary categories according to the energy methods they employ.[11] The best-characterized family of primary transporters, known as ATP-binding cassette (ABC) transporters, is the first group. These transporters use energy from ATP hydrolysis to drive substrate extrusion.[12] The second group includes secondary transporters that extrude their substrates using electrochemical gradients across the membrane, primarily those made up of sodium ion gradients or proton motive force. These include several significant families, including the multidrug and toxic compound extrusion (MATE) family, the resistance-nodulation-division (RND) family, the small MDR (SMR) family, and the major facilitator superfamily (MFS).[13] These groups also vary in terms of their distinct structural traits, substrate preferences, and transport processes. Both prokaryotic and eukaryotic organisms contain efflux pumps, but the examples of pathogenic bacteria, drug-resistant fungi, and rapidly dividing malignant cancer cells serve to highlight the physiological roles, functional diversity, and clinical significance of these ever-so-effective and obstinate therapeutic challenges.[14]

MECHANISM OF ACTION

These efflux pumps safeguard the internal milieu of the cell by actively extruding toxic compounds, including therapeutic drugs. These transport proteins show specificity for a variety of substrates that they may recognize and bind through both specific and nonspecific molecular interactions, permitting the effective accommodation of a wide variety of chemical structures.[15] Following substrate identification, the pump and its left-hand partner undergo a conformational shift that permits the substrate to move across the cell membrane and be expelled into the surrounding environment. While those categorized under the MFS, RND, and MATE transporters use the energy stored in electrochemical ion gradients-proton or sodium gradients, ABC transporters exhibit their specificity and are driven by the hydrolysis of ATP.[16] The ability of these efflux pumps to transport a variety of substances, including antibiotics, antifungal, antiviral, and chemotherapeutic medicines, is crucial for the development and maintenance of MDR in cancer cells and microbialpathogens.[17]

1. Toxic compounds/drugs (Antibiotics, antifungals, antivirals, and chemotherapeutics)

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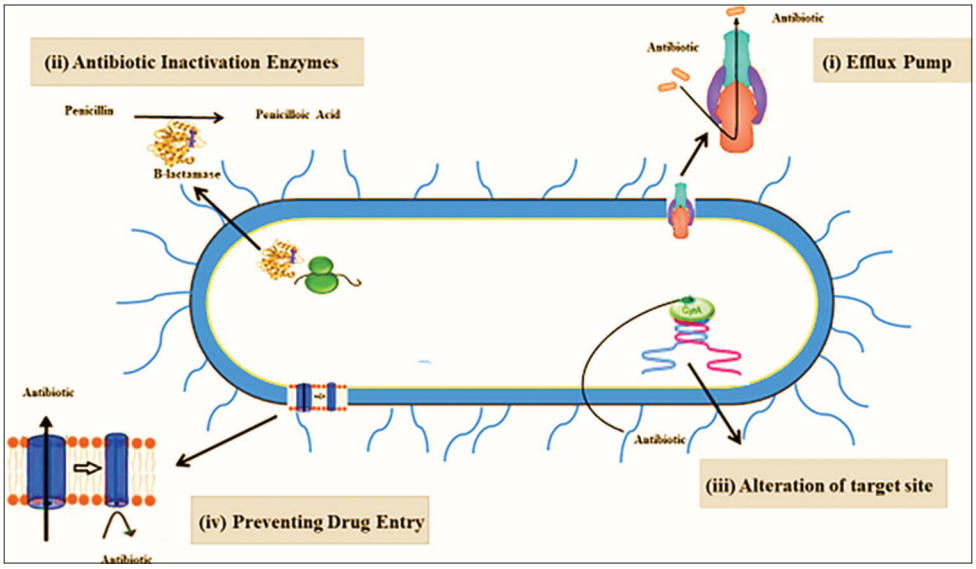

AQ7 **Flow Chart 1:** Efflux pump mechanism

2. Recognition by efflux pump (Specific + Non-specific Interactions)
   ↓
3. Conformational change (Pump + Partner protein)
   ↓
4. Substrate transport across membrane
   ↓
5. Expulsion into external environment
   ↓
6. Energy sources
   - MFS/RND/MATE → Ion gradients
   - ABC Transporters → ATP hydrolysis
   ↓
7. Outcome: MDR (Cancer cells and microbial pathogens).

