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The ABC subfamily A transporters: multifaceted players with incipient potentialities in cancer.

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Abstract
Overexpression of ATP-binding cassette (ABC) transporters is a cause of drug resistance in a plethora of tumors. More recent evidence indicates additional contribution of these transporters to other processes, such as tumor cell dissemination and metastasis, thereby extending their possible roles in tumor progression. While the role of some ABC transporters, such as ABCB1, ABCC1 and ABCG2, in multidrug resistance is well documented, the mechanisms by which ABC transporters affect the proliferation, differentiation, migration and invasion of cancer cells are still poorly defined and are frequently controversial. This review, summarizes recent advances that highlight the role of subfamily A members in cancer. Emerging evidence highlights the potential value of ABCA members as biomarkers of risk and response in different tumors, but information is disperse and very little is known about their possible mechanisms of action. The only clear evidence is that ABCA members are involved in lipid metabolism and homeostasis. In particular, the relationship between ABCA1 and cholesterol is becoming evident in different fields of biology, including cancer. In parallel, emerging findings indicate that cholesterol, the main component of cell membranes, can influence many physiological and pathological processes, including cell migration, cancer progression and metastasis. This review aims to link the dispersed knowledge regarding the relationship of ABCA members with lipid metabolism and cancer in an effort to stimulate and guide readers to areas that the writers consider to have significant impact and relevant potentialities.

Key words: ABCA transporters, cancer biology, metastasis, drug resistance, cholesterol homeostasis

1. Introduction

Metastasis and drug resistance are two major leading causes of death in cancer patients. The development of resistance to conventional and targeted therapies may lead to cells characterized by a high level of malignancy that are capable of colonizing and proliferating in distal organs. Extensive studies have been conducted to understand the biochemical, genetic and epigenetic mechanisms that are responsible for drug resistance, with the goal of eventually defining strategies

to overcome such challenges. Resistance-mediating factors may be present in tumor tissues prior to treatment (intrinsic resistance) or may develop after the drug treatment of tumors that are initially responsive (acquired resistance) (for a review, see [1, 2]). Tumor heterogeneity, however, renders this distinction a rather academic issue because acquired resistance may be caused by the presence of a rare, resistant, more aggressive subpopulation of cells in the original tumor that can be selected during treatments. In addition to tumor cell intrinsic mechanisms, the tumor microenvironment may also protect cancer cells from cytotoxic agents, thus allowing them to develop acquired resistance and leading to disease relapse (for a review, see [3, 4]). In this complex scenario, multiple studies have convergently highlighted the role of the ATP-binding cassette (ABC) transporters. The past three decades have given rise to a boom in studies documenting the contribution of some ABC transporters, particularly ABCB1, ABCC1 and ABCG2, to multidrug resistance. These members act as cell membrane pumps that are capable of extruding drugs from cancer cells, and consequently, overexpression of these transporters has been widely associated with adverse patient outcomes in many different tumors. A plethora of data and reviews is available and it is beyond the purpose of this review to offer an overview of the role of these conventional ABC transporters in resistance (please refer to [5, 6] for the most recent updates in the field). More recently, extensive evidence indicates that several ABC transporters also play roles in the regulation of cancer cell proliferation, differentiation, migration and invasion (for a review, see [6, 7]); are responsible for intracellular peptide transport, including major histocompatibility complex class I antigen presentation; and are emerging as an essential part of the signaling network that orchestrates the activation and polarization of macrophages and affects the fate of myeloid progenitors [8-12]. Thus, the importance of these molecules in cancer is extending beyond their role in drug resistance. However, while the general process by which chemotherapeutic and some targeted agents are exported out of resistant cells is well defined, the contribution of ABC transporters to these biological processes is much less delineated and is frequently controversial.

In this review, we focus on the role of the ABC transporters of subfamily A and their association with tumor progression. Several ABCA members have been found to regulate cellular lipid trafficking and cholesterol homeostasis, and their dysregulation is the cause of severe disorders associated with lipid transport (see below for more details). However, only limited and, sometimes controversial information is available regarding their role in cancer. This review summarizes the clinical and mechanistic connections between the ABC transporters of subfamily A and tumor progression that have emerged from dispersed literature. Particularly, we report the studies on the role of these transporters in cholesterol homeostasis and membrane lipid trafficking, and we relate these findings to the incipient evidence of the involvement of cholesterol in the regulation of crucial cellular processes, such as intra- and intercellular signaling and communications, as well as cell migration and proliferation. We highlight not only the numerous critical issues in the field but also point out the areas of potential interest and those that are in need of further studies.

2. The A subfamily of ABC transporters

The ABC transporters are essential proteins found across all living organisms [13] that harness the energy of ATP hydrolysis to drive the import of nutrients inside prokaryotic and eukaryotic cells [14, 15] or the export of toxic compounds or essential lipids across prokaryotic and eukaryotic membranes (for a review, see [16]). Encoded by 48 genes, the ABC transporters are subdivided into

seven subfamilies, identified by the letters A through G. Typically, the structure of a full ABC transporter consists of two transmembrane domains (TMDs) and two nucleotide-binding domains (NBDs) that bind their substrate and ATP, respectively. In particular, the hydrophobic TMDs form a pore in the membrane and dictate which ligands can be recognized, whereas the NBDs are the powerhouse of the ABC transporters, carrying out ATP binding and hydrolysis. Located in both the plasma membrane and the membranes of intracellular compartments, ABC transporters utilize the alternating access mechanism, an inward- to outward-facing conformation, to transport often against the concentration gradient, their substrates which include xenobiotics, metabolites and signaling molecules (for more details, see [16, 17]).

Figure 1 shows a schematic representation of the typical ABC subfamily A transporter structure. The members of this subfamily are characterized by a special structural feature of two symmetrical halves and, between them, a long cytoplasmic regulatory domain interrupted by a stretch of highly hydrophobic residues that dips into the membrane [18]. In addition, these transporters contain two large extracellular domains (ECDs) between the first and second membrane-spanning segments of each TMD [19].

The ABCA subfamily of transporters consists of 12 members denoted ABCA1 to ABCA13 (originally, a nonfunctional human gene was erroneously named *ABCA11*), which are divided into two subgroups according to their chromosomal location and phylogenetic analysis. One subgroup is formed by five genes, *ABCA5, A6, A8, A9,* and *A10,* which are located in a cluster on human chromosome 17, while the other includes members (*ABCA1, A2, A3, A4, A7, A12* and *A13*) that map to six different chromosomes. In addition, all genes included in the clusters are significantly shorter than the other members of the subfamily (38-40 exons instead of 50-52) lacking the C motif in their structure [20].

Mutations in ABCA transporters have been identified as the cause of severe disorders associated with impaired lipid transport, such as harlequin ichthyosis, a disease arising from defective lipid transport in the skin [21] caused by loss of ABCA12 function [22]; Stargardt disease the most prevalent inherited macular dystrophy [23] associated with disease-causing sequence variants in the gene ABCA4 [24]; and Tangier disease, which is a recessive disorder caused by loss-of-function variants in the ABCA1 gene resulting in reduced cholesterol efflux from cells and lack of circulating high-density lipoprotein (HDL) [25]. By disrupting the outflow of free cholesterol, mutations of the ABCA1 gene also cause a toxic accumulation of cholesteryl esters within cells. In ABCA1 knockout mice, the absence of ABCA1 in the pancreatic β-cell indeed lead to accumulation of cellular cholesterol, which in turn, resulted in impairment of β-cell function based on defective insulin exocytosis [26, 27]. The translatability of this finding was confirmed in humans, in which mutations in ABCA1 [28] result in significantly lower plasma HDL and have a role in metabolic syndrome and diabetes [27]. In addition, functional and genetic association studies suggest either a putative preventive function (e.g., ABCA1, ABCA5 and ABCA7) or a predisposing role (e.g., ABCA2) in Alzheimer's disease pathophysiology, and this connotation may be again related with cellular cholesterol trafficking (for a review, see [29]).
Furthermore, allelic variants of ABCA7, a transporter that mediates the release of cellular cholesterol and phospholipids to form HDL [30], were found to modulate susceptibility to Sjögren's

syndrome, one of the more common inflammatory autoimmune rheumatologically diseases that affect exocrine glands [31].
These genetic associations suggest the contribution of ABCA transporters in the maintenance of lipid homeostasis and indeed several studies in different cell types have confirmed that the best-defined physiological functions of these molecules are related to their ability to transport lipids and cholesterol (please refer to **Table 1** for a summary).

