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Role of P-Gp in Treatment of Cancer

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Abstract

P-glycoprotein (P-gp), a member of the ATP-binding cassette (ABC) family of transporters, plays a crucial role in the development of multi-drug resistance (MDR) in cancer treatment. P-gp actively pumps chemotherapeutic drugs out of cancer cells, reducing their intracellular concentrations and thereby diminishing their efficacy. This review explores the mechanisms by which P-gp contributes to MDR, including intrinsic and acquired resistance. It also discusses various strategies to inhibit P-gp, such as blocking drug binding sites, interfering with ATP hydrolysis, and altering cell membrane integrity. The potential of fourth-generation P-gp inhibitors and other novel approaches to enhance the effectiveness of cancer therapies is also examined. Understanding and overcoming P-gp-mediated MDR is essential for improving therapeutic outcomes in cancer patients.

Keywords

P-Glycoprotein (P-Gp), Multi-Drug Resistance (MDR), Cancer Treatment, ABC Transporters, Chemotherapy Resistance, P-Gp Inhibitors, Drug Efflux Mechanisms Fourth-Generation Inhibitors

1. Introduction

Cancer is a disease characterized by the uncontrolled proliferation of cells [1]. The global impact of cancer is significant, with millions of new cases and deaths each year [2] [3]. Early detection minimizes the effects of cancer, making anticancer drugs essential for tumor treatment [4] [5]. However, a major challenge in cancer treatment is the development of multi-drug resistance (MDR), where cancer cells become resistant to multiple drugs, reducing treatment efficacy [6].

MDR is characterized by the ability of tumor cells to develop cross-resistance to both functionally and structurally different compounds [6] [7]. This phenomenon can occur before treatment (intrinsic resistance) or develop after exposure

to chemotherapeutic drugs (acquired resistance) [8]. A primary factor contributing to MDR is the utilization of adenosine triphosphate (ATP) binding cassette (ABC) transporters [9].

These transporters, including P-glycoproteins (P-gp) and MDR-associated proteins, are crucial in reducing drug accumulation in cells, thereby diminishing drug activity [10]. P-gp, a transmembrane protein, plays a pivotal role in MDR by actively effluxing drugs from cancer cells, leading to decreased intracellular drug accumulation and reduced drug efficacy [11].

MDR is particularly problematic in cancers such as breast cancer and ovarian cancer. In these cancers, P-gp overexpression leads to resistance against commonly used chemotherapeutic agents, complicating treatment and reducing survival rates. The significance of P-gp in personalized medicine lies in its potential for tailoring treatments based on P-gp expression levels. By understanding the role of P-gp in individual patients, clinicians can make more informed decisions about the selection and dosage of anticancer drugs, potentially leading to improved treatment outcomes.

This review will discuss the role of P-gp in MDR, strategies to overcome P-gp-mediated MDR, and the clinical implications of these strategies [12].

2. Permeable-Glycoproteins (P-Gp)

2.1. Discovery, Structure, and Function

Permeable glycoproteins, also known as P-gp, were first discovered in 1971 by a scientist Victor Ling [12]. P-gp was first discovered in the cells of a multi-drug-resistant hamster ovary [12]. They are generally found in the body's epithelial region and are defensive, as they expend foreign substrates from the body and protect it from harmful xenobiotics. P-gp protects the host body by ejecting foreign substances from the cell. These P-gps are present on the epithelial surface in more numbers; in kidneys, it is present in the proximal tubules, the liver biliary epithelium, the heart, the adrenal cortex, and in the endothelial region of the body is present in the blood-brain barrier (BBB). P-gp is also known as efflux transporters, as they efflux foreign substrates coming into the cells. P-gp is located mainly on the surface of neoplastic cells, where they are known to inhibit the entry of the drug into the cell. P-gp protects the host body by preventing the entry of toxins into the body and their efflux to the external surface, thereby increasing the secretion of substances such as metabolites and xenobiotics produced in the bile, lumen, and gastrointestinal tract (GIT). In general, efflux transporters are inhibited to ensure drug delivery [13].