EFFLUX PUMPS IN MICROBIAL MDR

The drug efflux structures in microorganisms and fungi are paramount resistance mechanisms against a battery of antimicrobial agents and seriously avert the effectiveness of modern-day healing regimens. In bacterial pathogens, these delivery systems actively expel antibiotics, together with fluoroquinolones, tetracyclines, chloramphenicol, macrolides, and β-lactams, allowing intracellular drug awareness to fall to subtherapeutic tiers.[18] ABC transporters and essential facilitator superfamily (MFS) transporters are the important components of the efflux-mediated drug resistance mechanism that fungal infections, especially Candida species, possess. The intracellular concentrations and effectiveness of azole antifungals are reduced using the lively movement of Cdr1p and Cdr2p ABC transporters.[19] ABC transporters and MFS transporters are the essential components of the efflux-mediated drug resistance mechanism that fungal infections, particularly *Candida* species, maintain. The intracellular concentrations and effectiveness of azole antifungals are decreased by the active action of Cdr1p and Cdr2p ABC transporters.[20] In clinical isolates of *Candida albicans*, MFS transporters, including Multidrug Resistance Protein 1 (MFS transporter in *C. albicans*), are also thought to be important in resistance mechanisms. These efflux systems often start working due to things in their surroundings that stress them out, or because they have been around medicine for too long. Furthermore, if the genes that control them change, it makes treatments even harder.[21] All these things together show how efflux pumps play a big role in making bacteria and fungi able to resist many medicines. This is a huge problem for the health of people everywhere. The main efflux pump groups that help bacteria resist medicines are shown in Figure 1. In Gram-positive bacteria, drugs are pushed out of the cell's cytoplasm by transporters such as EmrA (ABC), NorM (MATE), and QacA (MFS). Tripartite systems such as Acriflavine Resistance Protein A/B and TolC Outer Membrane Channel (E. coli tripartite efflux pump system) (AcrAB-TolC) (RND) and MacAB-TolC (ABC) bridge both membranes in Gram-negative bacteria to export medications. These pumps greatly increase MDR using energy from ion gradients or ATP hydrolysis.[22]

EFFLUX PUMPS IN CANCER MDR

A primary mechanism cancer develops resistance to multiple drugs, making chemotherapy less useful, is by overproducing efflux pumps. These pumps include members of the ABC transporter group. One of the most studied and commonly found transporters in drug-resistant cancer cells is P-gp, which the ABCB1 gene encodes.[23] P-gp functions by actively moving various chemotherapy medicines – such as doxorubicin, paclitaxel, vincristine, and daunorubicin – out of cells. This prevents the drugs from building up inside cells and doing their job of killing cancer. While this expulsion might lessen some of the harsh side effects of chemotherapy,

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it mainly helps cancer cells survive and grow even when constantly exposed to drugs.[24]

Efflux pump expression regulation in tumors is quite complex and multifactorial. Most of such ontogenically activated pathways, like those involving Protein Kinase B (PI3K)/Akt, Mitogen-activated protein kinase (MAPK), and Wingless/integrated pathway (Wnt/β-catenin), could upregulate the transcription of such efflux transporter genes, thus enhancing resistance to drugs. The environment around a tumor, with its low oxygen, lack of nutrients, and oxidative stress, can cause cells to produce efflux pumps as a way to adapt [Figure 2]. Genetic changes, such as deoxyribonucleic acid (DNA) methylation, histone acetylation, and non-coding RNA control (such as microRNAs), also play a big part in how efflux gene expression is managed, often causing them to stay active in resistant tumors. These elements form a strong, ever-changing system that helps cancer cells survive even when treated with chemotherapy, making efflux pumps very important when trying to overcome resistance in cancer treatment.[25]

