

# Roles of ABCA1 in cancer (Review)

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**Abstract.** Studies have indicated that anticancer drugs targeting cholesterol metabolism have clinical significance. From the perspective of the mechanism of cholesterol excretion from cells, ATP-binding cassette (ABC)A1 has an essential role that cannot be ignored. ABCA1 is located on the cell membrane and able to mediate the efflux of lipids, such as intracellular cholesterol, thereby initiating reverse cholesterol transport to reduce the intracellular cholesterol level. Therefore, inducing the expression of ABCA1 may become a new breakthrough point in cancer therapy.

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## 1. Introduction

Certain studies have indicated that cancer cells have an enhanced ability to proliferate and invade caused by changes in their metabolism, among which abnormal cholesterol metabolism has a key role. It is mainly manifested as abnormally increased or abnormally accumulated cholesterol in cancer cells, and inhibiting the increase of cholesterol levels may slow down the proliferation of cancer cells. An important factor affecting intracellular cholesterol levels is protein transport (1).

ATP-binding cassette (ABC) transporters are localized to the plasma membrane and function as a class of lipid transporters. Energy is obtained by hydrolyzing ATP, thereby mediating the efflux of intracellular phospholipids and free cholesterol, which combine with non-fat or low-fat apolipoprotein A-I (apo A-I) on the cell surface to form high-density lipoprotein (HDL) to then initiate the reverse cholesterol transport process (2,3). When exploring the association between cholesterol and malignant cancers, it was observed that the accumulation of excessive intracellular cholesterol may promote the development of cancer cells to a certain extent (4). Phillips (5) indicated that high cholesterol levels were positively associated with the aggressiveness of prostate cancer. Abnormally active cholesterol metabolism in cancer cells leads to proliferation, survival, invasion, metastasis and enhanced adaptation to the cancer microenvironment (6). ABCA1 is also closely related to cancer resistance mechanisms (7); thus, inducing the expression of ABCA1 may provide novel therapeutic strategies for cancer prevention, inhibition and even treatment, bringing new hope for the treatment of cancer patients (8).

## 2. Influence of intracellular lipid microenvironment on cancers

As mentioned earlier in the introduction, cholesterol has an important role in the development of cancers, such as participation in the proliferation, migration and invasion of cancer cells. Luo *et al* (9) indicated that the abnormal cholesterol metabolism of cancer cells leads to proliferation, survival, invasion, metastasis and enhanced adaptability to the cancer microenvironment, thereby promoting the occurrence and development of cancers. Changes in membrane cholesterol and cholesterol-rich membranes have been observed to affect the progression and invasion of cancers (9). Cholesterol homeostasis is critical for cellular function and survival, and dysregulated cholesterol homeostasis is known to be associated with a variety of cancers, including prostate cancer (10), and alterations in lipid metabolism are increasingly recognized as a hallmark of prostate cancer cells (11). A large number of studies suggested that a variety of genes related to cholesterol synthesis exhibit increased activity in cancer cells, thereby promoting the growth, migration and metastasis of various cancer cell types, including gastric cancer, glioma and prostate cancer (12-14). In addition, it was reported that the expression of low-density lipoprotein receptors (LDLR) is upregulated in various cancer cells, which was significantly associated

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with poor clinical prognosis in patients with small cell lung cancer (15-18). Elevated expression of LDLR in patients with pancreatic cancer was associated with an increased recurrence rate. However, silencing of HDLR by short hairpin RNA in pancreatic cancer cells significantly reduced the cholesterol uptake, thereby inhibiting the proliferation of pancreatic cancer cells. Treatments related to the synthesis, uptake and esterification of cholesterol may alleviate cancer progression (19-21). It was reported that altering the intracellular lipid microenvironment by affecting various metabolic pathways of cholesterol has an important role in the proliferation and invasion of certain types of cancer cell (22,23). Table I summarizes the specific effects of intracellular cholesterol levels on cancer; as one of the major efflux pathways of cellular cholesterol, ABCA1 may be an important determinant of prostate cancer aggressiveness and a potential therapeutic target (24,25).

