Physiol. Res. 53: 235-243, 2004

MINIREVIEW

ATP-Binding Cassette (ABC) Transporters in Human Metabolism and Diseases

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Received March 16, 2003
Accepted June 20, 2003

Summary

The ATP-binding cassette (ABC) superfamily of active transporters involves a large number of functionally diverse transmembrane proteins. They transport a variety of substrates including amino acids, lipids, inorganic ions, peptides, saccharides, metals, drugs, and proteins. The ABC transporters not only move a variety of substrates into and out of the cell, but also are also involved in intracellular compartmental transport. Energy derived from the hydrolysis of ATP is used to transport the substrate across the membrane against a concentration gradient. The typical ABC transporter consists of two transmembrane domains and two nucleotide-binding domains. Defects in 14 of these transporters cause 13 genetic diseases (cystic fibrosis, Stargardt disease, adrenoleukodystrophy, Tangier disease, etc.). Mutations in three genes affect lipid levels expressively. Mutations in ABCA1 cause severe HDL deficiency syndromes called Tangier disease and familial high-density lipoprotein deficiency, which are characterized by a severe deficiency or absence of high-density lipoprotein in the plasma. Two other ABCG transporters, ABCG5 and ABCG8, mutations of which cause sitosterolemia, have been identified. The affected individuals absorb and retain plant sterols, as well as shellfish sterols.

Key words

ABC transporter • Lipid metabolism • Cholesterol • Mutation

Introduction

The ATP-binding cassette (ABC) superfamily of active transporters is composed of about 50 functionally diverse prokaryotic and eukaryotic transmembrane proteins (Higgins 1992, Michaelis and Berkower 1995). These proteins are fundamental to membrane transport of a broad variety of substrates including amino acids, lipids, lipopolysaccharides, anorganic ions, peptides, saccharides, metals, drugs and proteins (Higgins 1992).

The ABC transporters not only move a variety of substrates into and out of the cell, but also are involved in intracellular compartmental transport. These proteins utilize energy derived from the hydrolysis of ATP to transport the substrate across the membrane against a concentration gradient. It has been estimated that the hydrolysis of two ATP molecules results in the transport of one molecule of substrate. Substrate specificity for each transporter is determined by the amino acid sequence in the transmembrane domain (TMD). As a result, there is usually little similarity between the transmembrane domains of different ABC transporters.

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Even if sequence similarity is noted, substrate similarity is not implied.

The typical ABC transporter consists of two transmembrane domains and two nucleotide-binding domains (NBDs) encoded by a single polypeptide (Fig. 1). ABC transporters may also represent a multi-component unit, in which a different gene encodes for each domain or half molecule (i.e. one TMD and one NBD, Fig. 2) (Dean and Allikmets 1995, Higgins 1995). The TMD contains 6-11 membrane-spanning α-helixes. In contrast, the hydrophilic NBDs of the ABC transporters are highly conserved. The amino acid identity in these regions varies from 30 to 50 % between transporters. NBDs consist of approximately 90-110 amino acids. Each nucleotide-binding domain contains two sequence motifs, the Walker A and Walker B motifs, which are common to the general category of nucleotide-binding proteins. The distinctive feature of all ABC transporters is the C motif that has the consensus sequence "LeuSerGlyGlyGln" (Hyde *et al.* 1990).

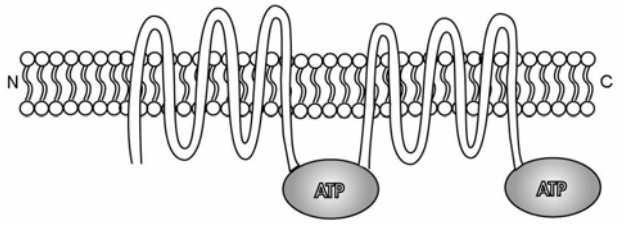

Fig. 1. Full ABC transporter consists of two transmembrane domains and two nucleotide binding domains encoded by a single polypeptide.

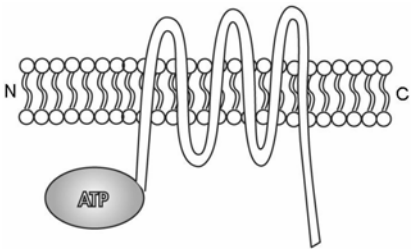

Fig. 2. Half ABC transporter consists of one transmembrane domain and one nucleotide binding domain.