REGULATION OF EFFLUX PUMP EXPRESSION

The regulation of efflux pump expression occurs at transcriptional and post-transcriptional levels. In bacteria,

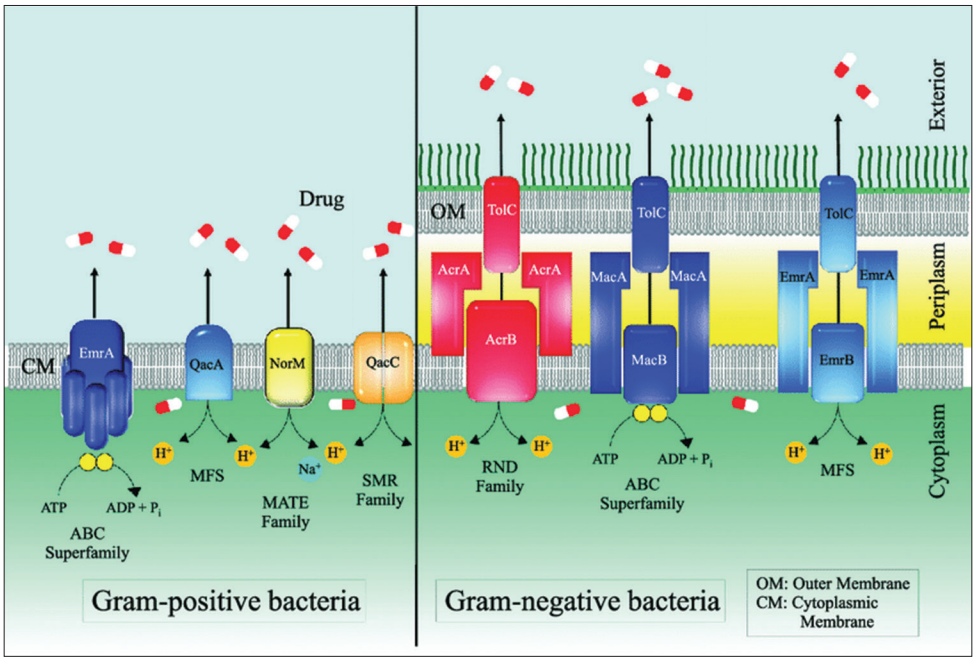

Figure 1: Efflux pumps in microbial multidrug resistance (Adapted from A. Sharma *et al*.)