Figure 2 shows both the mRNA and protein expression levels of ABCA transporters in organs and normal tissues. Notably, while ABCA1, ABCA3, ABCA5 and ABCA9 are detected almost ubiquitously in most human body organs and tissues, the expression of other transporters, such as ABCA2 and ABCA7 is substantially confined to the brain and immune system. Whether this different distribution reflects different functions remains difficult to determine. With few exceptions, the mRNA expression of ABCA transporters was found to be different than the protein expression. In general, their protein expression level is higher than their mRNA expression level (e.g., ABCA1 in the lung and stomach), indicating that many members of ABC trasporters have multiple levels of regulation, including posttranscriptional mechanisms.

3. Regulation of ABCA transporter expression

In addition to promoter hypermethylation, which has been described as a regulatory mechanism of ABCA1 expression [32], several studies have indicated that the expression of ABCA transporters is regulated by transcription factors, including the liver X receptor (LXR) and sterol regulatory element-binding protein2 (SREBP2), which regulate many genes involved in cholesterol biosynthesis pathway [33, 34]. LXR acts as a sensor of cholesterol homeostasis in a heterodimeric complex with retinoid X receptor (RXR). Under high-cholesterol/high-oxysterol conditions, LXR interacts with RXR in the nucleus, inducing *ABCA1* transcription [35, 36] (**Figure 3A**). Under low-cholesterol conditions or after exposure to cholesterol-lowering drugs, such as statins and zoledronic acid, the mRNA expression of ABCA members is mainly regulated by SREBP2 (**Figure 3B**). In particular, SREBP2 negatively influences *ABCA1* expression [37, 38], while *ABCA7* mRNA expression is upregulated by lowering cholesterol through SREBP2 [39]. The regulatory function of LXR extends beyond the transcriptional level. In fact, in cells with normal cholesterol levels, LXRβ can interact directly with ABCA1 C-terminal residues 2247-2251, blocking ATP binding to the NBD. In contrast, in cells with high levels of cholesterol and oxysterols, LXRβ dissociates from ABCA1, thus freeing the transporter for Apolipoprotein A1 (ApoA1) binding, with a subsequent increase in free cholesterol efflux [40].

Posttranscriptional regulation of ABCA members via miRNAs and RNA-binding proteins (RBPs) has also been described. In particular, the expression of ABCA1 was found to be inhibited by miR-33, miR-96, miR-27, miR-144, miR-145 and miR-148 in different human cells [41-44]. In contrast, the RBP human antigen R has been reported to bind to the 3'-UTR of the *ABCA1* sequence and to increase its expression by enhancing the protein translation of the transporter [45]. In melanoma cells, downregulation of ABCA2 and ABCA5 was described as a consequence of the expression of the oncosuppressor miR-205 after chemotherapy [46].

In addition, a complex regulatory network involving the long noncoding RNAs NEAT1 and MALAT1 as well as miR-335-3p has been recently described to affect the expression of ABCA3 in acute lymphoblastic leukemia. In particular, MALAT1 and NEAT1 inhibit the expression of miR-335-3p, which negatively affects ABCA3 expression, thereby contributing to the development of chemoresistance [47].

Posttranslational regulation of ABCA transporter expression is also important for modulating the activity of these transporters. For example, ABCA1 may bind ApoA1, the main component of HDL (see below) and the transporter is protected from calpain-mediated proteolysis when bound to ApoA1 [48-50]. In contrast, Caveolin-1 binds to ABCA1 and enhances its degradation by increasing movement into the interior of the cell [51].
The activity of ABCA1 is also sensitive to other factors. In addition to stabilizing the transporter, the binding of ApoA1 to ABCA1 activates multiple cellular signaling pathways, such as the Janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3), protein kinase A, Rho family G protein CDC42, protein kinase C and ERK pathways, which in turn regulate the activity of the transporter [52-55].
Furthermore, adenosine, acting through the A2A and A3 receptors, may upregulate ABCA1 by cAMO-PKA-CREB activation and STAT inhibition, respectively. Notably, methotrexate results in increased levels of adenosine, thereby promoting ABCA1 expression [56].

Interactions among members of the ABCA subfamily to regulate their functions have also been described. For example, ABCA12 was shown to form a complex with ABCA1 and LXRβ, which maintains ABCA1 stability but inactivity; in the presence of an LXRβ ligand, ABCA12 dissociates from ABCA1, enabling its functionality on the plasma membrane.

Additionally, an increased cellular cholesterol content inhibits the ubiquitination and subsequent proteasomal degradation of ABCA1, thereby increasing the protein expression and free cholesterol efflux [57]. Although the specific mechanism by which cholesterol controls the ubiquitination of ABCA1 is not known, a role for the cholesterol-sensitive E3 ligase has been suggested [58] indicating the fine-tuned modulation of ABCA1 activity in response to fluctuations in cell cholesterol levels.

4. Impact of ABCA transporters in cancer biology

4.1. Functions

The roles of ABC transporters in cancer are strictly related to their capabilities to export drugs or toxins (canonical function of detoxification) or to extrude numerous signaling molecules, including cholesterol and other lipids that may impact the biological processes affecting cancer cell proliferation, survival and migration at different levels and through different mechanisms. A scheme depicting the major substrates of ABC transporters, based on information derived from the UniProt database (www.uniprot.org, [59]) and the literature, is shown **in Figure 4** (for further details, see [7, 10, 60, 61]).

As mentioned above, many members of the ABCA subfamily of transporters are thought to play important roles in lipid transport and trafficking, including the maintenance of plasma HDL and cholesterol levels and the regulation of efflux from cells [62, 63]. For some ABCA transporters the substrates are well defined: ABCA1, ABCA3, and ABCA7 export cholesterol and phospholipids [30, 64, 65]. In particular, ABCA1 and ABCA7 actively export phosphatidylcholine, phosphatidylserine and sphingomyelin from the cytoplasmic to the exocytoplasmic leaflet of membranes [66] and ABCA3 is required for transporting mostly saturated phosphatidylcholine to the lung surfactant membranes filling the lamellar bodies in lung epithelial type II cells [67]. In addition, ABCA12 is a transporter of glucosylceramide [68], while ABCA4 imports N-retinylidene-phosphatidylethanolamine [15]. ABCA2 has a well-described role in cholesterol transport while its involvement in phosphatidylethanolamine, phosphatidylserine and sphingomyelin was only suggested [69, 70]. For the other ABCA transporters the data reported thus far are scarce. For example, ABCA5 and ABCA8 were described to stimulate cholesterol efflux in neurons [71] or in fibroblasts [72], but definitive evidence is lacking.
In general, the field is dynamic, novel information are accumulating and the overall picture is made even more complicated by the fact that ABCA members besides being described on the surface cell membrane, have also been reported on the reticulum and Golgi apparatus, mitochondria and nuclear membranes (**Figure 4**). Undoubtedly, ABCA transporters are best associated with cholesterol, which is an important component of cellular membranes, regulating membrane fluidity and functionality.

Membrane cholesterol offers structural support, strongly affects the stability and functionality of growth factor receptors, integrins and cell surface glycoproteins and regulates endocytosis, intracellular signaling pathway activation, cell adhesion and motility [73]. For example, the ligand-binding ability of CD44 to hyaluronan is governed by its cholesterol-dependent localization to cell membrane microdomains [74], while other studies have indicated that growth factor receptor (i.e., IGF1R, EGFR and HER2) signaling events are dependent on the cholesterol content of lipid rafts [75-77]. In addition, cholesterol can directly bind and activate specific proteins, such as the oncogenic smoothened protein. Both cholesterol and smoothened can work in concert in Hedgehog signaling, a pathway that plays a critical role in embryonic development and tumorigenesis [78, 79]. Therefore, cholesterol trafficking and homeostasis in tumor cells may strongly impact tumorigenesis and tumor progression.
Different mechanisms participate in the regulation of intracellular cholesterol levels, including *de novo* cholesterol synthesis (endogenous source), cholesterol export to the extracellular milieu, cholesterol metabolic conversion to cholesteryl ester, oxysterols, bile acids, and steroid hormones and/or the uptake of cholesterol-containing lipoprotein particles from the extracellular milieu (exogenous source) (for a review, see [80]). Deregulations along the cholesterol metabolic pathway may favor the accumulation of metabolites with tumor-promoting activity. On the other side, the aberrant accumulation of unesterified cholesterol is toxic to cells, thereby supporting the need for tight regulation of its intracellular levels. Most mammalian cells cannot catabolize cholesterol by breaking down the sterol backbone and converting it into bile acids, a function restricted to liver cells. Therefore, the tight regulation of its intracellular levels is crucial for the cells. ABCA1, and to a lesser extent, ABCA7 [81], ABCA8 [72] and ABCA12 [82], have been described to play a role in the efflux of cholesterol. In contrast, ABCA2 attenuates cholesterol efflux through a poorly characterized pathway [65], is involved in the uptake of low-density lipoprotein (LDL), thereby

favoring the increase of cholesterol inside the cells, and participates in intracellular cholesterol trafficking [69]. The importance of the ABCA1 transporter for cholesterol efflux has been demonstrated in many studies, particularly in macrophages [83, 84], and is related to its ability to promote cholesterol efflux from cells to extracellular acceptors, such as ApoA1, to generate HDL particles. HDL is a key lipoprotein that transports excess cholesterol from peripheral tissues to the liver where cholesterol is converted to bile acids for excretion [85]. This cholesterol transport system is often referred to as "reverse cholesterol transport" (for more details see [86, 87]). A simplified scheme is shown in **Figure 5.**

