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ABC TRANSPORTERS AND CHOLESTEROL METABOLISM

Gerd Schmitz and Wolfgang E. Kaminski

Institute for Clinical Chemistry and Laboratory Medicine, University of Regensburg, 93042 Regensburg, Germany

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1. ABSTRACT

ATP-binding cassette (ABC) proteins form a group of highly conserved cellular transmembrane transporters. Studies over the past year have implicated ABC transporters in cellular lipid trafficking processes. This notion has recently been confirmed and extended by the finding that the ABC transporter ABCA1 is a key regulator of high-density lipoprotein (HDL) metabolism and macrophage targeting to the RES or the vascular wall. Expression of a large number of ABC transporters in monocytes/macrophages and their regulation by cholesterol flux render these transporter molecules potentially critical players in chronic inflammatory diseases such as atherosclerosis.

2. INTRODUCTION

Energy dependent transport processes controlling the import and export of biologic substances is a prerequisite for the maintenance of basic functions of living cells. They take place at the plasma membrane, which forms the biologic interface between the cytoplasm and the extracellular milieu, and at a number of intracellular membrane complexes and cellular organelles. Two major cellular lipid transport processes can be distinguished (1-4): (i) An inbound transport through the plasma membrane, which involves complex transport mechanisms such as phagocytosis, endocytosis and pinocytosis that are mediated by clathrin-dependent and clathrin-independent transport routes (5-7). The latter represent at least three distinct endocytic pathways which are initiated by caveolae, macropinosomes and micropinosomes. (ii) The secretory (vesicular) transport route along which *de novo* synthesized lipids are translocated from the endoplasmic reticulum (ER) via the Golgi-complex to the plasma membrane or subcellular compartments.

ATP binding cassette (ABC) transporters constitute a gene family of molecules that mediate the unidirectional transmembrane transport of a multitude of specific substrates (8,9). The energy required for the translocation of substances across cell membranes is provided by the hydrolysis of ATP. Biologically active ABC transporters are composed of two tandemly linked functional units, each composed of an ATP binding cassette and a complex transmembrane domain (8,9). Alternatively, functional ABC transporters can be formed by dimerization of two half-size transporters, each containing one ATP binding cassette and one transmembrane domain. Within the cell, ABC transporters are present in the plasma membrane, peroxisomes, the ER, the Golgi complex, the mitochondrion and intracellular secretory vesicles (10). Substrates that are translocated by ABC transporter include lipids, peptides, amino acids, carbohydrates, vitamins, ions and xenobiotics (8-10). In the past decade, considerable efforts were made to study the role of ABC transporters in tumor cell therapy, however, their physiological function and the mechanisms by which they translocate substrates across membranes still remain largely unknown. Available data support the notion that ABC transporters form functional multiunit complexes as shown for SUR1 which