Some ABC transporters are not directly involved in transporting substrates, but appear to be part of ion channels (such as the cystic fibrosis transmembrane regulatoror or the sulfonylurea regulaator). In these cases, it appears that the hydrolysis of ATP is linked to movement of the protein itself (for cystic fibrosis transmembrane regulator) or to other proteins (for sulfonylurea regulator) to regulate opening and closing of ion channels (Obmolova *et al*. 2000).

Many ABC transporters are major determinants of human disease. Among the first ABC transporters to be identified in man was the P-glycoprotein (Pgp) multigene family (Juliano and Ling 1976, Juranka *et al.* 1989, Endicott and Ling 1989) of which Pgp1 plays a critical role in drug resistance in human cancers.

At present, there are approximately 50 known ABC transporters in human. Phylogenetic analysis is used to divide ABC transporters into seven distinct subfamilies of proteins. The subfamilies are named ABCA-ABCG.

Defects in 14 of these transporters cause 13 genetic diseases, the most common of which are cystic fibrosis, Stargardt disease, adrenoleukodystrophy, and Tangier disease (Table 1).

Human ABC gene subfamilies participating in lipid transport

ABCA subfamily

This is a unique group that, in contrast to any other human ABC transporters, lacks a structural counterpart in yeast. The structural hallmark of the ABCA subfamily is the presence of a stretch of hydrophobic amino acids thought to span the membrane within the putative regulatory domain. Up to now, 12 ABCA-encoding genes have been identified, but only four ABCA transporters have been fully characterized. Full transporters are further divided into two subgroups based on phylogenetic analysis and intron structure (Luciani *et al.* 1994). The first group includes seven genes dispersed on six different chromosomes, ABCA1 (9q22-q31), ABCA2 (9q34), ABCA3 (16p13,3), ABCA4 (1p22), ABCA7 (19p13,3), ABCA11 (4p16), ABCA12 (2q35), whereas the second group contains five genes (ABCA5, ABCA6, ABCA8, ABCA9 and ABCA10) arranged in a cluster on chromosome 17q24 (Klugbauer and Hofman 1996, Allikmets 1997, Azarian and Travis 1997).

A pairwise comparison of the published full nucleotide sequences for ABCA cDNAs shows an overall identity of around 60 % among the different genes, irrespectively of the pairs analyzed. Cross-species conservation of individual genes is extremely high, exceeding 85 % identity (Luciani *et al.* 1994).

The gatekeeper of the reverse cholesterol transport pathway is an ATP-binding cassette called ABCA1, a 2261 amino acid integral membrane protein

(Rust *et al*. 1999, Oram and Vaughan 2000, Santamarina-Fojo *et al*. 2001). ABCA1 transports cellular cholesterol and phospholipids (mostly phosphatidylcholine) to cell surface-bound apolipoproteins (Oram and Yokoyama 1996, Oram 2000). This protein therefore represents the first and rate-controlling step in the reverse cholesterol transport pathway. Our knowledge of ABCA1 functioning is still insufficient. Although the exact structure of ABCA1 is unknown, electron microscopic analysis has suggested a structural model for a closely related ABC transporter called P-glycoprotein (Rosenberg *et al*. 1997). This model predicts that the two membrane-spanning domains form a large aqueous chamber in the plasma membrane that opens through pores on the cell surface and within the membrane lipid phase. Because the chamber does not open to the cytosol, P-glycoprotein is believed to act as a "floppase" by translocating lipophilic compounds from the inner aspect of the plasma membrane into the aqueous environment of the ABC transporter chamber. Both the cell-surface and inner membrane pores are estimated to be relatively large, allowing for simultaneous translocation of multiple molecules. This may explain why the ABCA1 pathway generates diffuse and irregular structures that protrude from the plasma membrane and interact with apolipoproteins (Lin and Oram 2000).

Because cholesterol is an integral and necessary membrane component, it is likely that ABCA1 targets specific pools of excess abundant cholesterol molecules for secretion. It is still not clear what mechanisms are involved in this process. However, some studies have shown that the interaction of apolipoproteins with cholesterol-loaded cells stimulates translocation of free cholesterol away from intracellular esterifying enzymes to sites accessible to apolipoproteins (Slatte *et al*. 1987, Oram *et al*. 1991, Rogler *et al*. 1995) that presumably contain ABCA1. The properties of these ABCA1 membrane domains are unknown, but they differ from cholesterol- and phospholipid-rich rafts that contain caveolae (Mendez *et al*. 2000). As one possible mechanism, the interaction of apolipoproteins with ABCA1 or a partner protein might stimulate translocation of intracellular cholesterol and phospholipids from the Golgi to plasma membrane ABCA1 by a signal-responsive vesicular transport pathway. Another possibility could be that ABCA1-containing vesicles travel to intracellular lipid deposits, ABCA1 pumps lipids into the vesicle lumen, and the vesicles transport the lipid cargo back into the plasma membrane (Takahashi and Smith 1999).