Alterations in cholesterol metabolism and homeostasis may also alter the functions of immune cells and profoundly affect the crosstalk between tumor cells and the tumor immune microenvironment (for a review, see [88]). The role of ABCA members in this field has just begun to emerge. For example, ABCA1 may affect macrophage activation. Specifically, depletion of membrane cholesterol in macrophages, which can be induced by tumor cells, increases PI3K activity and mTORC2-mediated AKT phosphorylation, pathways previously linked with IL-4-mediated macrophage activation in different contexts [12, 89] and with the maintenance of the protumor functions of tumor-associated macrophages (TAMs) [90, 91]. Notably, genetic deletion of ABCA transporters involved in cholesterol efflux, such as ABCA1, reverses the tumor-promoting functions of TAMs and reduces tumor progression, pointing to a potentially novel anti-tumor therapeutic strategy [12].

In addition to cholesterol transport, ABCA members have been linked to the release of other lipids, including intermediate sterols with extra methyl groups [64], phospholipids and sphingolipids [66]. They are all involved in crucial biological processes, such as cell survival, death, inflammation and immune signaling. It is highly plausible that ABCA members, at least ABCA1, ABCA2, ABCA3 and ABCA7 (see above), contribute to the regulation of plasma membrane lipid composition and functionality through their lipid transport activity. However, how the lipid composition of the plasma membrane is modulated by ABCA transporters and whether this modulation affects plasma membrane functionality as well as associated signals are important unresolved issues.

Notably, some ABCA transporters, particularly ABCA2, ABCA3, ABCA5 and ABCA13, are also present in the membranes of: **i.** lysosomes, wherein they can determine drug resistance by storing the drugs into lysosomal compartement and possibly promoting drug extrusion from the cell; **ii.** exosomes, which are nanosized membraned vesicles that mediate cell-cell communication by transferring messenger mRNAs, miRNAs, DNA and proteins (for a review, see [92]). Exosomes can mediate tumor progression and therapeutic resistance in recipient cells by distributing nucleic acids and proteins that may increase cell survival and DNA repair in tumor cells or promote cell migration and the establishment of distant metastatic niches (for a review, see [93]). In addition to their effects on recipient cells, exosomes may increase the therapeutic resistance of donor cells by reducing intracellular drug concentrations and by disposing of pro-apoptotic proteins such as caspases [92]. To date, some evidence indicates a role for ABCA2, ABCA3 and ABCA13 in resistance to conventional chemotherapeutics, such as doxorubicin, methotrexate and cisplatin, and/or to targeted agents, such as imatinib, paclitaxel, and mitoxantrone [94-103].

4.2. General molecular mechanisms of actions

Most of the available information is related to ABCA1 and its involvement in the regulation of cholesterol homeostasis and levels in macrophages. As mentioned, ABCA1 exports free (unesterified) cholesterol and phospholipids from the plasma membrane to ApoA1 [66]. The molecular mechanism by which ABCA1 mediates the cellular binding of ApoA1 and the nascent HDL assembly is not well understood. Several pieces of evidence indicate that ApoA1 interacts directly with a specific conformation of the ABCA1 extracellular domain during the initial step of HDL formation, while others support the role of the floppase activity of ABCA1, which may "flop" both phosphatidylserine and/or phosphatidylinositol (4,5) bis-phosphate (PIP2) to the cell surface in order to maximize cholesterol efflux [104, 105]. In general, two models have been proposed to explain nascent HDL assembly: in the direct loading model, ApoA1 acquires lipids directly from ABCA1 while it is bound to the transporter, whereas in the indirect model, ApoA1 acquires lipids from the specific membrane domains created by the phospholipid translocation activity of ABCA1 (for a schematic representation see [105]). For the other ABCA transporters, that have been reported to contribute to cholesterol/lipid trafficking and efflux, the mechanisms of action are even less defined [72, 106-109]. For example, despite having the highest homology with ABCA1 (54%), ABCA7 exhibits distinct, very high expression level in myelolymphatic tissues, and different mechanism of action with respect to ABCA1. In macrophages, ABCA7 functions by stimulating their phagocytic capacity both *in vivo* and *in vitro* rather than by mediating HDL biogenesis [39, 110, 111]. In T cells, both ABCA1 and ABCA7 were reported to modulate T cell development and function, ABCA1 acts in cooperation with ApoA1 through the regulation of cellular cholesterol content [112], while ABCA7 acts by altering the content and distribution of lipid rafts [113] through the export of phospholipids from the inner to the outer leaflet of the plasma membrane.

The floppase activity of some ABCA transporters (demonstrated for ABCA1, ABCA7 and, thus far, hypothesized for ABCA3 and ABCA12) may also have an important impact on the regulation of intracellular signaling. For example, any modulation in the levels or activity of ABCA1 may vary the quantity of phosphatidylinositol phosphates (PIPs), particularly PIP2, in the inner leaflet of the plasma membrane, wherein they can act as scaffolds for the recruitment of proteins with a specific PIP binding domain. PIP2 is linked to a diverse set of signaling functions, such as actin polymerization and cytoskeletal dynamics [114] and the downstream protein kinase B (PKB)/AKT signaling pathway, which is important for cell growth, survival, proliferation, and motility and provides crosstalk between different signaling pathways. In addition, increased cellular PIP2 levels lead to increased rates of receptor-mediated endocytosis [115, 116], providing another level of intracellular signaling regulation. Therefore, as a consequence of ABCA1 PIP2 floppase activity, AKT phosphorylation or endocytic vesicle formation may decrease [117, 118] and tumor cell behavior may be significantly altered. Moreover, the ABCA1-mediated "flop" of PIP2 out of the inner leaflet was found to impact immune cells. Kagan JC and Medzhitov R demonstrated that the PIP2-binding adaptor TIRAP recruits MyD88 and Toll-like receptors (TLRs) to the plasma membrane to initiate TLR signaling [119] and that the "flop" of PIP2 may decrease TLR trafficking to the plasma membrane, thereby influencing the expression of inflammatory genes in response to TLR ligands.

Finally, several ABCA subfamily transporters, such as ABCA2 and ABCA3, are also involved in the intracellular trafficking of LDL, [65, 120]. Indeed, apart from hepatic and central nervous

system cells (which are efficient in synthesizing cholesterol *de novo*), cells acquire cholesterol mainly via the receptor-mediated uptake of LDL particles. After binding to its receptor (LDL-R) on the plasma membrane, LDL is internalized by clathrin-mediated endocytosis. In the acidic pH environment of endosomes, LDL dissociates from its receptor, which is recycled to the plasma membrane, whereas LDL cholesterol is delivered to late endosomes/lysosomes. The process by which free cholesterol is generated in these compartments and transferred to the plasma membrane remains poorly understood (for details, see [121]). The ABCA2 and ABCA3 proteins are predominantly localized in late endosomes/lysosomes and are thought to be directly involved in the intracellular trafficking of LDL. ABCA2 overexpression induces a phenotype similar to that of cholesterol-depleted cells by sequestering unesterified cholesterol into endolysosomal compartments [69], while ABCA3 participates in a final step of LDL processing and intracellular cholesterol trafficking [120], functioning as a lipid pump for the translocation of phospholipids and cholesterol into lamellar bodies [122]. As a consequence of its activity in the endolysosomal compartmentalization of sterols ABCA2 directly linked to cancer drug resistance *in vitro* [94] and to tumor cell migration and metastasis [123], and it was also shown to play roles in macrophage lipid metabolism and neural development. However, the mechanistic relationship between ABCA2 and these biological processes is still poorly defined (for a review, see [65]), and there are no clinical data demonstrating a correlation between ABCA2 expression and cancer, supporting the need for additional studies.

4.3. Effects of ABCA expression on tumor progression: evidence from experimental and clinical data

In general, high-level expression of *ABCA* genes is associated with drug resistance and worse patient outcomes in a variety of cancers. The overall scenario is complicated by the fact that the available information is heterogeneous and variable in different tumors, indicating controversial and complex relationships that may be influenced by the disparate cellular context. This review aims to render this scattered information more easily available for the readers, who may refer to specific studies when appropriate.