In addition to its natural form, P-gp is known to have two isoforms that belong to the gene family. These structures are divided into two classes known as drug transporters: the class I isoform, also known as (MDR1/ABCB1) and class II (MDR2/ABCB4), whose function mainly includes transporting phosphatidylcholine into bile [14]. Each molecule of P-gp has the potential to identify and transport drugs with varying chemical structures ranging from 250 g/mol in

cimetidine to 1202 g/mol in cyclosporin. In the other organs in which P-gp is present, the expression of P-gp in the intestinal epithelium plays a major role in orally administered drugs, especially due to its ability to alter absorption and elimination through bile and urine. P-gp prevents the toxic effects caused by chemotherapeutic agents in the bone marrow. Evaluating drugs based on their sensitivity to P-gp is crucial in the pharmaceutical industry, particularly for new therapeutics. The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) require documentation of these evaluations for new drug approvals. Research on drug interactions with P-gp has become an essential aspect not only of cancer treatment but also of a broad range of activities related to drug discovery [15] [16].

The P-gp structure has an ABC transporter divided into two halves, one half of which consists of a transmembrane domain (TMD) and the other of which consists of a cytosolic domain. X-ray structures showed that P-gp had an inward V-shaped structure [16]. The binding of drugs occurs inside the cavity in the cytoplasm inside the membrane. Drug binding occurs on two sides of the membrane, where the binding takes place on one side of the membrane and is released on the other side. These structures provide favorable conditions for the modification of the binding of ATP and favor the conformational change via NBD dimerization. P-gp facing outward has high-energy states while transporting the drug. NBDs in P-gp must be bound by nucleotide as the cellular concentration exceeds the binding constant. Based on the structure, it can be clearly stated that the inward-facing site has a high affinity for drug binding, which is essential for drug binding and inhibition [17].

2.2. Mechanism of Action in Drug Efflux

P-gp is known for its ability to expel different xenobiotics from cells. Most of the cells interacting with P-gp are usually hydrophobic substances by interacting through an ATP-dependent transporter that interacts with anticancer agents, beta-adrenoreceptors, immunosuppressants, steroid hormones, cardiac glycosides, and calcium channel blockers [18]. Drugs with weak permeability also undergo gradual extrusion, a slow process. P-gp is known to expel many substances into the intestinal lumen through blood through this process. P-gp can expel the drugs, especially into the lumen space of hepatocytes and renal tubules. On the basis of its mechanism, P-gp dramatically decreases the absorption rate, thereby altering the drug's bioavailability, primarily through the oral route [19].

2.3. Tissue Distribution and Physiological Role

In addition to this, P-gp can also limit drug uptake into the bloodstream from brain cells [20]. Overexpression of P-gp in the tumor is responsible for the expulsion of drugs from tumor cells. As a result of overexpression, cell internalization does not occur in anticancer cells, making them ineffective in chemotherapy treatment. P-gp acts as a barrier to drug efflux in chemotherapy. To overcome this

resistance developed by P-gp, various strategies are developed to ensure safe drug delivery. These strategies involve drug inhibition and provide different strategies to bypass drug efflux [21].

3. P-Glycoprotein (P-Gp) and Multi-Drug Resistance (MDR)

To counteract MDR mediated by P-gp, various strategies have been developed, with P-gp inhibitors gaining significant attention. These inhibitors function by directly or indirectly interfering with the efflux mechanism of P-gp, thereby increasing intracellular drug concentrations and restoring drug sensitivity in tumor cells [18]. P-gp is a critical player in MDR, posing a significant challenge to cancer treatment. Understanding the mechanisms of P-gp and developing effective P-gp inhibitors are essential for improving therapeutic outcomes. Fourth-generation P-gp inhibitors and new anticancer drugs offer hope for overcoming MDR, but further research and clinical validation are needed [6].

3.1. Consequences of P-Gp Overexpression in Cancer

P-gp, a transmembrane protein, plays a pivotal role in MDR, a phenomenon that renders cancer cells resistant to a variety of structurally and functionally diverse chemotherapeutic agents. The overexpression of P-gp in tumor cells leads to decreased intracellular drug accumulation, thereby reducing drug efficacy and contributing to treatment failure [22].