ABCA2, ABCA3, and ABCA7 mRNA levels have been reported to be upregulated by the sustained cholesterol influx mediated by modified low-density lipoprotein (Kaminski *et al.* 2001). ABCA3 may play an important role in the formation of pulmonary surfactant, which is composed mainly of phospholipids and specific surfactant proteins (Johansson and Crustedt 1997).

ABCA4 is proposed to be transmembrane transporters for N-retinylidenephosphatidylethanolamin. ABCA4 protein transports vitamin A derivatives in the outer segments of photoreceptor cells and therefore performs a crucial step in the visual.

ABCA transporters also play an important role in genetic diseases. Mutations in ABCA1 cause a severe HDL deficiency syndrome called Tangier disease (Hoffman *et al.* 1965). Tangier disease is a rare autosomal recessive disorder characterized by a severe deficiency or absence of high-density lipoprotein in plasma and accumulation of cholesterol esters in macrophages and other reticuloendothelial cells of tissues including tonsils, thymus, lymph node, bone marrow, spleen, liver, gallbladder, and intestinal mucosa. Many patients also have lipid deposits in neuronal Schwann cells, smooth muscle cells, and fibroblasts. Lipid-free apolipoproteins are unable to remove cholesterol and phospholipids from fibroblasts isolated from Tangier disease patients, which is consistent with a defective ABCA1. Charasteristic features of Tangier disease include large yellow-orange tonsils, neuropathies, splenomegaly, hepatomegaly, ocular abnormalities, hyper-cholesterolemia and cardiovascular disease (Assmann *et al.* 1995). Familial high-density lipoprotein deficiency had features of an autosomal dominant disorder characterized by clear manifestations of low HDL in the heterozygotes, with no obvious features of cholesterol ester deposition in cells. Genetic analysis has revealed that Tangier disease is due to mutations on both alleles of ABCA1, whereas familial high-density lipoprotein deficiency is due to a mutation on a single allele (Brooks-Wilson *et al.* 1999, Rust *et al.* 1999, Bodzioch *et al.* 1999).

It has been shown that ABCA1 polymorphisms also plays a role in the plasma lipid levels. Three novel polymorphisms were identified in the promoter region of the ABCA1 gene, and associations of the common polymorphisms with the plasma levels of lipids, angiographic indices of the severity, progression, and regression of coronary atherosclerosis were assumed

(Lutucuta *et al*. 2001). The -477C/T variant was strongly associated with the severity of coronary atherosclerosis and modestly associated with the plasma levels of HDL cholesterol and ApoAI, whereas the other two polymorphisms were not associated with plasma lipid levels.

Table 1. List of human ABC transporters, their functions and diseases caused by *ABC* genes

Transporter name	Function	Disease
ABCA1	Cholesterol and phospholipids transport	Tangier disease, Familial hypoapoproteinemia
ABCA2	Drug resistance	unknown
ABCA4	Rod photoreceptor retinoid transport	Stargardt/fundus flavimaculatis, Retinitis pigmentosa, Cone-rod dystrophy, Age-related macular degeneration
ABCB1	Drug resistance	unknown
ABCB2	Peptide transport	Immune deficiency
ABCB3	Peptide transport	Immune deficiency
ABCB4	Bile-acid transport	Progressive familial intrahepatic cholestasis-3
ABCB6	Iron transport	unknown
ABCB7	Iron transport	X-linked sideroblastosis and anemia
ABCB11	Bile-acid transport	Progressive familial intrahepatic cholestasis-2
ABCC1	Drug resistance	unknown
ABCC2	Bile-acid transport	Dubin-Johnson Syndrome
ABCC4	Nucleoside transport	
ABCC6	unknown	Pseudoxanthoma elasticum
ABCC7	Chloride ion channel	Cystic fibrosis
ABCC8	Sulfonylurea receptor	unknown
ABCD1	Very long chain fatty acids transport	Adrenoleukodystrophy
ABCE1	Oligoadenylate-binding protein	unknown
ABCG1	Cholesterol transport	unknown
ABCG2	Drug resistance	unknown
ABCG5	Sterol transport	Sitosterolemia
ABCG8	Sterol transport	Sitosterolemia