At the experimental level, the expression of ABCA2, ABCA3, ABCA5, ABCA12 and ABCA13 was mainly associated with drug resistance and malignant progression in a variety of tumors including neuroblastoma, acute lymphoblastic leukemia, and prostate, lung, pancreatic and renal cancers [94, 103, 124-128]. However, the specific roles of these ABCA transporters in tumors are multifaceted, and their associations with tumor malignancy are more complex than those reported for the conventional ABC members that mediate multidrug resistance by acting as drug pumps. Particularly, ABCA3 expression defines a class of cancer stem cells with inherently high resistance to chemotherapeutic agents [125] and ABCA5 was found to be associated with tumor stemness and metastatic propensity in osteosarcoma [129]. Furthemore, ABCA2 deficiency inhibits prostate tumor metastasis and decreases the chemotactic potential of cells, conceivably due to altered sphingolipid metabolism [123]. Most of the available information regards ABCA1. However, also in this case, it is still not possible to define a general relationship since the expression of ABCA1 shows either a positive or negative relationship with tumor aggressiveness depending on the type of cancer tumor. Several studies support an oncogenic role of ABCA1. For example, in prostate cancer and in ovarian cancer, cells expressing high levels of ABCA1 exhibited enhanced growth and

migration capacity [130-132] and overexpression of ABCA1 in colorectal cancer led to epithelial to-mesenchymal transition and increased cell invasion stabilizing Caveolin-1 [133]. In triple-negative breast cancer, overexpression of ABCA1 significantly blocked doxorubicin therapy-induced cell membrane polarization and subsequently prevented tumor cell death [134]. However, other reports have indicated an opposite tumor suppressive role of ABCA1. In fact, overexpression of ABCA1 was shown to reduce the formation of tumors derived from xenografts of human cancer cell lines [135]. In addition, in their recently published work, Moon SH and coworkers [136] described how p53 blocked the mevalonate pathway, which is responsible for the biosynthesis of cholesterol and nonsterol isoprenoids and is implicated in multiple aspects of tumorigenesis (reviewed in [137]) by transcriptionally inducing the ABCA1 gene. Similar to p53 loss, ablation of ABCA1 promotes murine liver tumorigenesis, supporting its role in tumor suppression.

At the clinical level, the prognostic impact of the ABCA transporters has been described in different tumor tissues, again revealing conflicting indications. Overall, the literature contains controversial data, likely due to the limited number of studies available, which were performed in a small series of patients, or to the different technologies used. Here, we provide an overview of the major studies on different cancers, in hopes of guiding readers to the appropriate information in which they are interested.

In **ovarian carcinoma**, high expression levels of *ABCA1, ABCA2, ABCA5, ABCA6, ABCA7, ABCA9* and *ABCA13* in primary tumors were statistically and independently associated with adverse outcomes [132, 138, 139] while *ABCA4* mRNA expression was significantly related to a better response to chemotherapy at diagnosis [139]. For ABCA1, this association was further confirmed by immunohistochemical staining and functional studies [132]. *ABCA8* was significantly overexpressed in chemoresistant variants of the A2780 ovarian cancer cell line [140], and analysis of its expression on the basis of The Cancer Genome Atlas (TCGA) clinical data (http://cbioportal.org; [141]) indicated that high *ABCA8* levels predicted a poor prognosis [142].

In **breast cancer,** the gene expression of *ABCA2, ABCA3, ABCA7, ABCA12* and *ABCA13* was upregulated, while the expression of *ABCA5, ABCA6, ABCA8, ABCA9* and *ABCA10* was significantly downregulated in tumors compared to that in normal tissues [143, 144]. However, decreased expression of ABCA3 was indicated to be an independent and adverse risk factor for tumor recurrence [145]. The expression of *ABCA1* and *ABCA12* was significantly increased in the tumors of patients with an incomplete pathological response to neoadjuvant chemotherapy and residual disease compared to that in tumors with a complete pathological response [146].

In **prostate cancer,** the gene expression of *ABCA1, ABCA8* and *ABCA11* was downregulated in tumors compared to that in noncancerous prostate tissues [32, 147], while *ABCA5* was upregulated [148]. Among prostate tumors, *ABCA8* showed high expression in TMPRSS2-ERG-positive tumors but was suppressed in fusion-negative tumors [147], while the *ABCA1* expression levels were inversely correlated with the Gleason grade [32]. At the protein level, ABCA5 was overexpressed in high-grade prostatic intraepithelial neoplasia tissue and in the urine of patients with high-grade tumors but not in those with benign prostatic hyperplasia or in the stroma. The detection of ABCA5 in the urine was therefore proposed as a specific diagnostic marker [149]. However, further studies are needed to validate this observation.

In **colorectal cancer**, *ABCA12* and *ABCA8* were the most upregulated genes, and *ABCA9* was the most downregulated gene [144]. Genetic variants (SNP polymorphisms) of *ABCA9* were associated with reduced survival in colorectal cancer patients who received oxaliplatin-based chemotherapy [150]. *ABCA13* overexpression is associated with improved outcomes in colorectal cancer [151].

Among **hematological tumors**, distinct overexpression of *ABCA2*, *ABCA3*, *ABCB2*, and *ABCC10* was observed in the bone marrow of children with acute myeloid leukemia compared with that in healthy bone marrow [152]. The expression of *ABCA3* was higher in the patients with poor responses to treatments and was induced *in vitro* after cell exposure to conventional chemotherapeutic agents, indicating a causative role in drug resistance [152]. Accordingly, ABCA3 confers multidrug resistance toward a broad spectrum of cytostatic agents enclosing imatinib in leukemia cells by lysosomal drug sequestration [96, 97, 100], while in B-cell lymphomas it modulates the release of exosomes carrying the CD20 antigen. Such exosomes may act as decoy targets upon rituximab exposure, allowing lymphoma cells to escape from humoral immunotherapy [95]. In acute lymphoblastic leukemia, both *ABCA2* and *ABCA3* were correlated with poor prognosis [153].

More sporadic data are available for **other tumors**. ABCA13 overexpression was associated with poor prognosis in renal cell carcinoma [103] and gastric adenocarcinoma [154]. The expression of ABCA13 elicits stem-like phenotypes of tumor cells and increases the risk of metastasis [103]. In addition, ABCA13 overexpression was associated with decreased progression-free survival in glioblastoma patients treated with radiation therapy and temozolomide [155].

Notably, in sharp contrast with the general observation in the majority of tumors, overexpression of *ABCA6* and *ABCA7* at diagnosis was associated with a better prognosis in two independent cohorts of patients with **Ewing sarcoma** [156].

Overall, experimental and clinical data highlight a role of ABCA subfamily members in promoting or suppressing tumor cell aggressiveness. These dualities likely depend on the substrates of these transporters and on their differential expression in different cellular contexts. More extensive studies are certainly required before these molecules can be considered as validated biomarkers of risk and responses, but the data obtained thus far support the investment. In particular, it would be important to clarify the interactions between at least some of the ABCA members and cholesterol, whose role in tumors was observed approximately one century ago [157-159], and is now recognized as a common feature of the metabolic reprogramming in cancer cells [160].

5. Cholesterol and its therapeutic implications in cancer

The gene expression profiles and underlying gene regulatory networks of different tumors revealed the importance of lipid metabolism for cellular transformation and the association of cancer with other metabolic diseases. Tumors share a common phenotype of uncontrolled cell proliferation and must efficiently generate energy to expand and disseminate. In particular, highly proliferative cancer cells show a strong avidity for lipids and cholesterol, which they satisfy by either increasing their uptake of exogenous lipids and lipoproteins or overactivating endogenous synthesis through

lipogenesis and cholesterol synthesis [161]. In normal cells, cholesterol synthesis is tightly regulated at the level of mevalonic acid production; however, this feedback mechanism is lost in malignancy and dysregulated cholesterol synthesis is frequently found in various cancer cell types [160]. Multiple mechanisms promoting deregulation of cholesterol homeostasis have been related to cancer (for a review, see [162-164]). For example, the levels of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme in the mevalonate and cholesterol synthesis pathway, and proteins involved in LDL uptake, such as LDL-R, are increased in proliferating cancer cells, resulting in increased cholesterol content and consumption. Consistent with these findings, activation of SREBPs and/or upregulation of SREBP target genes have been observed in glioblastoma [165], prostate cancer [166], breast cancer [167], and melanoma [168], and proteins involved in cholesterol efflux, such as ABCA1, were found to be downregulated. These events are frequently associated with poor prognosis/survival [32, 169, 170]. In addition, cholesterol is a precursor for estrogens and androgens, hormones involved in modulating cell proliferation, migration, invasion and apoptosis in different cancers (for a review, see [164]). Therefore, affecting cholesterol trafficking and homeostasis may be a promising therapeutic approach in cancer.