3.2. The Efflux Mechanism of P-Gp Involves the Following Steps

Figure 1 demonstrates the process in which the P-gp transporter works in the MDR cancer cell. The drug passively enters the cell. The cell rejects the drug through the use of the P-gp transporter using ATP as the energy source. It is important to note that this is not the only use of the P-gp transporter. It is used in the immune system as well.

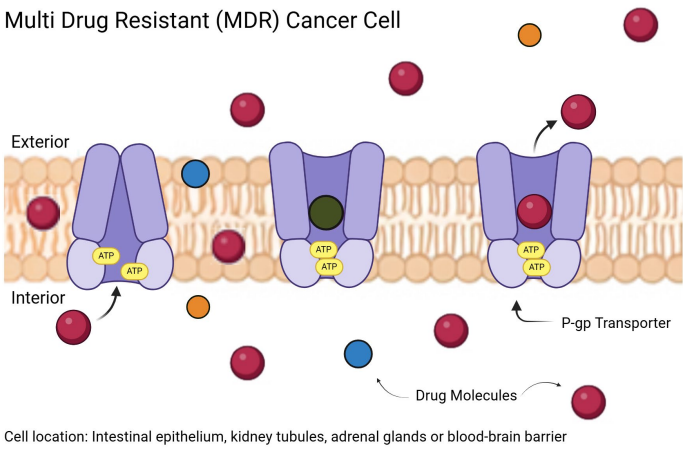

Figure 1. P-glycoprotein (P-gp) actively effluxes drug molecules from the cell, reducing intracellular drug concentrations. Created in BioRender. Oroszi, T. (2024) https://BioRender.com/g70q995.

1) **Drug Binding:** The process begins with the drug binding to the P-gp transporter at a high-affinity site located within the cell membrane.

2) **ATP Hydrolysis:** Upon drug binding, ATP hydrolysis occurs, providing the energy required for the conformational change in P-gp.

3) **Drug Extrusion:** The conformational change facilitates the movement of P-gp, leading to the expulsion of the bound drug from the intracellular to the extracellular compartment.

4) **Conformational Reset:** Following drug extrusion, P-gp undergoes a reset in its conformation, returning to its original state to initiate another cycle of drug efflux.

4. Strategies to Overcome P-Gp Mediated Multi Drug Resistance

4.1. P-Gp Binding Sites

P-gp binding sites are found in the membrane-embedded region between two T.M. halves. The R site in Phodamine-123, the anthracyclines, the P site in prazosin and the progesterone, and H binding site in colchicine have multiple substrate binding sites for drug binding and competition studies. Co-crystalization of P-gp alongside cyclic peptides gives specific insight into the binding sites for polyspecific drugs. Cyclic peptides are marine sources that reverse MDR activity reverses, P-gp exhibits structural specificity and homotrimeric structural symmetry. These structures gave insight into how P-gp can differentiate binding sites, stoichiometry, and orientations [23].

The structural activity relationship (SAR) was determined for cyclic peptides to understand the side-chain variations in their interactions with P-gp. Peptides containing similar structures were classified into new compounds named QZ-Ala, QZ-Val, QZ-Leu, and QZ-Phe. These cyclic peptides block the transport of substrate inhibition and sensitize cancer cells for P-gp binding through antineoplastic drugs. QZ-Ala has the highest stimulating effect, while QZ-Phe has the least effect [24].

4.2. Strategies to Overcome MDR

Several strategies have been developed to overcome MDR, including [6] [25]:

- **P-gp Inhibitors:** These inhibitors block P-gp activity, allowing higher intracellular concentrations of anticancer drugs. They are classified into three generations, with fourth-generation inhibitors derived from natural sources showing promise [6].
- **Nanotechnology:** Nanoparticles can deliver drugs directly to cancer cells, bypassing P-gp-mediated efflux [26].
- **Combination Therapies:** Using P-gp inhibitors alongside chemotherapeutic agents can enhance drug efficacy [27].
- **Monoclonal Antibodies:** These antibodies target P-gp and other MDR-related proteins, improving drug delivery and effectiveness [28].