### 3. Effect of ABCA1 on the intracellular lipid microenvironment

*ABCA1 and plasma membrane remodeling and lipid redistribution.* ABCA1 is known as the main efflux channel of intracellular cholesterol. Although there is still no perfect model to explain the mechanism, the latest efflux mechanism is widely recognized (8). Multiple studies suggested that the binding of apo A-I to ABCA1 may lead to the redistribution of phospholipids and cholesterol on the outside of the plasma membrane, thereby changing the intracellular lipid microenvironment and remodeling the plasma membrane, which facilitated the binding of apo A-I to lipids and maintained intracellular cholesterol homeostasis (26-29). After the combination of the two, the plasma membrane is remodeled in two ways: Horizontal and vertical. The vertical remodeling promotes the net transport of phospholipids to the outer leaflets of the plasma membrane through ABCA1, resulting in an imbalance in the packing density of the two leaflets of the phospholipid bilayer, thereby regulating the lipid density of the plasma membrane (30). In horizontal remodeling, ABCA1 is enabled by hydrolysis of ATP, causing the phospholipid and cholesterol molecules that constitute the plasma membrane to translocate laterally on the cell membrane, resulting in the redistribution of lipids from non-lipid rafts to lipid rafts, which in turn changes the lipid distribution of the entire plasma membrane (31-33). Therefore, it may be speculated that ABCA1 changes the intracellular lipid microenvironment through plasma membrane remodeling and lipid redistribution.

*ABCA1 and intracellular lipid efflux.* All cells in the body are able to synthesize cholesterol, but most of them lack effective metabolic pathways and may only be excreted from cells through a series of transporters (34). Among them, ABCA1 is able to use the energy provided by ATP to promote the efflux of free cholesterol and phospholipids in cells, and combine with apo A-I on the cell surface to form new HDL, which in turn initiates the reverse cholesterol transport process to transport cholesterol from peripheral tissues back to the liver (35-37). At this stage, it has been indicated that numerous factors (such as IGF-1), are able to directly or indirectly regulate the expression level of ABCA1 to affect the intracellular cholesterol level (38). The importance of ABCA1 for cholesterol efflux is currently

widely recognized, but the pathway to the plasma membrane remains to be fully elucidated (39). Yoshioka *et al.* (40) provided three models of cholesterol efflux mechanisms. They are the channel transport model, the mushroom-like protrusion model and the endocytosis-exocytosis transport model. The channel transport model is widely accepted and is presented in Fig. 1 to indicate how ABCA1 is able to regulate the intracellular microenvironment by transporting intracellular lipids.

### 4. ABCA1 and cancer cell proliferation, invasion and metastasis

The above studies proved that a series of life activities of cancer cells are closely related to the level of intracellular cholesterol and ABCA1 indirectly affects the proliferation, metastasis and invasion of cancer cells by regulating the level of intracellular cholesterol (41-44). ABCA1 mediates the transmembrane transport of free intracellular cholesterol and phospholipids to apo A-I, which has an important role in maintaining the normal metabolism of intracellular cholesterol. As indicated by Prochazka *et al.* (45), in non-small cell lung carcinoma H1299 cells, overexpression of ABCA1 enhanced drug resistance. ABCA1 is strongly expressed in normal breast epithelium and the reduced expression of ABCA1 in breast cancer appears to be associated with poor prognosis (46). Activated liver X receptor and overexpression of ABCA1 have been reported to reduce cholesterol levels and cancer growth in mouse prostate cancer xenografts (47). Maslyanko *et al.* (48) also indicated that high cholesterol levels may promote the proliferation of breast cancer cells in a mouse transgenic model, specifically by upregulating the protein expression of ABCA1 to maintain the cholesterol balance in the body and inhibit the proliferation of cancer cells. It was also indicated that cholesterol efflux has an important role in the treatment of lung cancer. Downregulation of ABCA1 was evident in all prostate cancers. It has been reported that when prostate cancer metastasizes, the cells contain high levels of cholesterol (49). Studies suggested that cancer-specific ABCA1 methylation and loss of protein expression directly led to elevated intracellular cholesterol levels in cancer cells, thus forming a microenvironment favorable for cancer progression (50). Liu *et al.* (51) indicated that microRNA-200b-3p acts as an oncogene in lung adenocarcinoma samples and in the human lung adenocarcinoma cell lines A549 and H1299 by targeting ABCA1, and overexpression of ABCA1 significantly inhibited the proliferation, migration and invasion of lung adenocarcinoma cells. Huang *et al.* (52) demonstrated that ABCA1 may protect the normal function of cells by maintaining low levels of cholesterol in mitochondria and have a certain inhibitory effect on the proliferation of cancer cells. Prostate cancer bone metastases exhibit clear metabolic differences from bone metastases of other cancer types, including increased levels of cholesterol. Regulation of cholesterol in the plasma membrane has been indicated to modulate the ability of cells to migrate (53). Furthermore, cholesterol-rich lipid rafts were reported to have an important role in the adhesion and migration of cancer cells (54,55). The activity of phosphoinositide 3-kinase is able to regulate the surface protein expression of ABCA1, which significantly increases the risk of cancer cells entering the blood to form metastases (56).

