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Perspective

A Short Note on a P-glycoprotein Drug Discovery

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ABOUT THE STUDY

The development of Multidrug Resistance (MDR) is a major obstacle to the long-term success of cancer treatment. P-glycoprotein (Pgp) is a well-known membrane transporter with the ability to deliver drug molecules from cancer cells, reducing the effectiveness of chemotherapy. Cancer cells regulate Pgp expression as an adaptive response to avoid chemotherapy-mediated cell death. Excretion transporters such as p-glycoprotein play an important role in drug transport in many organs. In the intestine, p-glycoprotein sends the drug back into the lumen, reducing absorption. The use of chemotherapy to treat cancer is limited by the development of resistant cancer cell variants. Tolerance can usually occur against individual cytotoxic drugs, usually through changes in the targets of those drugs, but more generally to many different drugs with different chemical structures and various mechanisms of action. This latter form of resistance is called Multidrug Resistance. MDR seems to be the main reason for the failure of cancer chemotherapy, as several different classes of chemotherapeutic agents are used to treat most types of cancer. Many different MDR mechanisms have been elucidated, including changes in cell cycle, failed apoptosis mechanisms, repair of damaged cell targets, and reduced drug accumulation. There are basically two mechanisms of drug uptake. For water-soluble hydrophilic drugs such as cisplatin, nucleoside analogs, and folic acid antagonists, the drug cannot cross the plasma membrane unless it returns back on an existing transporter/carrier or penetrates through the hydrophilic channels of the membrane. Resistance to such drugs due to reduced accumulation occurs because of individual mutations in the carrier that confer resistance to a single drug. For hydrophobic drugs such as the natural products vinblastine, vincristine, doxorubicin, daunorubicin, actinomycin D, etoposide, teniposide, and paclitaxel, invasion occurs by diffusion across the progenitor membrane without a specific drug carrier. The only way to keep such drugs out of cells is by activation of energy dependent transport systems.

Drugs that induce p-glycoproteins, such as rifampicin, can reduce the bioavailability of the other drugs. P-glycoprotein inhibitors such as verapamil increase the bioavailability of sensitive drugs. Key substrates for p-glycoprotein include calcium channel blockers, cyclosporine, dabigatlan etexilate, digoxin, erythromycin, loperamide, protease inhibitors, and tacrolimus. Due to individual differences in drug transport, it is difficult to predict clinically significant interactions. P-glycoprotein is one of the drug transporters that determine the uptake and outflow of many drugs. This process affects plasma, tissue concentrations and the ultimate effect. P-glycoprotein acts as a trans membrane drain pump, pumping its substrate from the inside to the outside of the cell. Drugs that induce or inhibit p-glycoproteins can interact with other drugs processed by the pump. P-glycoprotein was first described in tumor cells. These cells showed overexposure of p-glycoprotein and reduced access to cytotoxic drugs. As this made the tumors resistant to various anticancer drugs, P-glycoprotein was also known as multidrug resistance protein. P-glycoprotein is also expressed in a variety of normal, non-tumorous tissues with excretory functions (small intestine, liver and kidney) and at blood tissue barriers (blood brain barrier, blood test barrier and placenta). Along with the Cytochrome P450 (CYP) own circle of enzymes, concomitant expression of P-glycoprotein is assumed to be an essential evolutionary model in opposition to probably poisonous substances. As an efflux transporter it limits the bioavailability of orally administered capsules *via* way of means of pumping them returned into the lumen. This promotes drug release into the bile and urine and protects some of tissues together with the brain, testis, placenta and lymphocytes. The substrates for p-glycoproteins are a lot of structurally various compounds. When the drug reaches the systemic circulation, p-glycoprotein limits its penetration into extra smooth tissues.

P-glycoprotein is also important for the blood-brain barrier as a defense against toxins and drugs that enter the central nervous system. P-glycoprotein plays a modest role in drug clearance. It is expressed in the luminal membrane of the proximal tubular cells of the kidney. P-glycoprotein delivers the drug into the urine. P-glycoprotein is an important mediator of drug interactions. The pharmacokinetics of a drug can change when co-administered with a compound that inhibits or induces p-glycoprotein.

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Inhibitors include clarithromycin, erythromycin, ritonavir, and verapamil. P-glycoprotein, like CYP3A4, has a very wide substrate range. It is involved in the transport of drugs from different drug classes including:

- Antitumor drugs, eg. Docetaxel, etoposide, vincristine.
- Calcium channel blocker (eg amlodipine).
- Calcineurin inhibitors such as cyclosporine, tacrolimus.
- Digoxin.
- Macrolide antibiotics (such as clarithromycin).
- Protease inhibitor.

Substrate of p-glycoprotein can be further divided into drugs that are not metabolized in humans such as digoxin and drugs that are substrates of both P-glycoprotein and drug-metabolizing enzymes. Some common pharmacological inhibitors of p-glycoprotein include amyodaron, clarithromycin, cyclosporin, corhitin, diltiazem, erythromycin, felodipine, ketoconazole, lansoprazole, omeprazole and other proton pump inhibitors, nifedipine, paroxetine, reselpin, sakinavir, sertralin, quinidine.