

## The Association Between Cancer and ABC Transporters

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### Abstract

Many cancers resist to chemotherapy drugs during treatment and it have been proposed various mechanisms in connection with drug resistance. High expression of ATP-dependent membrane proteins as a family of ATP binding cassette (ABC) are one of the main reasons for drug resistance so that P-glycoprotein (a member of this family) plays an important role in drug resistance. ATP-binding cassette (ABC) transporters are an example of ATP-dependent pumps. ABC transporters are ubiquitous membrane-bound proteins, present in all prokaryotes, as well as plants, fungi, yeast and animals. These pumps can move substrates in (influx) or out (efflux) of cells. In mammals, ABC transporters are expressed predominantly in the liver, intestine, blood-brain barrier, blood-testis barrier, placenta and kidney. In addition, multidrug resistance associated protein as other membrane of this family is involved in drug resistance. These proteins have property of endogenous substrates transferring. Over-expression of these proteins in cancer cells is most important obstacle to treat cancer. However, drug resistance can occur through other ways such as anti-cancer drugs associated with metabolism purines and pyrimidines or microtubules dysfunction. In this review, mechanisms of drug resistance were described.

**Keywords:** Cancer; Chemotherapy; Treatment; ABC transporters; Drug resistance

### Introduction

Membrane transport proteins can be divided into four types: ion channels; transporters; aquaporins and ATP-powered pumps. Genes from all four categories are ancient -- with members present in most, if not all, prokaryotes, as well as in virtually all cell types of all eukaryotes. Transporters in eukaryotic cells move ions, sugars, amino acids and other molecules across all cellular and organelle membranes (cell surface, mitochondrial, endoplasmic reticulum, Golgi apparatus and other vesicles) -- with the possible exception of nuclear membranes (which have pores). The portion of the cell exposed to the lumen is called the apical surface; the rest of the cell (i.e. sides and base) makes up the basolateral surface. Movement of ions or other molecules into the cell is called influx; movement of ions or other molecules out of the cell is termed efflux. Membrane transport proteins can be either passive or active. Passive transporters (also called uni-ports or facilitative transporters) transport substrates down a concentration gradient. By contrast, active transporters (or cotransporters) couple the movement of one type of ion or molecule against its concentration gradient, to the movement of another ion or molecule down its concentration gradient. Like ATP pumps, cotransporters mediate coupled reactions in which an energetically unfavourable reaction is coupled to an energetically favourable reaction. When the transported molecule and cotransported ion move in the same direction across a membrane, the transporter is called a symporter; when they move in opposite directions, the transporter is called an antiporter (or exchanger). If the intracellular net charge following transport becomes more negative, the process is termed electronegative; if the intracellular net charge becomes more positive, the process is called electropositive; if the resulting intracellular net charge remains unchanged, the process is termed electroneutral. Chemotherapy is one of the most effective treatments for metastatic tumors. As cancer cells simultaneously resist to different drugs without any structural and functional relationship with each other therefore drug resistance is still one of the major obstacles in chemotherapy. It has been clarified different ways to overcome drug resistance after three decades. According to reported studies, drug resistance against any

new drug is possible. Thus, the ability to anticipate and overcome drug resistance is likely very effective in improvement of chemotherapy. Yet, it has not been determined why some patients with cancer treated by chemotherapy while it has not obtained improvement in another patients. It seems that genetic variation and epigenetic alterations of tumors in different patients have prominent role to complex drug resistance [1]. Factors that influence access of tumor cells to anticancer drugs lead to interference in drug delivery of into the cells and thus poor absorption of drugs, increase of drug metabolism or excretion and ultimately decreasing of its blood level and spreading to tumor mass [2,3]. In addition, another factors influence drug resistance at inside of cells cancer due to genetic and epigenetic changes that along with factors related to tumor extracellular matrix or tumor location lead to drug resistance [2]. Resistance to natural hydrophobic result from increase of ATP-depended pumps activity is one of the most common drug resistance during cancer [4]. Today, most attention to eradicate drug resistance in cancer cells is devoted to this class of drug carriers [5,6]. Drug resistance can be through reduction of drug entry into cells. However, this mechanism express for drugs with endocytosis property. In addition, the activation of body detoxification systems such as glutathione S-transferase, cytochrome P450 oxidase leads to drug resistance in cancer [7,8]. Over-expression of ATP-depended transporters is most common reason for drug resistance against a wide range of anti-cancer drugs. P-glycoprotein as a glycoprotein is most common of ATP-depended transporters in cells