Table I. Effect of cholesterol levels on cancers.

Cancer type	Cholesterol intake	Cholesterol synthesis	ABCA1 expression	Function	(Refs.)
Prostate cancer	HDLR high expression	High expression of squalene monooxygenase	Low expression (methylation)	High cholesterol promotes tumor development	(44,46)
Glioblastoma	-	High expression of HMGCR	Low expression	High cholesterol promotes tumor development	(25)
Pancreatic cancer	LDLR high expression	-	Low expression	High cholesterol promotes tumor development	(31,32)
Breast cancer	LDLR high expression	-	Low expression	27-HC promotes cell proliferation and metastasis	(43)
Lung cancer	-	-	Low expression	HDL-C is negatively correlated with the occurrence and development of lung cancer	(48,67)
Ovarian cancer	-	High expression of cholesterol synthase	Low expression (methylation)	High cholesterol promotes tumor development	(56,57)

ABC, ATP-binding cassette; LDLR, low-density lipoprotein receptor; HDL-C, high-density lipoprotein cholesterol.

Table II. ABCA1 and cancer cell proliferation, invasion and metastasis.

Cancer type	Cancer cell proliferation, invasion and metastasis	(Refs.)
Prostate cancer	High levels of cholesterol can modulate the ability of cells to migrate	(49)
Breast cancer	Reduced expression of ABCA1 in breast cancer appears to be associated with poor prognosis	(46)
Non-small cell lung carcinoma	Upregulation of the expression level of ABCA1 enhances drug resistance	(45)
Lung adenocarcinoma	Overexpression of ABCA1 significantly inhibits the proliferation, migration and invasion of lung adenocarcinoma cells	(53)

ABC, ATP-binding cassette.

In Tables I and II, the specific effects of ABCA1 in cancer cells are summarized, linking abnormal cholesterol levels to aberrant ABCA1 expression, regulation of ABCA1 expression levels, which may be utilized for inhibiting cancer cells to proliferate, metastasize and invade.

### 5. ABCA1 and cancer therapy

It is promising to treat cancer by regulating the expression level of ABCA1, thereby regulating the level of intracellular cholesterol. Of note, cancer cells require excess cholesterol to maintain high levels of proliferation, which has been widely accepted (57). Available epidemiological data indicated that low serum cholesterol as well as statins reduce the risk of prostate cancer, demonstrating that cholesterol metabolism has a

role in the development of aggressive prostate cancer (58). Therefore, it may be speculated that high expression of ABCA1 is able to mediate cholesterol efflux, resulting in the reduction of intracellular cholesterol in prostate cancer cells to achieve the purpose of inhibiting cancer growth. Ovarian cancer is a common gynecological malignancy. Although chemotherapy is able to delay the disease, the post-operative survival rate is not high. Studies have indicated that ABCA1 has a key role in drug resistance and prognosis (59). According to the latest research, patients with ovarian cancer with high methylation of RASSF1C (functions as an oncogene in cancer cells) and low ABCA1 expression have shorter survival (60). In conclusion, existing studies suggest that moderately high expression of ABCA1 has a positive effect on the treatment of prostate cancer and breast cancer.