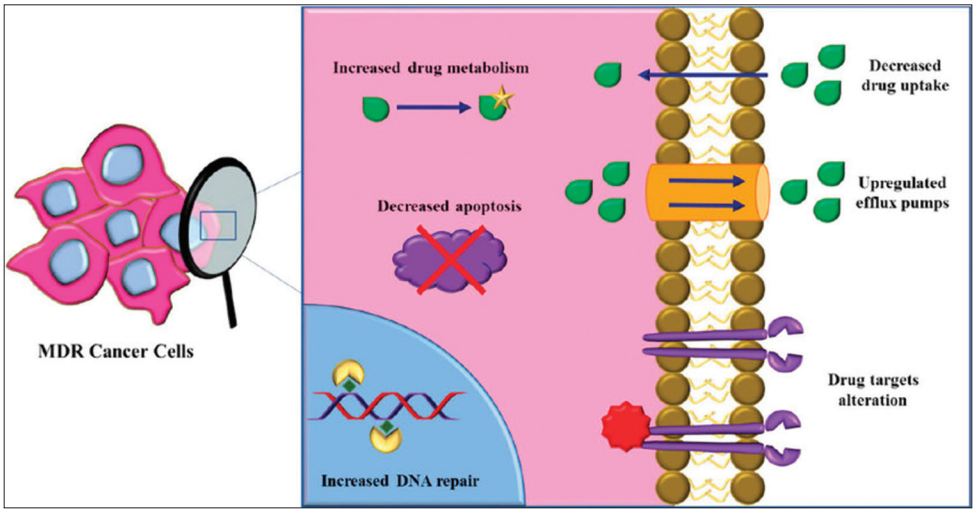

Figure 2: The picture shows the mechanisms behind multidrug resistance in cancer cells, including increased drug metabolism, reduced uptake, efflux pump up regulation, drug target alteration, reduced apoptosis, and enhanced DNA repair[26] (Adapted from C. Martinelli, *et al*.)

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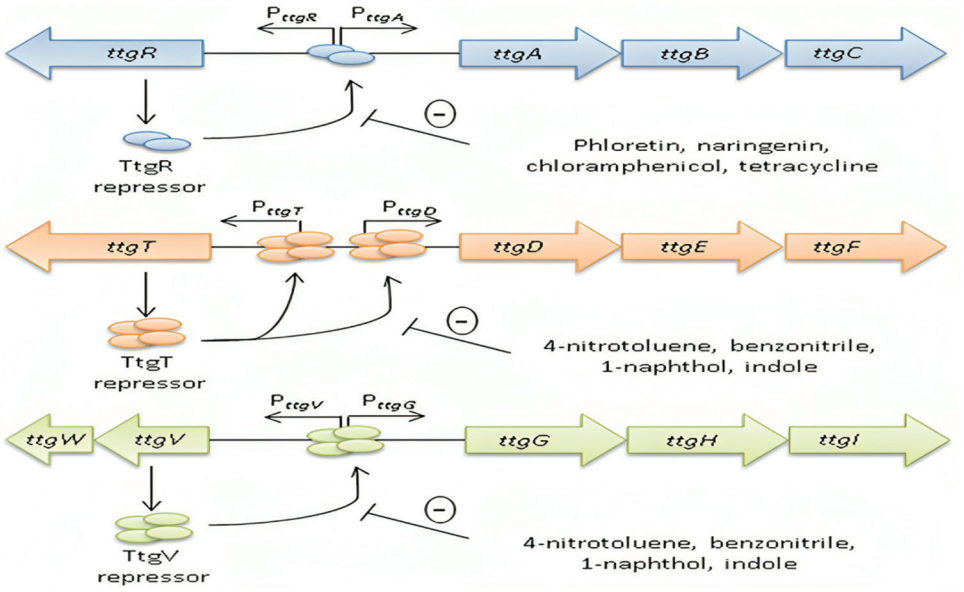

AQ8 **Figure 3:** Regulation of efflux pump expression (adapted from J.L. Ramos *et al.*)[30]

multiple antibiotic resistance regulator A, superoxide response regulator S, and regulator of antibiotic resistance A, three other bacterial regulators called usually respond to environmental stressors, but antibiotics and oxidative damage are some examples, to activate genes like AcrAB-TolC in *E. coli*.[27] They bring together larger coordinated stress-response networks relation to multimodal resistance: OH influx in which hypersensitive cells collapse. They exert influences in efflux pump expression dysregulated by signaling such as PI3K/Akt and MAPK/extracellular signal-regulated kinase (ERK), and Wnt/β-catenin pathways in cancers. Tumor microenvironments such as hypoxia and nutrient deprivation trigger these pathways, resulting in many ABC transporters, such as P-gp, MRP1, and breast cancer-resistance protein (BCRP), having their expression turned up with added complexity in contributing to resistance.[28]

There are also epigenetic modifications that regulate efflux genes: Hypomethylation usually leads to increased drug resistance through regulation by DNA methylation and histone acetylation. Furthermore, non-coding RNA, including microRNAs, adds its role to regulating efflux pump activity through mRNA stability and translation. In essence, all these mechanisms combine to ensure efficient drug efflux that would lead to resistance in both bacterial resistance and cancer.[29]