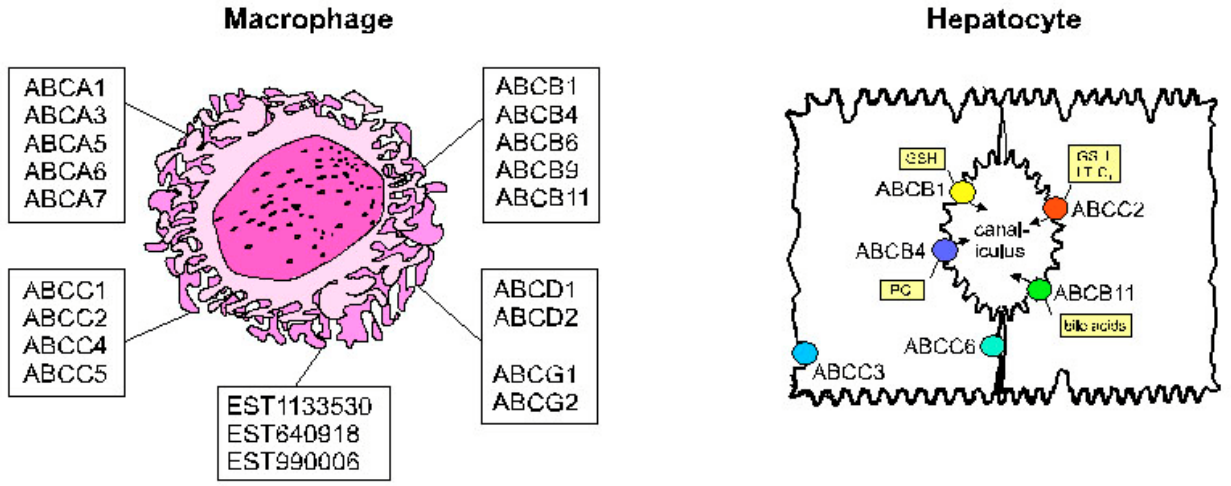

Figure 1. ABC transporters that are regulated by cholesterol in macrophages (ref. 20) (left) and ABC molecules that are involved in hepatic secretory processes (right); EST, expressed sequence tag; GSH, glutathione-conjugated substrates; LT, leukotriene; PC, phosphatidylcholine

is intimately associated with the K^+ channel KIR6.1 (11) and CFTR which interacts with the endocytic adaptor complex AP-2 (12). It is thus conceivable that ABC molecules are implicated in multiple biologic activities depending on the specific assembly of the active complex they engage in and their respective interaction partners.

3. DISCUSSION

3.1. ABC lipid transporters

In recent years, compelling evidence has accumulated to suggest that ABC transporters are intimately involved in cellular lipid transport processes. This novel concept originated from the initial observations that the long-known multidrug transporters ABCB1 (MDR1) and ABCB4 (MDR3) are capable of translocating phospholipids between the innner and outer plasma membrane leaflet (13-15) and the finding that the adrenoleukodystrophy gene ALDR (ABCD1) functions as a peroxisomal transporter for very long chain fatty acids (VLCFA) (16). The notion that specific ABC transporters exert critical functions in cellular lipid trafficking has been convincingly substantiated in the past two years by the identification of additional members of the ABC gene family for which a pivotal role in the regulation of cellular lipid transport and the homeostasis of lipid and lipoprotein metabolism could be demonstrated. This group of lipid transporters currently comprises the multidrug related protein ABCC2 (MRP2) (17) and the bile salt exporting pump BSEP (ABCB11) (18), which were shown to play an essential role in the hepatic secretion of bile acid glutathione conjugates, the Stargardt disease gene ABCR (19), the Drosophila *white* homolog ABCG1 (20) and the phospholipid/cholesterol co-transporter ABCA1 (21-23). In parallel with the identification and characterization of ABC lipid transporters experimental evidence was provided that these molecules are implicated in the pathogenesis of a number of hereditary diseases which include HDL-deficiency syndromes such as Tangier disease, familial degenerative liver disorders, chorioretinal diseases, the neurodegenerative disorder adrenoleukodystrophy, and pseudoxanthoma elasticum (Table 1). The heterogeneity of these diseases provides evidence that ABC lipid transporters serve important functions in diverse physiologic regulatory systems including lipid metabolism, liver secretion, chorioretinal function and connective tissue integrity.

3.1.2. Macrophage ABC lipid transporters

Recent experiments from our laboratory showed that human macrophages express a variety of ABC transporters which are regulated by cholesterol uptake and HDL dependent cholesterol efflux (20). A synopsis of macrophage ABC transporters that are regulated by cholesterol flux is shown in Figure 1. We found that almost 90% of the currently known human ABC genes (n = 43) were expressed in macrophages (20). Most of these genes were upregulated during *in vitro* monocyte differentiation into macrophages. A significant portion of all ABC transporters studied showed cholesterol influx or efflux dependent gene regulation. This strongly suggests that a multitude of ABC molecules may be involved in macrophage cholesterol homeostasis (20). For example, transporters whose expression is upregulated by cholesterol import may be involved in lipid export processes that compensate for cholesterol overload of the cell. On the other hand, ABC proteins that are downregulated by sustained cholesterol influx are possibly involved in transport processes that facilitate cholesterol import. Because of the significant portion of cholesterol-responsive members among the as yet known human ABC family transporters and the assumption that the coding regions for ABC molecules may occupy 2- 5% of the human genome (24), it can be expected that the total number of cholesterol-sensitive ABC proteins will considerably increase in the future (20).