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[9]. During chemotherapy this protein is seen approximately 50% of human cancers [10]. It is noteworthy that p-glycoprotein is not only transporter in cancer cells with drug resistance property and there is another transporters involved in the development of drug resistance. Multidrug resistance associated protein family is considered as membrane proteins involved in drug resistance that have pivotal role to transfer drug and probably development of drug resistance such as MRP1 that has similar structure to p-glycoprotein [11]. Here we reviewed the relationship between drug resistance and cancer.

## Methodology

In order to obtain better results, we searched papers related to drug resistance during cancer using keywords such as drug resistance and cancer, drug resistance and cancer cell line in databases of web of science, PubMed and Scopus. In final, the papers were read and summarized.

## Details of the ABC proteins

By definition, ABC proteins possess an ATP binding cassette, also known as the 'nucleotide-binding domain' (NBD). The NBD contains several highly conserved motifs, including the Walker A and Walker B sequences, the ABC signature motif, the H loop and the Q loop. ABC transporters also contain trans-membrane domains (TMDs), each of which comprises several hydrophobic  $\alpha$ -helices. The ABC transporter core unit consists of four domains, two NBDs and two TMDs. The two NBDs together bind and hydrolyse ATP (thereby providing the driving force for transport), while the TMDs participate in substrate recognition and translocation across the lipid membrane. Some ABC genes encode proteins that are 'half-transporters' (meaning that two subunits bind as homodimers or a heterodimer), whereas others are 'full-transporters'. The ABC family is a member of the P-loop-containing nucleoside-triphosphate hydrolase clan (CL0023). The definition of the clan in the Pfam database is: 'A collection of evolutionarily-related Pfam entries. This relationship may be defined by similarity of protein sequence, tertiary structure or profile, as defined by the Hidden Markov model'. At the moment, clan CL0023 contains 55 protein families, including the ABC family.

## Multidrug Resistance Mutation (MDR1)

The word mutation refers to a change in an animal's genetic code. The phrase 'multidrug resistance mutation 1 (*MDR1*)' refers to a specific mutation that can occur at a gene known as the *MDR1* gene, also known as the *ABCB1* gene. The *MDR1* gene codes for the production of a protein known as p-glycoprotein. This protein was originally discovered in cancer cells. During research, it was found that some lines of cancer cells are resistant to chemotherapy that is effective against other cancer cells. Further testing showed that these resistant cell lines contained a protein called p-glycoprotein, which sat on the cell membrane of these cancer cells and pumped chemotherapy drugs out of the cell. In this way, p-glycoprotein helped cancer cells resist the effects of chemotherapy drugs.

## Cancer and drug resistance

As above noted, it seems that a variety of ABC transporters involved in drug resistance during cancer formation. Today, most clinical studies are conducted on the role of drug resistance of p-glycoprotein. Its expression is very high in many human cancers, including cancers related to gastrointestinal tract, small intestine, colon, liver, pancreas, hematopoietic system, genitourinary system and cancer related to childhood such as neuroblastoma and fibro sarcoma [12,13]. It is

noteworthy that it has been observed increase of *MDR1* expression gene in tumor tissues that has not p-glycoprotein under normal condition such as myeloma and sarcoma also seen [14].