STRATEGIES TO INHIBIT EFFLUX-MEDIATED RESISTANCE

To increase antibacterial and anticancer effectiveness and eliminate efflux-mediated MDR, a number of methods are now being researched. Among these tactics are efflux pump inhibitors (EPIs), which block the action of efflux pumps such as P-gp and raise intracellular drug concentrations while restoring drug sensitivity. Examples of these include verapamil, tariquidar, and reserpine.[31] Nanoparticle-based drug delivery represents another methodology in which various carriers, such as liposomes and polymeric nanoparticles, cover the available drugs. These systems have been designed with the specific intention of circumventing efflux mechanisms, thus favoring the cellular uptake of the drug while increasing its bioavailability.[32] Gene-targeting approaches such as RNA interference and clustered regularly interspaced short palindromic repeats/CRISPR-associated protein 9 are targeting the efflux pump genes for silencing or knockout with precision, thus decreasing the expression of the pump and increasing drug efficacy. In combination therapies, co-administration of EPIs with either antibiotics or chemotherapeutics causes additive or synergistic effects. This responds by inhibiting efflux activity and thereby curtailing resistance potential. These methods collectively serve as a promise for answering efflux-driven MDR treatment across infectious diseases and oncology[33] [Figure 4].

DISCUSSION

Efflux pumps actively pump out a wide variety of therapeutic agents, leading to intracellular concentrations of drugs beneath the threshold needed for therapeutic action, thus making them central in MDR. This mechanism is seen in almost every type of microbial pathogen and in cancer cells, making the problem of treatment much more complicated.[35] Such efflux pump overexpression in bacteria, fungi, and neoplasm cells is a major line of defense against the effects of toxic chemicals and can thus lead to therapeutic failure and disease recurrence. It has been established in bacteria that the antibiotic expulsion ability of efflux pumps is important for fluoroquinolones, tetracyclines, and β-lactams evacuation because they are worthy candidates for antimicrobial