The inhibition of *de novo* cholesterol biosynthesis through the mevalonate pathway using statins or amino-bisphosphonates has received considerable attention in recent years (for a review, see [164, 171]). At the preclinical level, statins suppress intracellular cholesterol synthesis through the inhibition of HMG-CoA reductase and exert pro-apoptotic, anti-angiogenic, and immunomodulatory effects. Consequently, the growth of a variety of cancer cell types, including breast, colorectal, lung, pancreatic, and prostate carcinoma, melanoma, and acute myeloid leukemia cells was prevented (for a review, see [172-174]). In addition, statins were reported to synergize with certain chemotherapeutic agents, such as doxorubicin, and to decrease the development of multidrug resistance *in vitro* [175-177]. In contrast, the results at the clinical level are variable, with some studies suggesting prolonged survival and others reporting no benefit. The epidemiological evidence is also controversial depending on the tumor histotype and the statin type (for a review, see [178]). Similar controversial evidence is available for other cholesterol-lowering drugs, such as inhibitors of farnesyl diphosphate synthase, another key enzyme in the mevalonate pathway. Zoledronic acid is a bisphosphonate currently approved for the treatment of bone metastases in patients with breast cancer and other solid tumors [179]. Preclinical evidence suggests that zoledronic acid exhibits potentially relevant anticancer activities by affecting tumor cells and/or the surrounding microenvironment and immune responses. In fact, this drug was found to render the bone marrow a less hospitable microenvironment for tumor cell colonization [180-182] and to stimulate immune responses either via the activation of γδT cells [183] or by triggering the switch of the TAM phenotype from the pro-tumoral M2 to the tumoricidal M1 phenotype [184]. However, data from randomized trials indicate that despite some benefits, zoledronic acid treatment may also be associated with an increased risk of treatment failure and worse overall survival [185-187]. A possible explanation for these findings may be that cancer cells activate compensatory mechanisms different from increased *de novo* synthesis to maintain high levels of free cholesterol, such as deregulation of cholesterol uptake, intracellular trafficking and efflux [188, 189]. Since ABCA members may alter the levels and localization of cholesterol inside the cells, the efficacy of cholesterol synthesis inhibitors is likely affected by the expression of these transporters in tumor cells. Further research is needed to verify this hypothesis.

In glioblastoma and prostate cancer, depletion of cholesterol by increased ABCA1 activity favors tumor cell death and suppression of growth [169, 190], indicating a selective vulnerability that may be exploited for therapy. LXR agonists that transactivate ABCA1 and other metabolic genes have antiproliferative effects on certain cancers [191]. In addition, celecoxib has been shown to sensitize tumor cells resistant to the tyrosine kinase inhibitor imatinib at least in part via the inhibition of ABCA2 [192]. Although these preclinical data may support the promising role of ABCA transporters as therapeutic targets, information are still speculative. In addition, it is necessary to consider that neither agonists nor antagonists of transporter function achivied pharmaceutical success despite the tremendous efforts to select specific inhibitors against the major mediators of drug resistance ABCB1 and ABCC1. Some of these agents are merely toxic, causing severe side effects due to their impact on normal cell functions [8], and others induce unwanted drug-drug interactions. A main limitation in the translation of *in vitro* findings to clinical evidence was due to the fact that most studies reporting the accumulation of chematerapeutic agents upon ABC inhibition failed to take into consideration the physiological functions of the transporters in a whole organism and the possible co-expression of many transporters within tumours and neighbouring tissues [193].

In addition to agents affecting ABCA members, new potential therapeutic targets to reduce intracellular cholesterol levels may include inhibitors of cholesterol esterification [194] or agents affecting transporters that regulate cholesterol intake or efflux. Ezetimibe, a drug that inhibits cholesterol absorption by blocking Niemann-Pick C1-Like 1-mediated cholesterol uptake, was demonstrated to exhibit antitumor activity in an *in vivo* murine prostate cancer model by inhibiting tumor angiogenesis [195]. Further investigation is needed to support and extend these promising data in experimental models.

6. Critical issues and perspectives

- Cancer cells have a distinctive plasma membrane lipid composition characterized by the loss of lipid asymmetry, which differs from that of normal cells and allows discrimination between different tumor types, from benign to malignant cancers and from localized to metastatic tumors [196]. By regulating cholesterol and lipid levels, ABCA transporters may have an active role in regulating cancer progression and may be exploited as novel diagnostic/prognostic biomarkers in cancer. Altered lipid composition and loss of lipid asymmetry of cancer cells may indeed result in altered permeability to chemotherapeutic drugs in comparison to the membranes of normal cells.
- Plasma membranes possess cholesterol and sphingolipid-rich lipid raft microdomains and deeper knowledge of which distinct ABCA members may affect the composition and distribution of lipid rafts and the mechanisms by which they mediate these effects is required to better define the value of these transporters as diagnostic and therapeutic mediators in cancer.
- ABCA transporters may alter the functionality of immune cells and the crosstalk between these cells and tumor cells, thus exerting putative profound effects on tumor progression.
- Many clinical studies support the role of ABCA members in the regulation of tumor aggressiveness and indicated these members as putative novel therapeutic targets. However,

despite cholesterol decreases and ABC transporters have been indicated to be very promising drug targets in experimental models, few clinical successes have been obtained thus far in practice by the use of agents reducing cholesterol synthesis or homeostasis, supporting the need for further investigation.

- We still do not know the precise role of cholesterol in cancer or the mechanism by which the cholesterol homeostasis dysregulation functions in tumor development. As previously mentioned, the functions of cholesterol in cells include structural functions as well as the modulation of signaling molecules in membrane rafts. Rafts are transient, membrane microdomains rich in cholesterol, whose formation is driven by lipid–lipid and lipid–protein interactions, and that function as platforms for conducting various cellular functions, such as vesicular trafficking and signal transduction [198]. Cholesterol can indeed affect the localization and signaling of growth factor receptors, integrins and cell surface glycoproteins, playing a central role in cell adhesion and migration. However, the current understanding of the mechanisms that relate cholesterol to lipid raft formation and maintenance remains limited ([199]).

7. Concluding remarks

Understanding the orchestration of this process and clarifying the functional relationship between ABCA members and lipid homeostasis is a challenging but essential task for the development of more effective targeted therapies. Emerging evidence indicates that ABCA transporters have critical implications as biomarkers of risk and response in cancers, while cholesterol-lowering drugs are receiving increased attention in drug repositioning strategies against cancer. This review highlights the possibilities and complex functions of these still poorly studied transporters and supports the need for additional investment and research. This field is highly dynamic, and new insights are required to overcome the current limitations in the efficacy of treatments that interfere with cholesterol or sphingolipid metabolism to provide additional therapeutic options to benefit patients.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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Figure legends

Figure 1. Schematic representation of a typical ABCA transporter structure.
Full-length ABCA transporters are composed of two hydrophobic transmembrane domains (TMD1 and TMD2) and two nucleotide-binding domains (NBD1 and NBD2). ATP binds to each of the NBDs. Members of subfamily A are characterized by two large extracellular domains (ECD1 and ECD2) (with a molecular weight greater than 200 kDa).