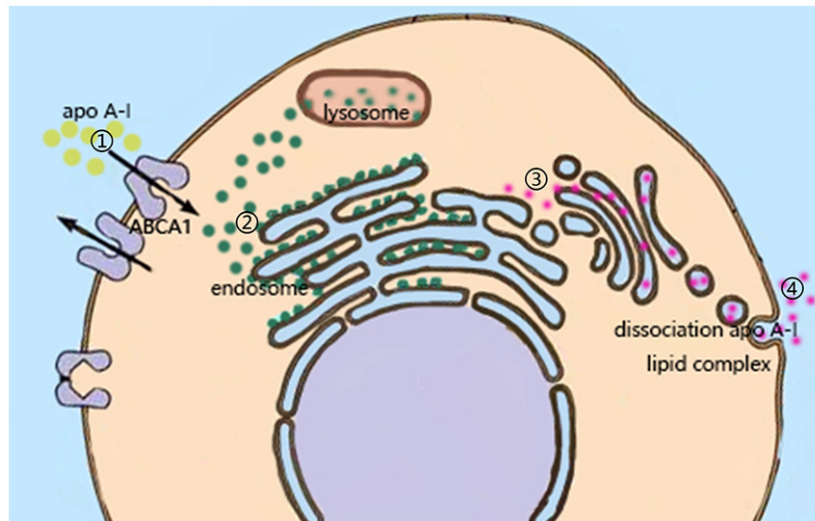


Figure 1. Mechanism of lipid efflux mediated by ABCA1. ① Low-density lipoprotein binds to ABCA1 to form a complex. ② The complex is internalized, part of it is transferred to the lysosome for degradation and the rest is located to the endosome. ③ The complex on the endosome combines with lipid to form the apoA-I/lipid complex. ④ The lipid complexes are resecreted through exocytosis, and after dissociation, they are conducive to the formation of high-density lipoprotein complexes. Apo, apolipoprotein; ABC, ATP-binding cassette.