4.3. P-Gp Substrates

P-gp has a variety of molecular structures with distinct chemical structures known to efflux through acting as substrates; these substrates differ not only in size but also in various chemical properties. Interference of the P-gp with the lipid bilayer is a basic criterion for classifying a compound as a substrate. Anticancer drugs that affect the nervous system, cardiovascular system, and other antimicrobials act as substrates in the efflux of P-gp [29]. In order to improve drug delivery, the efflux pump is inhibited, and the following steps can achieve this inhibition:

- Through competitive or non-competitive blocking at the site of action of the drug.
- Interfering with ATP hydrolysis.
- Alteration of the integrity of the cell membrane in lipids.

The main aim of this inhibition is to improve the drug availability and uptake to the targeted site and improve cancer chemotherapy treatment by blocking the action of P-gp. There are specific inhibitors transported using P-gp. These inhibitors are Verapamil, Cyclosporin A, and transflupenthixol [30].

4.4. Specific Cancer Types and MDR

MDR is particularly problematic in cancers such as breast cancer and ovarian cancer. In these cancers, P-gp overexpression leads to resistance against commonly used chemotherapeutic agents, complicating treatment and reducing survival rates [31] [32].

4.5. P-Gp Inhibitory Activity in Natural and Synthetic Polymers

Specific polymers such as polysaccharides, PEG derivatives, and thiolated polymers are known for their modulatory action of P-gp [33]. From the known natural polymers, anionic polysaccharides such as xanthan, gellan gum, and sodium alginate are known to improve oral bioavailability and overcome MDR. Rhodamine 123, isolated from the rat intestine, is inhibited at different concentrations of PEG without any relation to molecular weight. Caco2 after pretreatment with surfactants composed of PEG and fatty acids increases the concentration of epirubicin intracellularly.

4.6. P-Gp Inhibitory in the Form of Antibodies and Peptides

Hydrophobic peptides play a crucial role in the reversal of MDR action because of their high affinity for P-gp substrates. Trans-membrane domain (TMD) peptide analogs interfere with the functioning of a target protein. The TMDs of ABC transporters act as P-gp inhibiting templates because of the development of small peptides related to the transmembrane segment of P-gp that act as potent inhibitors. In addition to chemotherapy, an alternative treatment includes immunization. *In vivo* drug substrate efflux is inhibited because of the antibody action targeted at extracellular epitopes of P-gp [18].

4.7. MDR Genes Inhibition

MDR is caused as a result of the overexpression of transcriptional proteins along with the amplification of MDR1 genes. By designing mechanisms that act through cancer-specific pathways, the overexpression of P-gp can prevent minor effects on the normal cells [34].

5. P-Gp Inhibitors

P-gp drug efflux can be inhibited to improve drug delivery. Inhibition of P-gp takes place through the following mechanisms. 1) inhibiting drug action by competitive or non-competitive binding; 2) interacting with ATP hydrolysis; and 3) altering the lipid membrane. When P-gp transporters, uptake and bioavailability of drugs increase rapidly increased at the organ site, especially chemotherapeutic drugs inhibit P-gp activity. Based on their activity, P-gp inhibitors are classified into three generations [22].

First-generation inhibitors have limited use due to their high serum concentration, as at high doses, they cause toxicity. First-gen inhibitors act as substrates for other enzymes that cause unpredictable pharmacokinetic interactions [22].

Second-generation inhibitors are known to inhibit the CYPA4 enzyme and inhibit ABC transporters. Despite lacking pharmacological activities, they have a higher P-gp affinity. As a result, a decrease in metabolism rate and inhibition of ABC transporters will permanently alter pharmacokinetic actions [22].

Third-generation inhibitors aim to specifically bind to P-gp with higher selectivity and inhibit them, lowering the toxicity. Third-generation inhibitors are designed with the help of structural activity relationship (SAR), an effective treatment with the least number of toxic reactions [22] [35].