Table 1. ABC transporters involved in the transmembrane transport of cellular lipids or lipophilic compounds that have been causatively linked to human diseases

ABC lipid transporter	Associated disease	Transported compound	References
ABCA1 (ABC1)	Familial HDL deficiency (Tangier disease)	cholesterol, phospholipids	(21-23, 61)
ABCA4 (ABCR)	Stargardt disease	retinoids	(19, 103)
ABCA4 (ABCR)	Retinitis pigmentosa	retinoids	(58,59)
ABCA4 (ABCR)	Cone-rod dystrophy	retinoids	(58)
ABCA4 (ABCR)	Age-related macular degeneration	retinoids	(60)
ABCB4 (MDR3)	PFIC3	PC	(37)
ABCB11 (BSEP)	PFIC2	bile acids	(31)
ABCC2 (cMOAT)	Dubin-Johnson syndrome	glutathione conjugates, LT C_4	(39)
ABCC6 (MRP6)	Pseudoxanthoma elasticum	?	(42-44)
ABCD2 (ALDR)	Adrenoleukodystrophy	VLCF	(16)

PFIC, progressive familial intrahepatic cholestasis; PC, phosphatidycholine; LT, leukotriene; VLCF, very long chain fatty acids

3.1.3. ABC transporter mediated lipid export from the liver

The bile canalicular membrane of mammalian hepatocytes contains several primary active ABC transporters that mediate the export of specific substrates into the bile canaliculus (25,26). This group of transporters currently comprises ABCB1 (MDR1) (27), ABCB4 (MDR3) (28), ABCB11 (BSEP) (29-31) and ABCC2 (MRP2, cMOAT) (32,33) (Figure 1). ABCB1 has been shown to transport a variety of short chain lipids (14) and studies in the human cell line CaCo revealed a role for ABCB1 in cholesterol transport from the plasma membrane to the ER (34). In contrast, ABCB4 specifically translocates phosphatidylcholine (13) and is required for phosphatidylcholine secretion into bile. This was evidenced by the finding that disruption of the murine ABCB4 homolog, mdr2, results in the complete absence of phospholipid from the bile leading to a significant reduction of serum HDL cholesterol and VLDL triglyceride levels (15,35,36). Defects in human ABCB4 cause progressive familial intrahepatic cholestasis type III (PFIC3) (Table 1.) (37). Another form of familial intrahepatic cholestasis, PFIC2, is caused by a defective ABCB11 gene (31). The ABC transporter encoded by this gene has been shown to function as an exporter of bile salt from the liver in vitro (17). ABCC2, a member of the MRP family of conjugate export pumps, transports a wide spectrum of conjugates of lipophilic substances with glutathione, glucuronate, or sulfate. These include leukotriene C_4, 17 beta-glucuronosyl estradiol and bilirubin glucuronosides (38). Mutations in ABCC2 have been reported to underly Dubin-Johnson syndrome (39) which is characterized by a selective abnormality in the excretion of conjugated anions into the bile (40). Another member of the MRP family ABCC6 (MRP6), which is exclusively expressed in the kidney and the liver (41), has recently been causatively linked to pseudoxanthoma elasticum, a disease presenting with skin abnormalities, visual defects and cardiovascular manifestations (42-44).

3.2. ABCA1 is a key regulator of HDL metabolism and cellular cholesterol and phospholipid export

Human ABCA1 is a 2201 amino acid polypeptide with a molecular weight of 220 kDa (45) and represents the prototype of ABC transporters of the A subfamily (24). It contains two highly conserved ATP-binding cassettes including the obligatory Walker A and B motifs and two transmembrane complexes, each composed of six membrane-spanning helices and thus conforms to the model of a full-size transporter (8,9). Like other members of the ABC A subfamily, ABCA1 contains a highly hydrophobic segment located between the two transmembrane domains (24). The ABCA1 cDNA is highly homologous (62%) to the human rim ABC transporter, ABCR, another member of the A subclass of ABC transporters (19) and expressed in a variety of human organs with highest expression levels in placenta, liver, lung, adrenal glands and fetal tissues (45). The human ABC1 gene, which is composed of 49 exons spanning a region of app. 70 kb (46), has been assigned to chromosome 9q31 (47,48). The promoter region of human ABCA1 has recently been cloned and *cis*-acting regulatory elements have been characterized (49). Until recently, only little was known about the physiologic function of ABC1 (24). The major breakthrough came last year when it could be shown that mutations in the human ABCA1 gene cause familial HDL-deficiency and Tangier disease (21-23).