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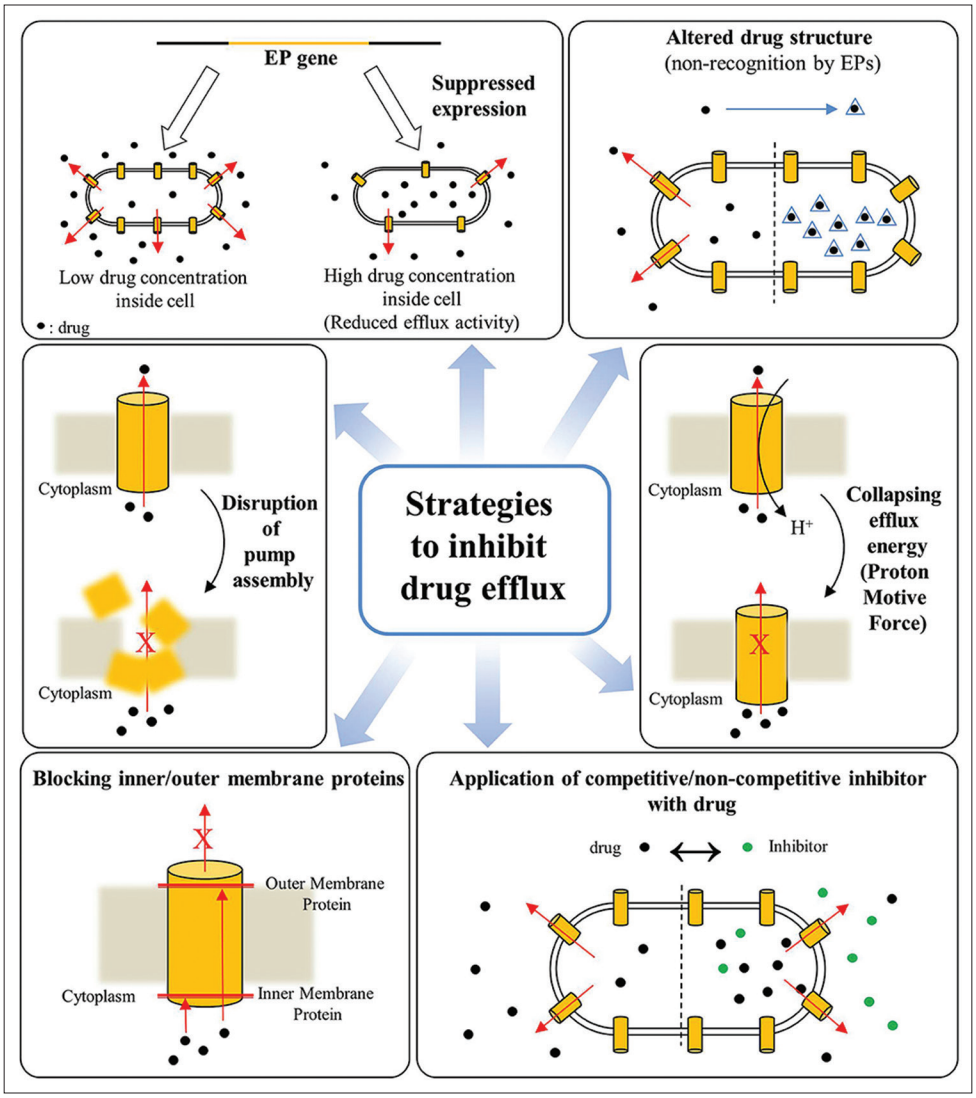

Figure 4: This image shows strategies to inhibit drug efflux in resistant microbes or cancer cells. These strategies include suppressing the expression of efflux pump genes, modifying drug structure, disrupting the assembly of efflux pump complexes, blocking membrane transport proteins, and co-administering drugs with inhibitors. Strategies to inhibit efflux-mediated resistance[34]

resistance development.[36] In fungi, efflux transporters, particularly ABC and MFS transporters, have been shown to mediate resistance to azoles and other antifungals, a major challenge encountered in treating infections caused by fungi, especially in immunocompromised patients.[37] In the case of cancers, increased expression of ABC transporters such as MDR -associated proteins, BCRP, and P-gp results in less chemotherapeutic drug accumulation within cancer cells, which directly lowers the efficacy of cancer therapy.[38] Events associated with oncogenic pathways such as PI3K/Akt, MAPK/ERK, and Wnt/β-catenin, through which drug resistance is enhanced through the overexpression of efflux transporters in these cells, can be linked to the regulation of those efflux pumps in the cells. At present, developing novel strategies to counteract MDR is a challenge, as most of the available approaches toward efflux pumps are not effective.[39] Although EPIs have shown potential in preclinical studies, their clinical applicability is limited due to adverse effects, poor pharmacokinetics, and indiscriminacy. Off-label inhibition of these efflux pumps is dangerous because they exist throughout normal and tumor tissues. Personalization will be necessary to make them suitable for different patients due to the high variability in efflux pump expression profiles among patients.[40]

The recent advances in high-throughput and omics technology have provided interesting aspects in understanding the underlying molecular mechanisms of efflux pump regulation, as well as discovering new regulators or substrates and new pathways! Fighting against MDR could also be through personalized medicine, incorporating efflux characterization in therapeutic modalities aimed at improving treatment success rates and reducing the possibility of developing resistance.[41] Selective and potent EPIs still remain a major focus in future work, notwithstanding these improvements. First, the EPIs should show minimal toxicity as well as exhibit

optimal pharmacokinetic characteristics to be clinically effective. Alternatively, combining EPIs and conventional antibiotics, antifungals, or chemotherapeutic agents could significantly increase drug sensitivity and nullify resistance. Thus, this would also add to a multifaceted strategy to combat MDR against both infectious diseases and cancer.[42]