Substances that can alter the effect caused by P-gp or inhibit them are called P-gp inhibitors. However, most of these inhibitors are obtained from natural sources; others are developed through prodrug concepts, synthetic peptides, and others. Cyclosporine-A and verapamil are primary P-gp blockers. These inhibitors can prevent P-gp from the efflux of xenobiotics and help these substrates exhibit their therapeutic effects. Inward V-orientation of the drug is observed when studied from crystallography; P-gp consists of both hydrophobic and van der Waals interaction along with some polar side chains, facilitating the formation of ligands through hydrogen bonds constituting for the inhibitor binding to P-gp. Despite the necessity to develop inhibitors, most drugs could not clear the clinical phase trails; one primary reason is that there is high tissue toxicity of drugs inhibiting P-gp. Verapamil and cyclosporine A showed low-affinity to P-gp, showing severe cardiac and immunosuppressive side effects [36].

Uncompetitive inhibitors consisting of drug-binding pockets bound to ATP-binding NBD are characterized by their competitive inhibition of NBD. A strategy was improved to reduce the effects related to P-gp, a polar molecule was added to the drug via chemical modification. Cell-penetrating macromolecules (CPMS) and antibody-drug conjugated (ADCS) are being used on a huge basis to improve

drug release to the specific site to reduce unwanted effects. The FDA approved the Gemtumuzab-ozogamicin combination, but it was later removed from the market due to its weak survival profile, and seemed to cause trouble to the patients consuming it. Brentuximab-vedotin, which could interfere with P-gp efflux, is among the few ADCS that were FDA approved to treat refractory Hodgkin's lymphoma and anaplastic large cell lymphoma. However, there are more efficient techniques and more effective compounds to overcome the efflux of P-gp [37].

Another effective method for treating P-gp-induced multi-drug resistance (MDR) in tumor cells via monoclonal antibodies. MRK16 and MRK17 are anti-P-gp monoclonal antibodies that are developed in order to overcome multi-drug resistance. Another type of monoclonal antibody, such as bispecific antibodies, immunotoxins, and radioisotopes, enhances antitumor activity. These are collectively known as conjugated monoclonal antibodies. The monoclonal UIC2 antibody is known to inhibit P-gp-mediated transport. UIC2 action alone cannot produce better results as it can bind only 10% to 40% of P-gp in the cell membrane. Using UIC2 and vinblastine, cyclosporine, and PSC833 will exhibit its action in a wider perspective. As a result, co-administration of UIC2 and these inhibitors can completely inhibit the activity of P-gp. Doxorubicin uptake increased in cells, especially in blood vessels, with the help of P-gp [30].

P-Gp Modulators

Depending on the affinity of P-gp towards its protein substrate, compounds are classified into three types based on their different chemical classes: first, second, and third-generation MDR reversal compounds. In addition to these three generations of P-gp modulators, another type is known as a fourth-generation inhibitor. This fourth generation is obtained from natural sources with diverse nature and chemicals with a low yield potential that aids in the discovery of new inhibitors. These natural products are known for their low side effects on humans [38].

However, liposomal doxorubicin faces challenges in overcoming multi-drug resistance. Although it is targeted in a multi-drug resistant subline of M109-HiFR cells (M109R-HiFR), foliate receptors remain unaffected [39].

6. Fourth-Generation P-Gp Inhibitors

Panax notoginseng is a saponin with reversed MDR of doxorubicin and can decrease P-gp overexpression. Along with this, Quercetin is a common natural flavonoid containing Chinese herbs such as Sophora japonica. Quercetin is known to decrease P-gp expression by inhibiting the shock factor at the MDR1 promoter, decreasing MDR1 transcription. Quercetin is also known to prevent arsenite overexpression caused by P-gp. Its sensitivity to cancer cells, especially in HL-60/DOX and K562/DOX, decreases the expression of P-gp in daunorubicin. The membrane potential induced in the mitochondria and its apoptosis is presumably because of quercetin reversal effect. In addition to Quercetin, its derivatives are known to reverse MDR effects. Flavonoids such as kaempferol were known to

exert more action compared to quercetin. In addition to being an MDR reversing agent, the interactions of quercetin and digoxin were proven to be lethal [40].