The HDL-deficiency syndrome Tangier disease (TD) is an autosomal recessive disorder of lipid metabolism which is characterized by almost complete absence of plasma HDL and deposition of cholesteryl esters in the cells of the reticulo-endothelial system with splenomegaly and enlargement of tonsils or lymph nodes (50). A subgroup of TD individuals present with premature atherosclerosis (50). TD patients exhibit an extremely rapid catabolism of HDL or its precursors, and abnormalities in cellular lipid metabolism (51,52). TD mononuclear phagocytes degrade internalized HDL in unusual lysosomes a process promoted by cholesterol loading with acetylated LDL (55). Moreover, the HDL_3 mediated efflux of newly synthesized and rehydrolysed cholesterol and phospholipids is markedly reduced in TD fibroblasts (56), and ABCA1 deficient fibroblasts exhibit a G_2-arrest in the cell cycle and accumulate ceramide (57).

Intriguingly, the localization of the as yet found mutations within the ABCA1 gene appears to determine the tropism for either the RES, as seen in the classical TD phenotype (yellow tonsils, splenomegaly), or the vascular wall, as in cases of HDL-deficiency associated with atherosclerosis. A similar pleiotropic genotype/phenotype relationship has been reported for other ABC transporters. As evidenced for ABCR, mutations in one and the same transporter gene can cause distinct chorioretinal diseases on the mutation site and the combination of mutations (19, 58-60).