CLINICAL IMPLICATIONS AND CHALLENGES

Although the performance of EPIs in preclinical and *in vitro* studies is encouraging, their clinical application faces several major obstacles. Major among these barriers is toxicity.[43] Next, pharmacokinetic problems related to poor absorption, rapid metabolism, or concomitant poor tissue penetration, complicating the development of efficient EPIs, limit the achievement of concentrations of drugs at target sites, thus restricting their effectiveness clinically.[44] There is also the hurdle of specificity: many of the EPIs are not very selective. Efflux pumps are often highly conserved across different cellular systems; thus, broad inhibition might affect normal as well as diseased cells, producing unwanted side effects. Moreover, the variations regarding expression and activity of efflux pumps in tumors and pathogens add another complication.[15] Individual patients might express different profiles of efflux pumps, which would, in turn, determine their success or failure in certain treatments. To untangle these hurdles, a clearer understanding of the biology of efflux pumps, their mechanisms of regulation, substrate specificity, and interactions with other cellular components is essential. The incorporation of personalized medicine by developing tailored therapies contingent on the patient-specific expression profile of efflux pumps could maximize efficacy and safety of the EPIs, thus enabling successful treatment of MDR infections and cancers.[45]

FUTURE PERSPECTIVES

The advances in high-throughput screening and omics technologies are shedding light on the regulation and function of efflux pumps. Genomic, transcriptomic, and proteomic profiling can be used to identify novel efflux pump regulators and new substrates connected to MDR.[46] These tools allow researchers to determine the exact isoform and pathway of efflux pumps, ultimately resulting in treatment approaches against MDR that are tailored for the various contexts of disease. For personalized medicine, the integration of efflux pump profiling with therapy holds great promise.[47] By assessing patient-profiled efflux pump expression profiles, clinicians can explore treatment options, maximizing the effect of antibiotics, antifungals, and chemotherapeutics while minimizing adverse effects. This type of personalized therapy is expected to slow down the emergence of resistance and improve clinical efficacy over time, especially among cancers and infectious diseases.[48] Nevertheless, the focus of drug development must remain on selective, potent, and safe inhibitors of efflux pumps for clinical purposes. Further evaluation of EPIs that are efficacious and non-toxic with a marked improvement in pharmacokinetic properties would be essential in the transition of EPIs into clinical practice.[15] Directing efforts toward the formation of smart drug combinations, particularly with the development of inhibitors specifically targeting resistance-conferring pumps, will help overcome current walls in the treatment of MDR infections and cancers.[49]

CONCLUSION

While many infectious diseases and cancer are developing resistance to human-made and endogenous agents under MDR, efflux pumps are an important mechanism for this trait. It seems likely that, overriding cytotoxic drugs in cancer therapy, the primary biological role of ABC transporters could be the export of nonessential substrate(s), an outcome supported by the abundant expression of pumps in the early stages of the development of cancer. A considerable amount of information can be found in the literature to show this connection. Yet, efflux pumps are so all-pervasive in cancer that there appears to be no incentive to investigate further their role. This study seeks to pursue generics development and investigate basic mechanisms for resistance generation. Essential and foundational research should be carried out: scrutinize the effect of ABC transporters and the enhancement required to carry out cytotoxic chemotherapy, including the level of expression of chemotherapeutic drugs, development of quantitative candidate assays, hematology, and pathology, as well as imaging. Summarizing, effective and successful targeting of these transporters to convert sensitivity to resistance offers brilliant potential for nullifying MDR without modulation. MDR is constantly on the march, while the same measures have hastened resistance training in many areas.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not required.

CONSENT FOR PUBLICATION

The authors agreed and expressed their approval for the publication.

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