The "Shengmai Injection", made by combining Panax ginseng and Ophiopogon japonicus, is known to reduce the expression of P-gp in the peripheral blood lymphocyte membrane. When combined with oxaliplatin and folinic acid, injection increases the survival rate of colon cancer [41]. Ligusticum chuanxiong is an active alkaloid used to obtain a calcium channel blocker known as tetramethylpyrazine. Tetramethylpyrazine is known to reverse the MDR actions in drugs such as doxorubicin, daunorubicin, and vincristine. Approximately 50% of drug efflux has been reduced in the MCF-7/DOX cell line that overexpressions P-gp. The combination of tetramethylpyrazine and Beta elemene had greater action towards MDR in cells resistant to the K562/DOX cell line.

A calcium channel blocker that helps treat MDR is Tetrandrine, obtained from Stephania tetrandra, which is classified as a bisbenzylquinoline alkaloid. Tetrandrine modifies the efflux of P-gp-induced drugs. The co-administering of vincristine together with Tetrandrine exhibits a synergistic action on cancer cells. As a result, there is a decrease in the expression of P-gp.

Peimine is an isosteroidal alkaloid extracted from the bulbs of Fritillaria thunbergia. Peimine accumulated daunorubicin in excess quantity in MDR resistant K562/DOX cell lines. Mahonia fortunei is used to develop a calcium channel blocker known as Berbamine. Berbamine inhibits cell growth by inducing apoptosis and simultaneously increasing rhodamine-123 concentration along with doxorubicin [42].

In addition to the natural plant extracts, oil emulsion known as Brucea javanica on simultaneous administration with vincristine, cisplatin, mitomycin C, 5-fluorouracil inhibits the effects of MDR effects downregulating the expression of P-gp [29].

Challenges and Limitations of Natural Source Inhibitors

1) **Bioavailability:** Natural source inhibitors may have poor bioavailability, meaning they are not readily absorbed and distributed throughout the body. This can limit their effectiveness in reaching tumor cells and inhibiting P-gp [43].

2) **Specificity:** Natural source inhibitors may lack specificity, meaning they can interact with other proteins and molecules in the body besides P-gp. This can lead to off-target effects and potential toxicity [44].

3) **Side effects:** Natural source inhibitors can cause side effects, especially at high doses or when combined with other medications. These side effects can range from mild to severe and may limit their clinical use [45].

4) **Chemical complexity:** Natural source inhibitors often have complex chemical structures, making it difficult to synthesize and modify them for improved efficacy or reduced toxicity [46].

5) **Yield and purification:** Obtaining sufficient yields of natural source inhibitors can be challenging, as they may be present in low concentrations in the source

material. Purification can also be complex, requiring multiple steps to isolate the active compound [47].

6) **Quality control:** Ensuring consistent quality and purity of natural source inhibitors can be difficult, as the composition of the source material can vary depending on factors like growing conditions and harvesting time [48].

7) **Drug interactions:** Natural source inhibitors may interact with other medications, potentially affecting their efficacy or causing adverse reactions [49].

8) **Clinical validation:** Many natural source inhibitors have not been extensively studied in clinical trials, so their safety and efficacy in humans remain uncertain [50].

7. Treating MDR-Induced Chemotherapy

7.1. Treatment Strategies

As there is little in drugs targeting P-gp, two alternative strategies were developed to overcome MDR-related chemotherapy. An approach is developing or modify an existing drug and using an alternative delivery system to prevent drug efflux mediated by the transporter. Down-regulation of the ABCB1 gene at the mRNA level or by inhibiting the transcriptional regulation gene [51].

7.2. Overcoming P-Gp Mediated Efflux by Designing New Drugs

An essential strategy to overcome MDR is developing anticancer drugs that do not relate to P-gp substrates. The required drugs can be obtained by identifying the latest lead compounds or chemically modifying existing drugs. In addition, it is a natural microtubule compounds that resembles P-gp [52].

In addition to the methods mentioned above, modifying the structures at specific sites alters the affinity towards P-gp and overcomes the resistance caused by the overexpression of P-gp. As a result, ixabepilone effectively treats metastatic breast cancer when administered in combination with capecitabine [52].