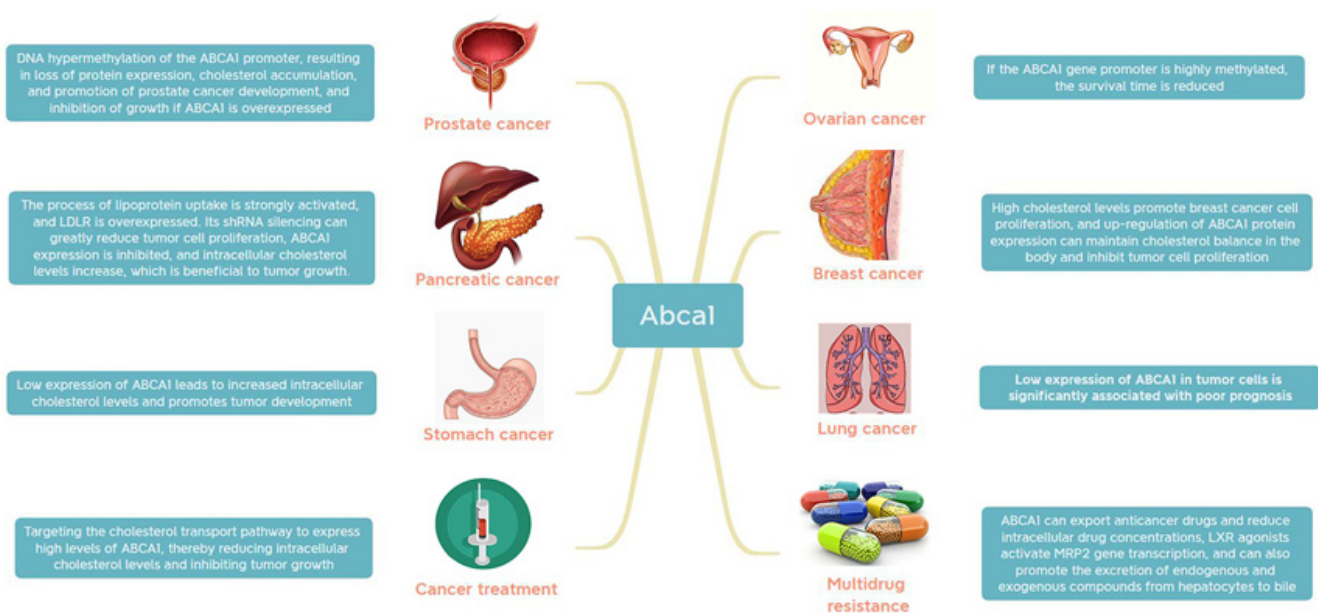


Figure 2. Roles of ABCA1 in various cancer types and cancer treatment (64,65,69,71,72). ABC, ATP-binding cassette; shRNA, short hairpin RNA; LDLR, low-density lipoprotein receptor; MRP2, multidrug resistance-associated protein 2.

## 6. ABCA1 and drug resistance of cancer

ABCA1, as a research hotspot in recent years, has received extensive attention due to its function, and as a major transporter regulating intracellular cholesterol, its role in cancer resistance has attracted much attention (8). Chemotherapy, as one of the most important cancer treatment methods, is still not able to completely remove cancer cells. Chemotherapy tolerance is one of the most common problems in chemotherapy failure. Therefore, overcoming the resistance of cancer cells to chemotherapeutic drugs is an important issue in cancer treatment (61). Multidrug resistance generally refers to the adaptability of cancer cells to increase drug output and

decrease drug uptake, and drug transporters have a key role in pre-targeted drug resistance (62). Existing studies suggested found that chemotherapy failure is directly related to ABC transporters and preventing the induction of ABC transporters in cancer cells may help avoid drug resistance (63). The high expression of transporters in cancer cells results in a variety of anticancer drugs being transported out of cells and unable to exert their anticancer effects (64,65), which has been observed in the drug resistance to curcumin, doxorubicin and nitidine in the treatment of breast and lung cancer (66-68). Chen *et al* (69) indicated that ABC transporters have a certain role in cancer stem cells through the reversal of inhibition of ABC transporter expression. There are numerous ways to overcome the

drug resistance that depends on high expression of ABCA1, such as valproic acid downregulating the expression level of ABCA1 through histone deacetylase 2, thereby enhancing the sensitivity of non-small cell lung cancer cells to cisplatin (70). ABCA1-dependent resistance to  $\alpha$ -tocopheryl succinate in mitochondria-targeted therapy of lung cancer was also reported (71). However, certain studies also indicated that when the expression level of ABCA1 in cancer cells was generally decreased, cholesterol accumulated and increased the order of bilayer phospholipids, thereby reducing the permeability of the membrane and finally promoting the resistance of cancers to membrane-active anticancer drugs (72). As indicated in Fig. 2, the role of ABCA1 in multidrug resistance has been widely recognized and measuring the expression of ABCA1 may be used to predict the response to anticancer drugs.

## 7. Conclusion and perspective

Cholesterol efflux minimizes the potential harm to cells by excess cholesterol, but cancer cells have evolved to exploit this link to promote malignancy. As one of the main transporters of intracellular cholesterol efflux, ABCA1 has been widely recognized and used in anti-atherosclerosis treatment (73); its ability to transport cholesterol also has great potential in cancer treatment (74). Further research on ABCA1 will help elucidate its transport function and mechanisms to inhibit the transport of chemotherapeutic drugs, as well as the related effects of its reduced expression level on cancer cells, so as to achieve the purpose of cancer treatment. By modifying and inhibiting this gene, mechanisms of cancer cell growth and efflux of chemotherapeutic drugs may be interfered with. This provides novel directions for research on lipid metabolism and offers new effective targets for cancer prevention, inhibition and treatment. ABCA1 in cancer and provides a new avenue for drug discovery and therapy.

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## Availability of data and materials

Not applicable.

## Authors' contributions

XY was responsible for the design of the review. XL, XY and LZ were responsible for revising the draft. KW drafted the manuscript, all authors approved the final draft. All authors

read and approved the final manuscript. Data authentication is not applicable.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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