ABCG subfamily (white)

The ABCG or White subfamily with its five fully characterized human members consists of half-size ABC proteins which probably dimerize to form active membrane transporters. Among the half-size molecules, ABCG proteins have a peculiar domain organization characterized by a nucleotide-binding domain at the N-terminus followed by six transmembrane-spanning domains (Klein *et al.* 1999). The founding member of this group, ABCG1, was described as the human homolog of the *Drosphila white* gene (Croop *et al.* 1997). Various transcripts of ABCG1 have been detected in different cells arising from alternative splicing events or the use of different transcription initiation sites (Lorkowski *et al.* 2001). Interestingly, the 12-amino acid linker region between the ATP-binding cassette and the transmembrane region is also subject to alternative splicing generating two major protein forms of ABCG1. The mammalian ABCG1 is involved in the transport of cholesterol and phospholipids in macrophages. ABCG1 shows the highest phylogenetic relationship to the ABCA subfamily, particularly to the ABCA1 gene. There is a significant similarity in the differentiation and sterol-dependent regulation of the ABCA1 and ABCG1 in human monocytes and macrophages. Even though there is an experimental evidence for the involvement of ABCG1 in cholesterol and phospholipid transport, no loss of function mutation of the ABCG1 gene has been described that would help to clarify the physiological function of ABCG1 (Croop *et al.* 1997).

The second well-known member of the ABCG subfamily, ABCG2, has been identified by different

approaches and is known as placenta-specific ABC, a breast cancer resistance protein (Doyle *et al.* 1998), and a mitoxantrone resistance-associated protein. The protein has been shown to be amplified and overexpressed in human cancer cells and is capable of mediating drug resistance even in absence of the classic multidrug resistance proteins MDR1 and MRP1 (Robey *et al.* 2001). Most interestingly, new evidence of the function of ABCG2 as a direct drug efflux pump is provided by data localizing the bulk of the ABCG2 protein to the plasma membrane, with a minor fraction found within intracellular membranes.

Two other ABCG transporters, ABCG5 and ABCG8, encoding sterolin-1 and -2 respectively, mutations of which cause the human disease called sitosterolemia have been identified. Both genes are arranged in a head-to-head configuration, and only 140 bases separate their two respective start-transcription sites (Lu *et al.* 2002). Expression of both genes is confined to the liver and intestines. Sitosterolemia (also known as phytosterolemia) is a rare autosomal recessively inherited metabolic disorder (Salen *et al.* 1992). Sitosterolemia patients develop tendon and tuberous xanthomas, hemolytic episodes, arthralgias, and arthritis, and premature coronary and aortic atherosclerosis leading to cardiac fatalities (Lee *et al.* 2001). Affected individuals have very high levels of plasma plant sterols (sitosterol, campesterol, stigmasterol, avenosterol, and others) and 5α-saturated stanols, particularly sitostanol, but their blood cholesterol levels may be normal or only moderately increased. Thus, in contrast to subjects, patients absorb and retain plant sterols (Salen *et al.* 1992) as well as shellfish sterols (Gregg *et al.* 1986). Clinical studies further show that affected individuals have an inability to excrete sterols, both plant sterols as well as cholesterol, into bile (Salen *et al.* 1989). Increased intestinal absorption, decreased hepatic excretion of sitosterol (the major plant sterol), and abnormally low cholesterol biosynthesis are reported to be features of sitosterolemia (Nguyen *et al.* 1990).

Five polymorphisms in the ABCG5 and ABCG8 genes have been identified (Hubáček *et al*. 2001) that influenced plasma lipid levels. The analyses indicated an association between a polymorphism (D19H) in exon 1 of ABCG8 and the plasma concentrations of campesterol. The finding of an association between plasma sitosterol concentrations and this nonconservative substitution suggests that the substitution of histidine for aspartic acid at amino acid 19 alters the function of ABCG8. Two other polymorphisms examined were also associated with plasma sterol concentrations. A common nonconservative substitution (T400K) was associated with the plasma concentrations of sitosterol, although the association of this polymorphism with plasma campesterol concentration was marginal (Berge *et al.* 2002). The substitution of valine for alanine at amino acid 632 was associated with plasma cholesterol concentrations, but was not consistently associated with any of the other sterols. The other two polymorphisms (Q604E) in ABCG5 and (Y54C) in ABCG8 were not associated with plasma lipid levels.

The functions of the ABCG3 and ABCG4 transporters are unknown.