Chemically modifying an existing compound such as vinblastine through fluorination produced a new compound such as vinflunine that reduces P-gp sensitivity compared to vincristine by up to 2.5 - 13 folds and reduced neurotoxicity and improved bioavailability [52].

On the basis of the structural complexity of naturally derived products, the precise position of therapeutic molecules in reducing P-gp-mediated efflux while retaining medicinal potency. Since P-gp is a hydrophobic compound, adding polarity to an existing drug will overcome P-gp-mediated efflux [52].

7.3. Treating MDR-Induced Chemotherapy

Overexpression of P-gp on cancer cells blocks the drug from entering the cells by acting as an efflux pump. Because of this, the drugs are pumped out of the cells prior to reaching the targeted organ. All these actions combine to develop cells to resist cancer treatment. As a result, the drugs are ineffective and cannot produce

the desired result. Therefore, different approaches were developed to overcome MDR mediated by P-gp. P-gp is known to act locally by targeting the drugs present in the plasma membrane. Therefore, we can overcome MDR by administering cytotoxic drugs in combination with inhibitors such as the verapamil or Cyclosporine that inhibit the efflux of P-gp and allow the drug to flow freely to the targeted region. In this way, both the chemotherapeutic agent and inhibitors can be injected into the carrier system, which overcomes the problems related to P-gp. Similarly, we can conjugate the antibody to the drug loaded with a carrier system that is an effective strategy that inhibits drug efflux.

We can also use nanoparticles to treat P-gp-associated MDR. Vincristine is loaded with MRK-16, a lipid nanoparticle exhibiting more significant cytotoxicity in human myelogenous leukemia cells compared to non-targeted cells. As discussed earlier, UIC2, a monoclonal antibody combined with first-generation inhibitors such as cyclosporine A, has radically increased the concentration of daunorubicin in P-gp tumors. This took into consideration that when a UIC2 antibody and a P-gp inhibitor are used at low concentrations, it inhibits P-gp activity in vivo. In a mouse model of leukemia, SP1049C, a non-ionic block copolymer with a hydrophobic core and hydrophilic tail containing doxorubicin, overcame P-gp-mediated drug resistance. Folic acid targets the overexpression of the folate receptor in tumor cells when combined with PEG-derived distearoyl-phosphatidylethanolamine in doxorubicin-containing liposomes. Although liposomal doxorubicin is targeted in a multi-drug resistant subline of M109-HiFR cells (M109R-HiFR), foliate receptors remain unaffected [39].

7.4. Counteracting P-Gp Action

P-gp-mediated efflux can overcome drug complexity to a delivery agent capable of modifying the mechanism related to the cellular entry. Nanocarriers, such as liposomes, have been studied extensively related to clinical applications. The first nanodrug was approved by the FDA in 1995. SP1049c is a formulation as the cytotoxic payload acting as a nonionic block copolymer-targeting P-gp. SP1049c is known to prevent resistance to P-gp-mediated doxorubicin in leukemia's mouse model. Abraxane is another drug known to solve the insolubility caused by paclitaxel, which is bound to albumin with the nanoparticle formulation, improving the aqueous solubility of polymer-drug conjugates in a water-soluble polymer that aids in bypassing P-gp related MDR.

ADCs are a sort of covalent transport system that combines antibodies and drugs. ADCs transporter drug molecules are water-soluble with high cellular uptake, and MDR resistant in P-gp-mediated efflux.

An anti-CD33 antibody with a disulfide bond is known as AVE9633. According to the study, P-gp plays an important role in leukemia cell lines resistant to AVE9633 and DM4 cytotoxicity. The addition of an ethylene oxide linker to maytansine DM1 in an ADC changes DM1 to a poor substrate of p-gp, boosting the therapeutic efficacy of ADC in the treatment of P-gp-expressing human xenograft

tumors. Monomethylauristatin E (MMAE) is chemically modified in FDA-approved brentuximab vedotin (BV) in treating Hodgkin lymphoma and anaplastic large cell lymphoma. MMAE is sensitive to P-gp and structurally optimizing the ADCs that prevent drug efflux, improving the therapeutic index [53].