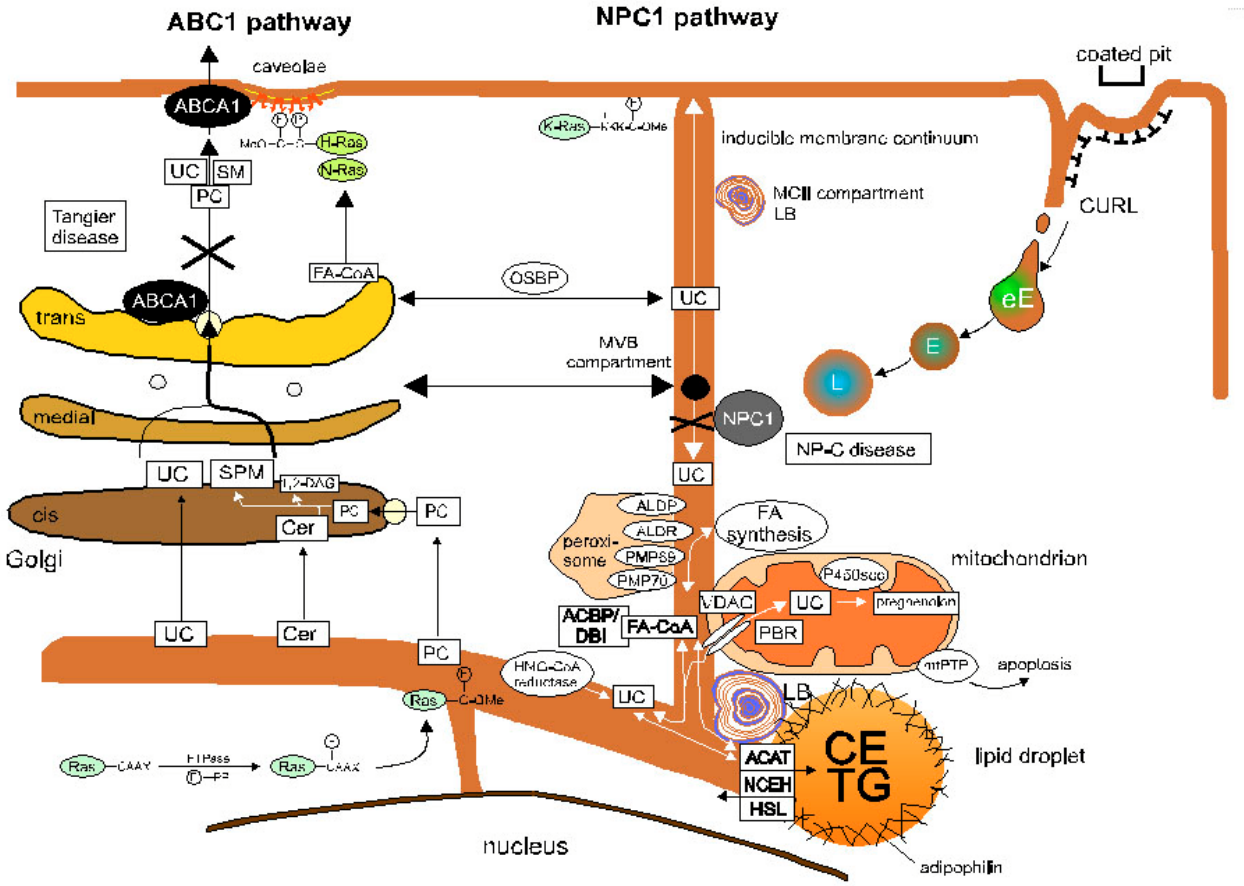

Figure 2. Cellular lipid pathways and associated transport complexes. The defective lipid transport routes in Niemann-Pick C disease and Tangier disease and their putative compensatory pathways to and from the medial Golgi are indicated (thick arrows). ABCA1, ATP-binding cassette transporter 1; ACAT, acyl CoA:cholesterol acyltransferase; ACBP, acyl-CoA binding protein (identical with DBI); ALDP, adrenoleukodystrophy protein; ALDR, adrenoleuko-dystrophy related protein; CE, cholesteryl ester; CURL, compartment of uncoupling receptor and ligand; DBI, diazepam-binding inhibitor; E, endosome; eE, early endosome; FA-CoA, fatty acid acyl-Coenzyme A; HSL, hormone-sensitive lipase; L, lysosome; LB, lamellar body; mtPTP, mitochondrial permeability transition pore; NCEH, neutral cholesteryl ester hydrolase; NP-C, Niemann-Pick disease C; NPC1, Niemann-Pick C1 protein; OSBP, oxysterol binding protein; PBR, peripheral benzodiazepine receptor; PC, phosphatidylcholine; P450scc, cytochrome P450 side chain cleavage complex; PMP, peroxisomal membrane protein; TG, triglyceride; UC, unesterified cholesterol; VDAC, voltage dependent anion channel, F-, farnesyl isoprenoid; P-, palmitate.

A recent study from our laboratory demonstrated that mice deficient in AbcA1 exhibit plasma lipid alterations that are consistent with those in TD (61). Moreover, evidence has been provided indicating that ABCA1 functions as an exporter of cholesterol and phospholipids (61,62) strongly supporting the notion that both lipid compounds are co-transported. ABCA1 appears to be localized on the plasma membrane, likely associated with caveolae and its expression on the surface is induced in macrophages by cholesterol loading (61). Available evidence thus suggests that ABCA1 functions as a cholesterol-responsive exporter of cholesterol and choline-backbone phospholipids at the plasma membrane and functions as a key regulator of HDL metabolism (Figure 2). The observation that ABCA1 is present in the cytosol and Golgi compartment of unstimulated fibroblasts, also raises the intriguing possibility that it may shuttle between the plasma membrane and the Golgi as constituent of a vesicular transport machinery.

3.2.1. ABCA1 mediated cholesterol trafficking and caveolae

Newly synthesized lipids are transferred to sphingolipid and cholesterol rich microdomains ("rafts") following sorting in the *trans*-Golgi network from where they are transported to the plasma membrane (63). Caveolae are cholesterol and sphingolipid rich specific membrane microdomains with characteristic ultrastructure that contain additional structural protein components designated caveolins (63). Caveolin is essential for the proper translocation of *de novo* synthesized cholesterol from the ER to the plasma membrane and enhanced caveolin expression causes an increase in cholesterol efflux from the plasma membrane (64,65). Recent work demonstrating that caveolin 1 is co-transported via the Golgi to the plasma membrane with HDL-like lipoprotein complexes support the concept that caveolae play a pivotal role in the regulation of cellular cholesterol export (66). Given this and the fact that ABCA1 functions as a

cholesterol exporter in the plasma membrane, it can be postulated that ABCA1 and caveolae are functionally associated. Evidence to support this hypothesis has recently been presented by Orsó *et al*. (61) who demonstrated that the absence of ABCA1 leads to abnormal caveolin gene expression and a perturbed processing of caveolin 1 in the Golgi. Because both caveolin and ABCA1 appear to be intimately involved in cellular cholesterol to plasma membrane transport, it is likely that ABCA1 are located in rafts/caveolae (Figure 2).