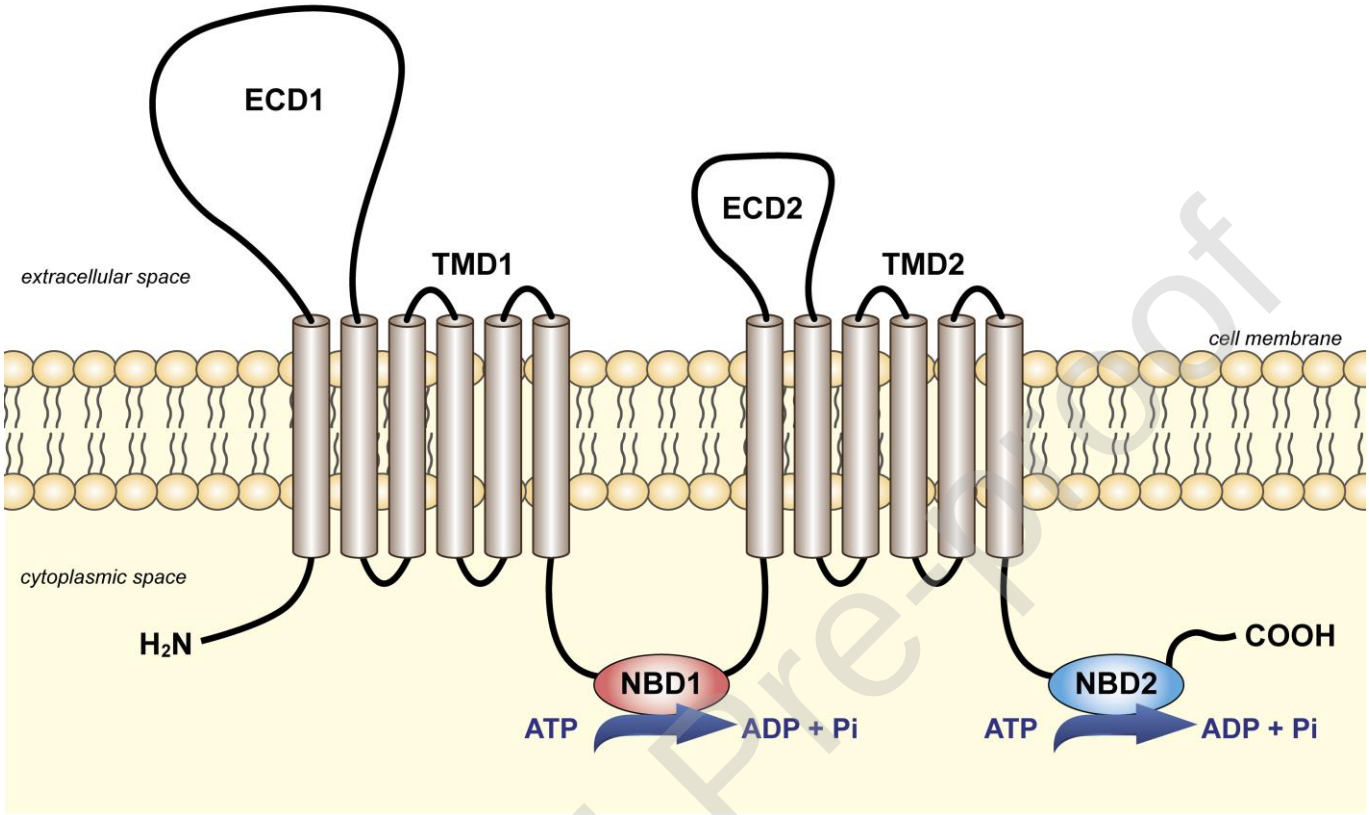
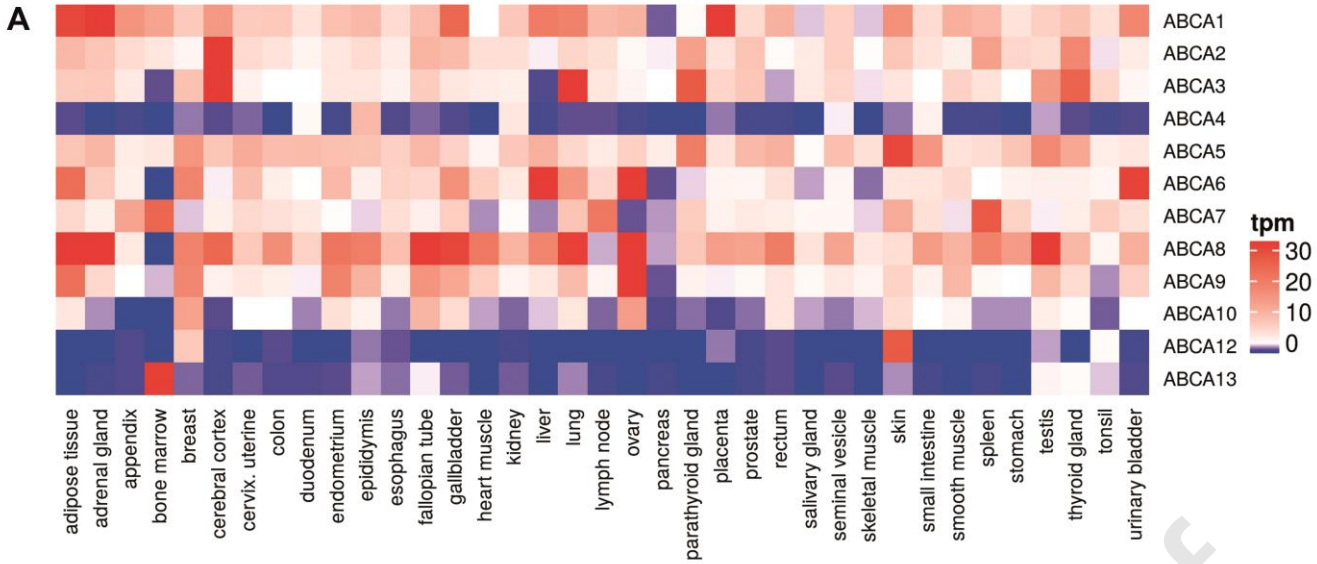


FIGURE 1

Figure 2. ABCA mRNA and protein expression in normal human organs and tissues.
(A) Heatmap of the ABCA gene expression in 37 different normal tissue types. The mRNA expression data are derived from the deep sequencing of RNA (RNA-seq) and are reported as the mean tpm (transcripts per million), corresponding to the mean values of the different individual samples from each tissue. Color-coding is based on the level of expression for each gene as tpm. (B) Schematic representation of the human body and the protein expression of ABCA in normal human organs and tissues. The boxes list the locations with a high level of ABCA expression, according to the Human Protein Atlas. The protein expression data were obtained from 44 normal human tissue types from antibody-based protein profiling using immunohistochemistry. Endocrine tissues include thyroid, parathyroid, adrenal glands and pancreas; gastrointestinal tract tissues include stomach, duodenum, small intestine, colon and rectum; reproductive tissues include breast, cervical uterine, endothelium, fallopian tube, ovary, and the vagina as female tissues and epididymis, prostate, seminal vesicle, and testis as male tissues; bone marrow and immune system include bone marrow, lymph node, tonsil, spleen and appendix. (*Data available from protein atlas version 18.1; www.proteinatlas.org. [200]).*



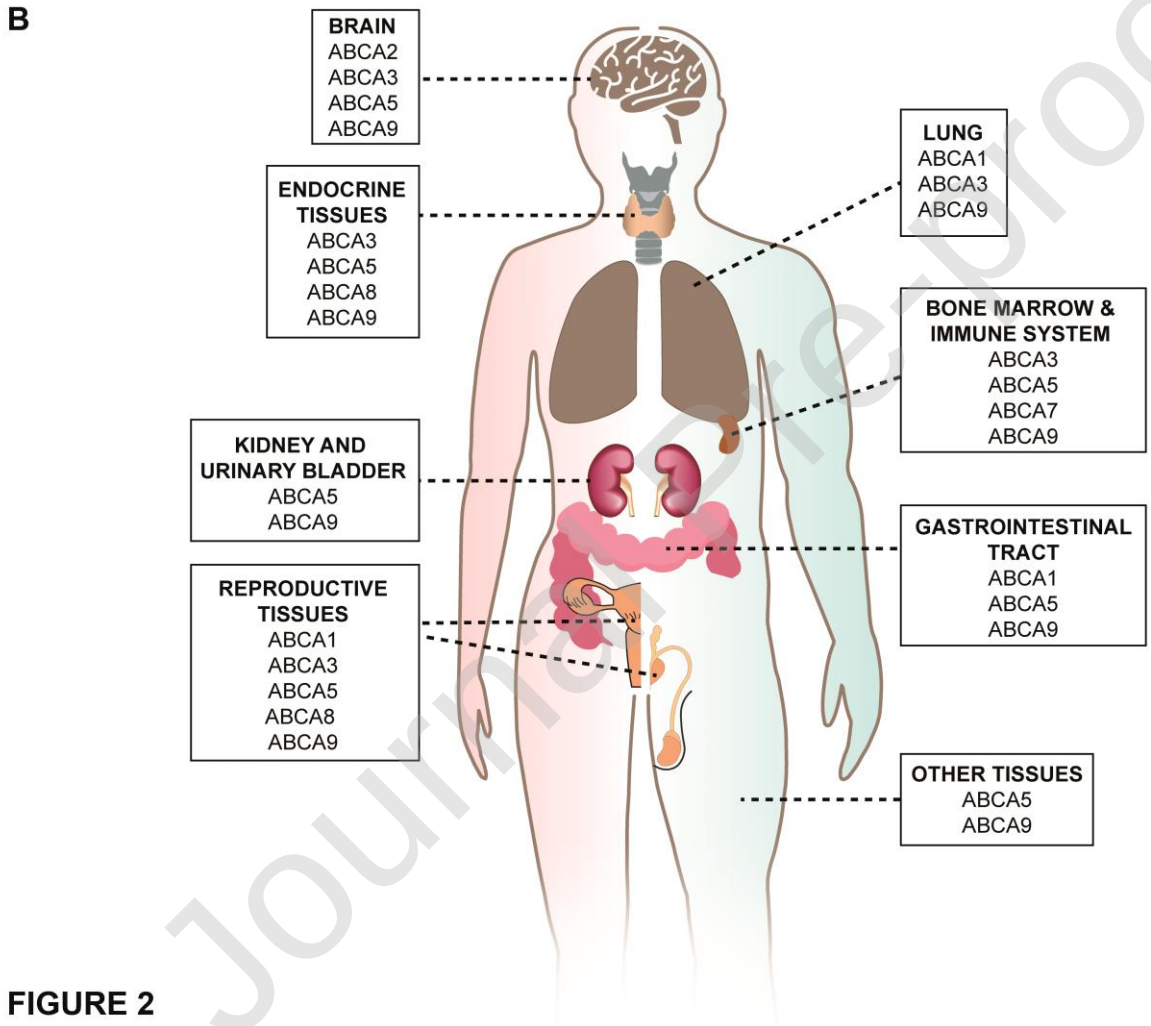


FIGURE 2

Figure 3. Model for the transcriptional regulation of *ABCA1* and *ABCA7* in response to cellular cholesterol levels.