7.5. Translating Strategies into Clinical Practice

Translating MDR-overcoming strategies into clinical practice involves considering patient outcomes, treatment personalization, and overcoming current therapy limitations. Clinical trials and real-world studies are essential to validate these approaches.

8. P-Gp in Antimicrobial therapy

8.1. The Role of P-Gp in Antimicrobial Resistance

In previous sections, we have discussed drug efflux and it is a common mechanism that leads to resistance in microorganisms whose mechanism can be similar to that of MDR in cancer-induced chemotherapy. Accumulation of antimicrobials in cells from simple eukaryotes to complex eukaryotes is integral to efflux pumps. The efflux pumps that cause MDR are present in almost all organisms, including bacteria, fungi, and protozoa. P-gp acts through ABC transporters that cause MDR in organisms. P-gp reduces the intracellular concentration of drugs by efflux that decreases the bioavailability of drugs in the body; therefore, the drugs do not exhibit their pharmacological actions. This mechanism has rendered many treatments useless in the treatment of infectious diseases. To overcome this problem, inhibitors are combined with antimicrobial agents to improve the antibiotic's life, strengthening their therapeutic effect. Furthermore, these inhibitors can increase their susceptibility to antimicrobial agents and suppress variants that may develop resistance as treatment progresses.

8.2. The Use of P-Gp Inhibitors in Enhancing Antimicrobial Therapy

Inhibitors such as Verapamil and Cyclosporine were examined for their antimicrobial activity on macrolides. It was clear that P-gp was effluxing Azithromycin, erythromycin, resulting in low drug concentrations at the site. As a result, inhibitors increase the concentration of drugs increasing their antimicrobial actions [41].

The addition of an ethylene oxide binder to maytansine DM1 in an ADC changes DM1 to a weak substrate of p-gp, increasing the therapeutic efficacy of ADC in the treatment of human xenograft tumors [41].

9. Emerging Research Areas and Future Directions

While fourth-generation P-gp inhibitors from natural sources are promising, they face challenges such as bioavailability, specificity, and potential side effects.

Addressing these issues is crucial for their successful clinical application.

Future research should focus on novel targets for overcoming MDR, integrating nanotechnology, and personalized medicine approaches. These advancements could lead to more effective and tailored cancer treatments.

10. Conclusions

P-gp plays a critical role in MDR, complicating cancer treatment. Understanding the mechanisms of P-gp and developing effective inhibitors are essential for improving therapeutic outcomes. Fourth-generation P-gp inhibitors and new anticancer drugs offer hope for overcoming MDR, but further research and clinical validation are needed.

The suppression of drug efflux is a major aspect of drug development. Chemical modification of drugs bypassing P-gp is not straightforward and does not have any explicit rules to overcome them, as P-gp can recognize wide structures that permeate cell membranes. On the other hand, the anticancer drug is modified without diminishing drug potency. When these two, drug delivery systems have the potential to develop a safe, high-dose-delivery of anticancer drugs that are noninvasive and target specific. Controlled drug release within the cell is a key aspect as drug accumulation is balanced through efflux and membrane transporters.

In comparison of P-gp and MDR, MDR transporters are limited in structural and mechanical studies. However, MDR transporters, on their biochemical characterizations, have potential in designing a drug on its structure.

P-gp activity in lymphocytes has been associated with cytokine production, immune cell stimulation, and cytokine production. Although P-gp activity in distal circulation macrophages is low, it is abundant in anti-inflammatory M82 phagocytes that infiltrate tumors. The development of dendrites is related to the expression of P-gp, and activation improves protein activities. Valspodar works by inhibiting P-gp, preventing D.C. maturation, and lowering osteoblast and CD40 cell expression. The expression is higher on natural fighter cells (N.K.). This is consistent with its downstream role, since the surface attachment of the Signaling pathway (Fas/FasL) of P-gp + NK cells to target sites triggers the production of inflammatory cytotoxic granulosa cells, which causes death at the desired target.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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