Beneath its function in cholesterol binding and transport (63,67) caveolin has been implicated in signal transduction. Overexpression of caveolin 1 inhibits signaling via the mitogen-activated protein kinase pathway (68) and reduction of its activity activates the pathway in NIH3T3 cells (69). Moreover, caveolin activates signaling via the insulin receptor (70) and inhibits protein kinase A (71). The precise mechanisms underlying these signaling events are still unknown and a possible mechanistic view is that caveolin binds signaling receptors and second messenger effectors through a cytoplasmic 'scaffolding domain' (72). Studies using dominant-negative caveolin mutants revealed that caveolin contributes to the cholesterol content of glycolipid domains at the cell surface which are essential for H-Ras, but not K-Ras signaling (73). This established the first link between the roles of caveolin in cholesterol trafficking and signaling (Figure 2). Moreover, it could be shown that H-Ras function is indeed associated with caveolae, whereas K-Ras operates in distinct subdomains of the plasma membrane (73).

3.2.2. ABCA1 and NPC1: two major regulators of cellular cholesterol transport

Similarly as hereditary HDL-deficieny such as TD, the neurovisceral lipid storage disorder Niemann-Pick type C disease (NP-C) permits valuable insight into the regulation of cellular cholesterol transport (74). In both diseases the RES is affected resulting in splenomegaly. NPC1 deficient cells are characterized by the accumulation of LDL-derived unesterified cholesterol and in sphingolipids in the internal membranes of multi-vesiculate late endosomes and in the trans-Golgi (75,76). A recent study suggests that cholesterol accumulation results rather from an imbalance of cholesterol flux among membrane compartments than a lysosomal transport block (77), which was has been commonly postulated. In contrast to NP-C, in the absence of functional ABCA1 *de novo* synthesized and rehydrolyzed cholesterol are deposited in lipid droplets. The transport of LDL-derived free cholesterol to the ER and the plasma membrane in NP-C cells is delayed compared with normal cells (Figure 2). Unlike in TD, plasma lipoprotein levels are not affected in NP-C and the patients do not develop vascular disease.

The gene mutated in NP-C, NPC1 (18q11), has recently been identified (78) and it was shown that transport of the NPC1 protein to the cholesterol-laden lysosomal compartment is essential for expression of its biologic activity (79). NPC1 contains 13 transmembrane domains which exhibit homology to the membrane receptor *patched*, the sterol-sensing domain of HMG-CoA reductase and the sterol regulatory element binding protein cleavage-activating protein (SCAP) (78,80,81). The exact biologic function of NPC1 is still unclear and it will be challenging to determine its detailed role in intracellular cholesterol trafficking. Recent experimental evidence reporting an increase in expression and phosphorylation of caveolin 1 in NPC1 deficient cells suggests an involvement of NPC1 in caveolar function (82,83). Because NPC1 is involved in the intracellular transport of cholesterol and sphingolipids, it is possible that NPC1 is indirectly implicated in the regulation of raft/caveolae function by altering the lipid composition of these functional membrane sites. On the other hand, ABCA1 and may also have an impact on caveolae composition and caveolin dependent cholesterol traffic since loss-of-function of ABCA1 leads to retention of caveolin 1 in the Golgi. It is thus tempting to speculate that ABCA1 and NPC1 may independently modulate raft/caveolae function.