At first, it has been thought that increase of p-glycoprotein expression can alone justify condition of drug resistance in cancer. In addition, it has been found that over expression of p-glycoprotein in cancer cells influence cells respond to drugs related to chemotherapy. While, it recently has been reported that besides p-glycoprotein, other factors have pivotal role in drug resistance, it is an important option that simultaneous use of p-glycoprotein inhibitors such as cyclosporine A and tam can inhibit drug resistance in cancer cells [12]. Some anticancer drugs interfere with the metabolism of purines, pyrimidines and folate so that inhibit cancer cell proliferation for example methotrexate. Resistance to methotrexate is due to changing in drug delivery, reduction of poly-glutamyl form, changing in drug target enzyme. Inactivity of thymidine kinase, thymidine phosphorylase, uridine kinase, uridine phosphorylase and orotate phosphoribosyltransferase as well as increase of CTP synthesis are consider as causes of resistance to this drug [15]. Vinca alkaloids are other class of anti-cancer drugs, which act by disruption in microtubule function. Drug resistance against these drugs occurs by p-glycoprotein that leads to their efflux and reduction of their accumulation in cells. In addition, changing in structure and function in alpha and beta tubulin caused by mutation or post-translational modifications lead to resistance to these drugs [16,17]. 5-Fluorouracil is one of the most important drugs that becomes to 5-fluoro 2-deoxyuridine monophosphate by thymidine phosphorylase and thymidine kinase in cell and then in presence of 5, 10-methylene-tetrahydrofolic folate form a stable covalent by thymidylate synthase so that this stable covalent inhibits thymidylate synthase. Thymidylate synthase inhibition leads to depletion of dTTP and impairment of synthesis and repairing of DNA [18]. Drugs such as chlorambucil, cyclophosphamide, and busulfan are alkylating drugs with anti-tumor property. These drugs have an ethylene ammonium ion in their structure that connects to N7 guanine position as a DNA nucleophilic part and inhibit DNA replication and transcription that result in cell death. Resistance to these drugs occur in levels of biochemical changing, tumor mass and interaction between the tumor-host [15,16].

## Discussion

Multiple cascades of signaling pathways of cell growth and proliferation, regulating molecules of cell cycle and genes affected from cytosolic and nuclear growth pathways are the most important factors, which can play pivotal role in occurrence of resistance phenomenon. Among the multiple cascades related to signaling pathways of cell growth and proliferation can mention to increase of activity of receptor HER2 and its components of signaling cascade in development of resistance to tamoxifen. This receptor is a tyrosine kinase receptor that leads to activation of various growth factors such as VEGF, EGF or TGF $\beta$ . The use of tamoxifen, as an antagonist of estrogen receptors in treatment of breast cancer cells with positive estrogen receptor has a special place. Unfortunately, in a third of cases are caused resistance to this drug [19,20]. HER2 expression is low in cancer cell lines treated by estrogen while its expression increases in some cancer cells resistance to tamoxifen [21-23]. Reduction of effects of estrogen on cells, either physical or pharmacological inhibition by tamoxifen is a reason to increase receptor expression. This claim has been proven in numerous studies [23,24]. In a study, it has been investigated simultaneous overexpression of receptor and resistance level on MCF7, a tissue transplanted into animal free-estrogen, and found that cancer cells

proliferate in absence of estrogen and simultaneously expression of HER2 receptor increase in them [25]. In addition, study on animals has been showed that treatment with tamoxifen for twenty days leads to increase of HER2 expression in cancer cells [26]. Many investigations have been conducted in order to answer this question what factors cause increase of HER2 expression in cells of resistant to tamoxifen and results suggest that increase of MUC1C expression in cancer cell lines leads to increase of p-HER2 so that this finding has been confirmed after incubation of GO-203 as MUC1C inhibitor [27]. In addition, it has been mentioned inhibitory effect of tamoxifen on expression of HER2 by increase of expression of PAX2 in cancer cells. Thus, it seems that given that increase of HER2 expression in tumors, strategies for overcome of this problem such as increase of PAX2 activity can be a useful way to treat cancer [28].

## Conclusion

Now-a-days a lot of information about drug resistance mechanisms in cancer cells is available. Despite advances in cancer treatment by chemotherapy, protective mechanisms of cells against cytotoxic compounds are a major obstacle to overcome cancer treatment. Increase of information about drug resistance mechanisms, can be useful to design promising strategies to overcome drug resistance. Some obtained findings about drug resistance reveal new mechanisms in association with drug distribution in body. These findings can be helpful to improve patients with cancer.

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## Author Contributions

This work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article was borne by the authors named in this article.

## Ethical Approval

This research does not contain any studies with human participants or animals and was performed by the authors alone.

## Conflict of Interest Statement

The authors declare that there is no conflict of interest regarding this study.

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