(A) A high cellular content of cholesterol, through its conversion to oxysterol, prevents the translocation of SREBP2 to the nucleus and induces positive regulation of *ABCA1*. Indeed, the oxysterols enter the nucleus and act as ligands of LXR, activating the LXR/RXR heterodimer on target genes such as ABCA1, with the consequence of increased cholesterol efflux through this transporter activity. (B) Cholesterol depletion induced by statins or zoledronic acid treatment induces the translocation of SREBP2 to the nucleus, activating the transcription of *ABCA7* and maintaining the expression of *ABCA1* at a low level.

ApoA1: apolipoprotein A1; Chol: cholesterol; HDL: high-density lipoprotein; HMG-CoA: 3-hydroxy-3-methylglutaryl-CoA; HMGCR: HMG-CoA reductase; LXR: liver X receptor; RXR: retinoid X receptor; SCAP: SREBP cleavage-activating protein; SREBP2: sterol regulatory element-binding protein 2.

FIGURE 3

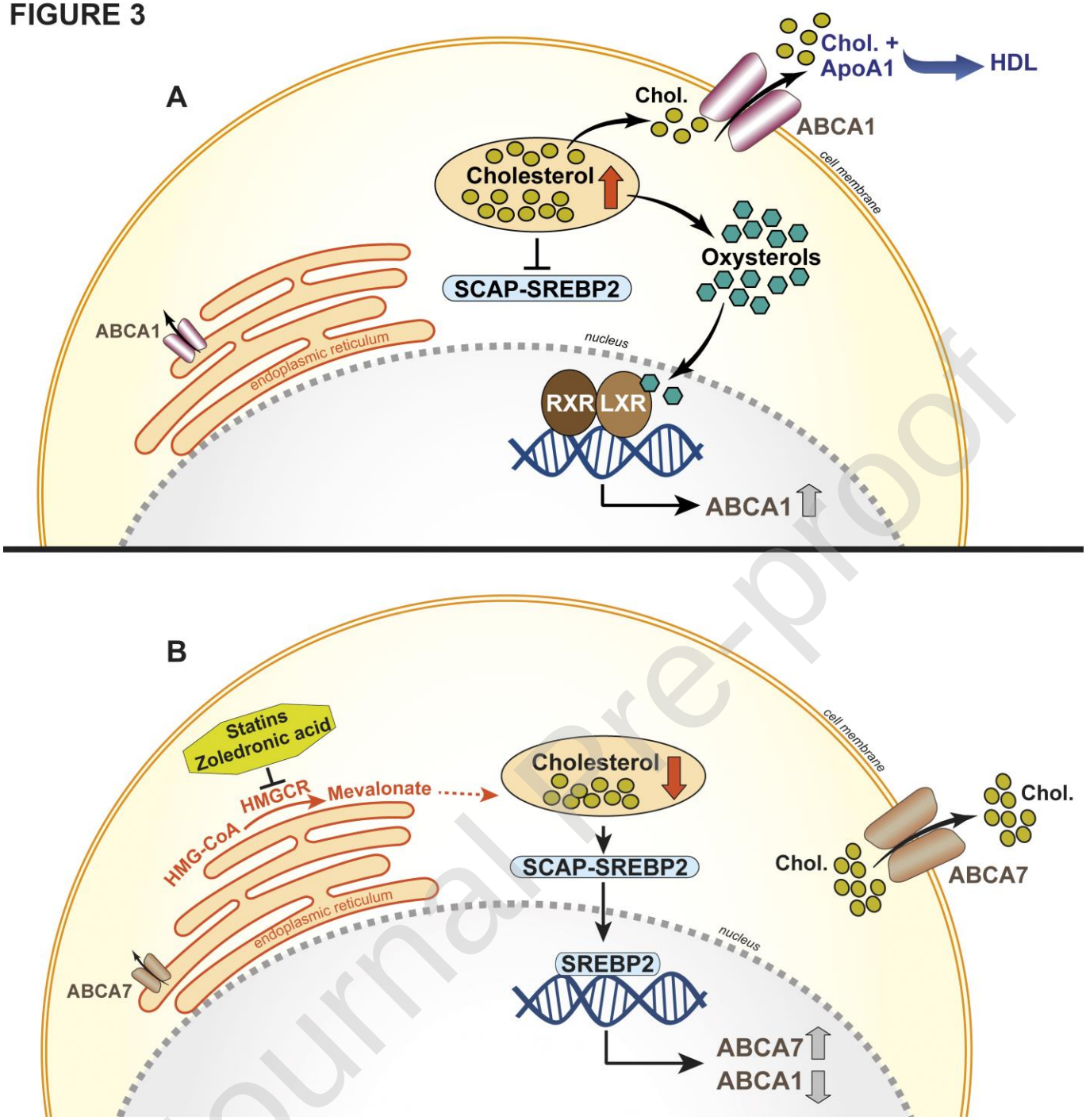


Figure 4. Schematic representation of subcellular ABC transporter localization and endogenous substrates exported.

The arrows represent the transport direction at the plasma membrane.

Aβ: amyloid-β; Aβ-peptides: amyloid-β peptides; Cer: ceramide; Chol: cholesterol; GlcCer: glucosyl ceramide; GSH: glutathione; GSSH: glutathione disulfide; LTC4: leukotriene C4; LPI: lysophosphatidylinositol; N-ret-PE: N-retinylidene-phosphatidylethanolamine; PAF: platelet activating factor; PC: phosphatidylcholines; PE: phosphatidylethanolamine; PG: phosphatidylglycerol; PGs: prostaglandins; PS: phosphatidylserine; SM: sphingomyelin; S1P: sphingosine-1-phosphate.