3.3 Mitochondrial integrity and ABC transporter mediated lipid transport

Mitochondria generate cellular energy in the form of ATP by the process of oxidative phosphorylation and a number of genetic mitochondrial diseases have been associcated with defects in mitochondrial DNA (84). Importantly, there is also an increasing mitochondrial deficit with aging (85) and chronic diseases of the elderly such as non-insulin-dependent diabetes mellitus (NIDDM) are characterized by cellular ATP deficit due to insulin resistance and impaired intracellular glucose in peripheral tissues (86). Within the mitochondrion, the adenine nucleotide translocator (ANT), pro-apoptotic Bax, cyclophilin D and the voltage dependent anion channnel (VDAC) are thought to assemble at the mitochondrial inner and outer membrane contact points to form the mitochondrial permeability transition pore (mtPTP) (87-89). The mitochondrial inner membrane contains a series of apoptosis-promoting factors including cyt c, apoptosis-inducing factor and inactive forms of caspases, which are released upon opening of the mtPTP (90). It has hence been proposed that the mtPTP is activated under conditions of reduced mitochondrial energy production and may thereby ultimately initiate the apoptotic cascade (90). In the hierarchy of energy-consuming processes (91), high energy consumers such as ABC transporters are likely to be among the effector molecules that are affected at a relatively early phase of ATP deficiency. It is hence conceivable that chronic mitochondrial stress may compromise the function of ABC molecules that are involved in the transmembrane transport of lipid compounds. It is an attractive hypothesis that the reduced HDL plasma levels observed in NIDDM patients suffering from mitochondrial deficit due to the chronic shortage of glucose in peripheral cells are associated with a compromised function of ABC transporters, such as ABCA1, which are critically involved in reverse cholesterol transport.

3.4 Oxysterol binding proteins and cholesterol transport

In addition to ABCA1 and NPC1, oxysterol binding proteins appear to be critical regulators of cellular cholesterol homeostasis. The first protein characterized as oxysterol binding, termed oxysterol binding protein

(OSBP) (92) translocates from the cytosol to the membranes of the Golgi apparatus upon binding of oxysterol (93) and has been implicated in the regulation of cellular cholesterol balance.

Oxysterols are oxygenated derivatives of cholesterol that have been suggested to promote atherosclerosis, aging, and cancer (94). Although their physiological functions remain largely, they have been associated with the regulation of cellular cholesterol metabolism (95). OSBP is a cytosolic protein that undergoes ligand-induced binding to the Golgi apparatus and has been implicated in the regulation of cellular cholesterol metabolism. Stably transfected cells overexpressing OSBP were shown to display a marked decrease in cholesteryl ester synthesis and an increase in cholesterol biosynthesis (96). Furthermore, the disruption of the Golgi apparatus was found to reduce the action of oxysterols on cholesterol synthesis (97) and the Saccharomyces cerevisiae homolog of OSBP, KES1, has been linked to the biogenesis of Golgi-derived transport vesicles (98). Recently, it was shown that members of the nuclear receptor superfamily are involved in mediating the functions of oxysterols. LXRs were found to bind oxysterols in the liver in the presence of abundant cholesterol and function as a ligand-activated transcription factor to up-regulate cholesterol catabolism to bile acids (99,100). Another member of this family, PPAR gamma, functions as a receptor for oxidized metabolites of cholesteryl esters and regulates macrophage gene expression upon uptake of oxidized low density lipoprotein (LDL) (101,102). In summary, current evidence supports the concept that OSBPs may play a role in organelle lipid composition and membrane traffic and thus may potentially interact with major regulators of cholesterol traffic such as ABCA1 and NPC1.

4. PERSPECTIVES

Our current knowledge of the function of ABC transporters and the nature of the substrates translocated by them is still rudimentary. The recent implication of ABC transporters in cellular lipid transport and the finding that human diseases are caused by defective ABC lipid transporters, have been milestones in the attempt to define the physiologic role of ABC transporters. Since it is now evident that a large number of ABC molecules are regulated by cholesterol, future work will focus on the characterization of their exact biologic function in cellular lipid metabolism. With more than 40 human ABC transporters currently known and an estimated equal number of transporters that still await to be identified, future work will establish more causative links between ABC lipid transporters and hereditary diseases with as yet unknown etiology. Moreover, the systematic identification of allelic variants of ABC lipid transporters and the evaluation of their significance in the pathogenesis of polygenic disorders such as atherosclerosis will be a major challenge for the next future.

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Send correspondence to: Prof. Dr. Gerd Schmitz, Institute for Clinical Chemistry and Laboratory Medicine, University of Regensburg, Franz-Josef-Strauß-Allee 11, D-93042 Regensburg, Germany, Tel:+49-941-944-6201, Fax: +49-941-944-6202, E-mail: gerd.schmitz@klinik.uni-regensburg.de