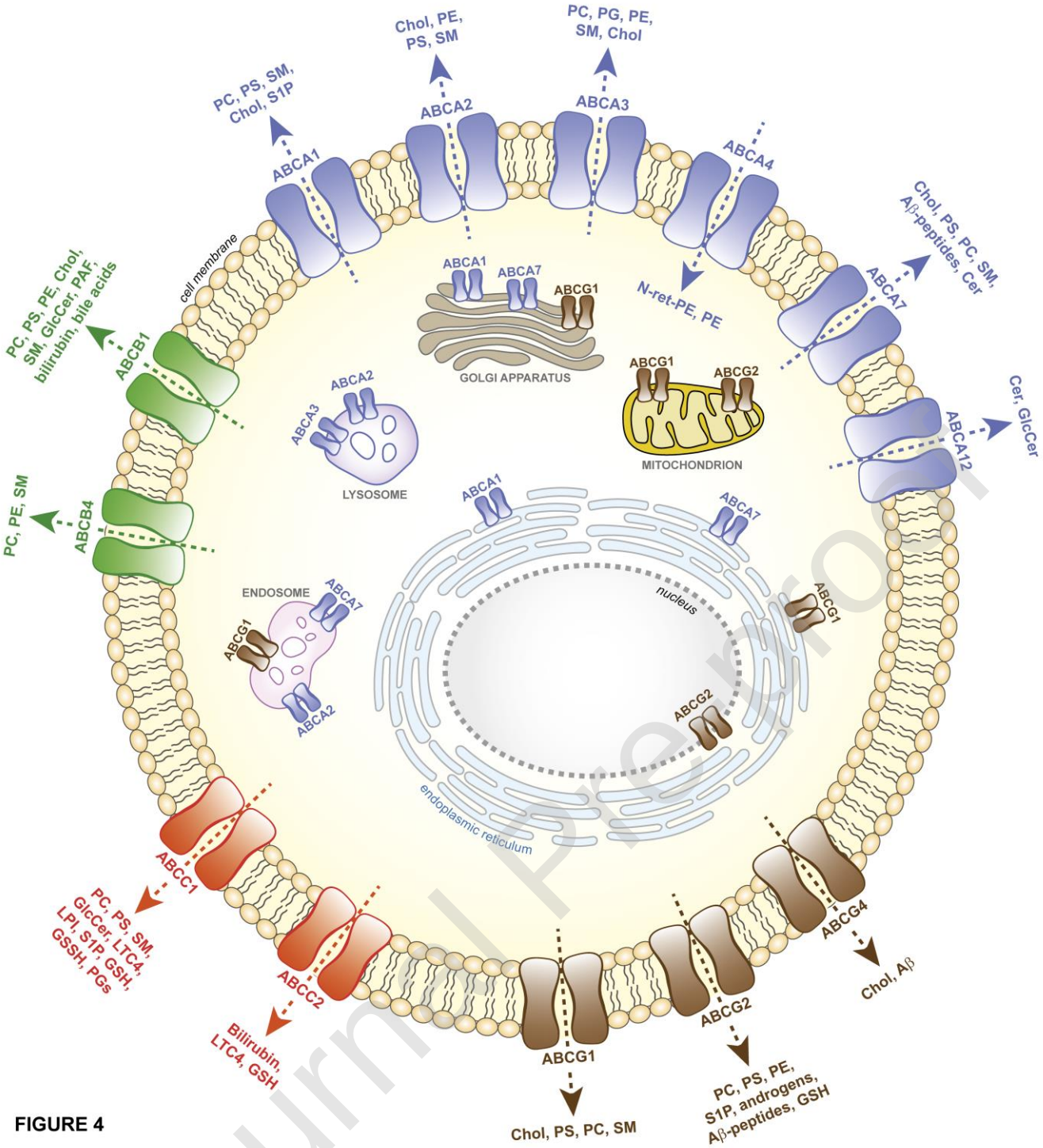


FIGURE 4

Figure 5. Schematic overview of reverse cholesterol transport.
ApoA1 is synthesized in both the liver and intestine and secreted as a lipid-poor form in blood. These lipoprotein particles pick up cholesterol from ABCA1 in macrophages and peripheral cells and are converted to nascent HDL. Accumulated cholesterol in the HDL form can be converted to cholesterol esters. HDL particles are further loaded in the bloodstream with cholesterol to form mature HDL, which in turn delivers its lipid cargo back to the liver through uptake mediated by the scavenger receptor SR-B1. Finally, cholesterol is converted to bile salts in the liver and secreted in this form into the bile.
ApoA1: apolipoprotein A1; HDL: high-density lipoprotein; SR-B1: scavenger receptor class B-type 1.

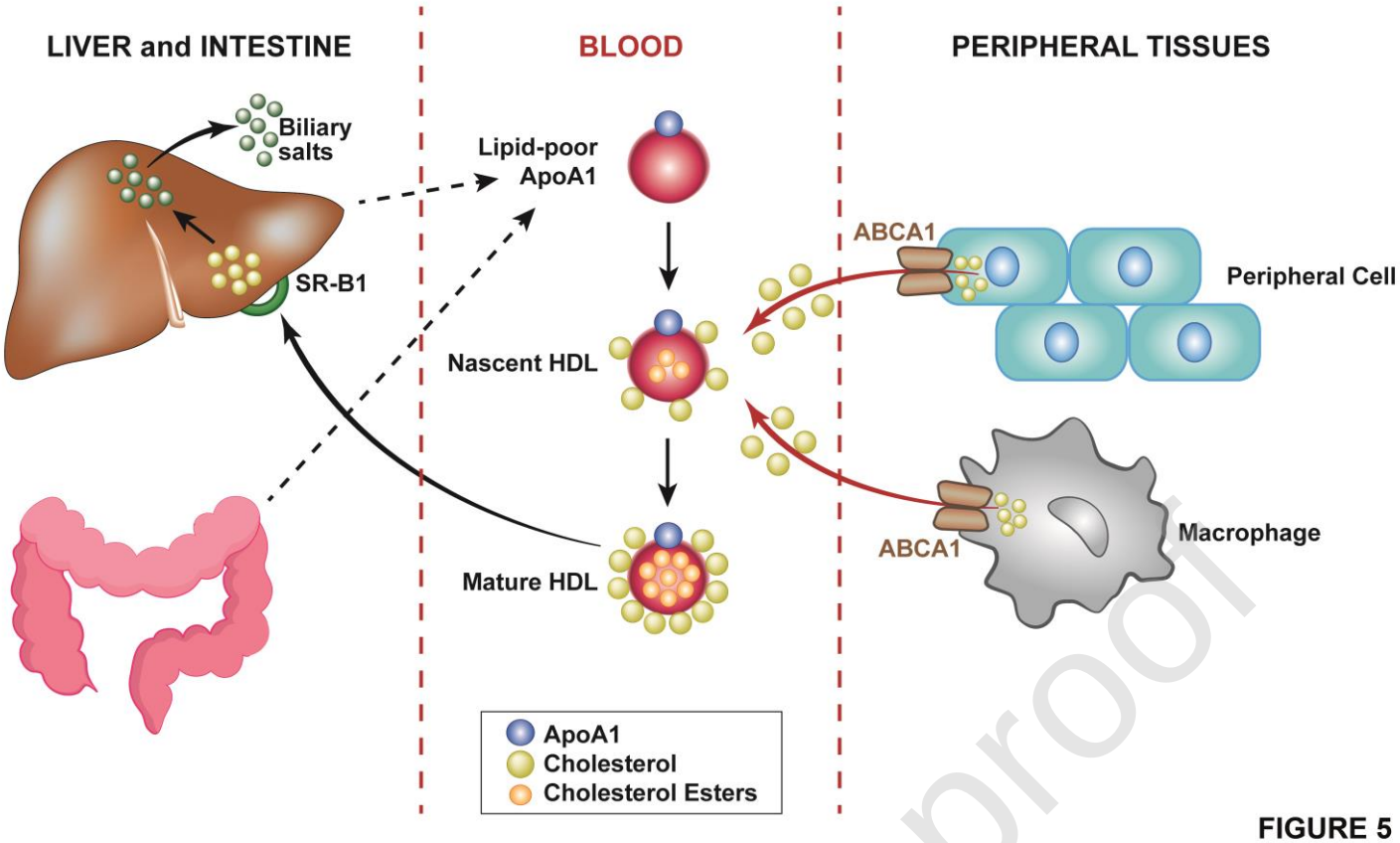


FIGURE 5

Table 1. Characteristics and physiological roles of ABCA transporter subfamily members.

Transporter	Chromosomal localization (*)	Protein weight (kDa) (**)	Cellular localization (**)	Physiological functions
ABCA1	9q31.1	254	Endoplasmic reticulum Golgi apparatus Plasma membrane	Cholesterol efflux [201] Phospholipid efflux [202]
ABCA2	9q34.3	270	Plasma membrane Cytoskeleton Lysosomal membrane Endosomal membrane	Cholesterol metabolism and trafficking [203] Sphingolipid metabolism [204]
ABCA3	16p13.3	191	Plasma membrane Lysosomal membrane Extracellular region	Transport of the lipid components of pulmonary surfactant [67] Cholesterol homeostasis [205]
ABCA4	1p22.1	256	Plasma membrane	Importer of N-retinylidene-phosphatidylethanolamine and phosphatidylethanolamine from the luminal to the cytoplasmic side of photoreceptor disc membranes [15]
ABCA5	17q24.3	186	Lysosomal membrane Endosomal membrane Golgi apparatus	Cholesterol efflux in neurons [206]
ABCA6	17q24.3	184	Nucleoplasm Plasma membrane	Macrophage lipid homeostasis [207] Placental lipid metabolism [208]
ABCA7	19p13.3	234	Plasma membrane Golgi apparatus Endoplasmic reticulum Endosomal membrane	Phagocytosis of macrophages [39, 110] Phagocytic clearance of amyloid-β in the brain [71] Cholesterol and phospholipid efflux [209]
ABCA8	17q24.2	179	Plasma membrane	Regulation of sphingomyelin production in oligodendrocytes [210] Cholesterol efflux [72]
ABCA9	17q24.2	184	Plasma membrane	Lipid transport [211] Monocyte differentiation and macrophage lipid homeostasis [212]
ABCA10	17q24.3	176	Plasma membrane	Macrophage lipid homeostasis [107]
ABCA12	2q35	293	Cytosol Plasma membrane	Lipid homeostasis in the skin [213]
ABCA13	7p12.3	576	Lysosome Plasma membrane	Neurodevelopment in the central nervous system [214] Lipid transport [215]

(*) GeneCards – The human gene database www.genecards.org [216]; (**) UniProt database: www.uniprot.org [59].