Other ABC gene subfamilies

ABCB subfamily

The ABCB subfamily is unique in that it contains both full and half transporters. Four full transporters and seven half transporters are currently identified as members of this subfamily. ABCB1 is the first human ABC transporter cloned and characterized through its ability to confer a multidrug-resistance phenotype to cancer cells (Juliano and Ling 1976). The functional sites of ABCB1 include the blood-brain barrier and the liver.

The ABCB2 and ABCB3 genes are half transporters that form a heterodimer to transport peptides into the endoplasm reticulum, which are presented as antigens by the Class I HLA molecules.

The ABCB4 and ABCB11 proteins are both located in the liver and are involved in the secretion of bile acids (van Helvoort *et al*. 1996). Mutations in the human ABCB4 gene are the underlying cause of progressive familiar intrahepatic cholestasis type 3 (Deleuze *et al*. 1996, de Vree *et al*. 1998). Patients have increased cholestatic serum markers and high γ-glutamyltranspeptidase levels. Mutations in the human ABCB11 gene are associated with progressive familiar intrahepatic cholestasis type 2, a disease characterized by low biliary bile salt concentration, elevated serum bile salt concentrations, and normal γ-glutamyltranspeptidase levels (Strautnieks *et al*. 1998).

The remaining four half transporters, ABCB6, ABCB7, ABCB8 and ABCB10 localize on mitochondria, where they function in iron metabolism and transport of Fe/S protein precursors (Kispal *et al*. 1997). The closest homolog of the transporter associated with antigen

processing (TAPs) (ABCB2 and ABCB3), the ABCB9 half transporter, has been localized on lysosomes.

ABCC subfamily

The ABCC subfamily contains 12 full transporters with a diverse functional spectrum that includes ion transport, cell surface receptor, and toxin secretion activities. MRP-like proteins are organic anion transporters, i.e. they transport anionic drugs as well as neutral drugs conjugated to acidic ligands (glutathione, glucuronate, or sulfate) and play a role in resistance to nucleoside analogs (Borst *et al*. 2000).

The ABCC1 protein is a chloride-ion channel that has a role in exocrine secretion, and its mutations in ABCC1 cause cystic fibrosis (Quinton 1999). Cystic fibrosis is a genetic autosomal recessive disease. Cystic fibrosis causes the production of abnormally thick and sticky mucus in several different parts of the body, predominantly in the lungs and other parts of the respiratory system (Dean *et al*. 1990). It also affects the pancreas, leading to serious digestive problems.

Mutations in ABCC2 cause Dubin-Johnson syndrome. Dubin-Johnson syndrome is inherited as an autosomal recessive disorder. The transport of bilirubin from the liver into the biliary system is abnormal with bilirubin accumulating in the liver. Affected people have life-long low-grade jaundice, which may be aggravated by alcohol, pregnancy, infection, and other environmental factors (Wada *et al*. 1998).

Mutation in ABCC6 caused pseudoxanthoma elasticum. Pseudoxanthoma elasticum is an inherited systematic disorder affecting the connective tissue, and is characterized by progressive calcification of the elastic fibers of the eye, skin, and vasculature (Neldner 1988). Mutation in ABCC8 caused familial persistent hyperinsulinemic hypoglycemia of infancy. This is an autosomal recessive disorder in which subjects display unregulated insulin secretion (Thomas *et al*. 1995).

The ABCC4, ABCC5, ABCC11, and ABCC12 proteins are smaller than the other MRP1-like genes and lack an amino-terminal domain that is not essential for transport function.

ABCD subfamily

The ABCD subfamily contains four genes in the human genome and two each in the *Drosophila* and yeast genomes. All of the genes encode half transporters that are located in the peroxisome (Shani *et al*. 1998), where they function as homo- and/or heterodimers in the regulation of very long chain fatty acid transport. Mutations in the ABCD1 gene have been identified in the majority of X-linked adrenoleukodystrophy (X-ALD). It is a neurodegenerative disorder characterized by progressive demyelination of the nervous white matter system and adrenal insufficiency (Mosser *et al*. 1993). Biochemically, the accumulation of very long chain fatty acids is the hallmark of all X-ALD forms.

ABCE and ABCF subfamilies

The ABCE and ABCF subfamilies contain proteins, which have ATP-binding domains that are clearly derived from others ABC transporters, but have no transmembrane domain and are not known to be involved in any membrane transport functions. The ABCE subfamily is comprised solely of the oligo-adenylate binding protein; the molecule recognizes oligo-adenylate that is produced in response to infection by certain viruses. Each ABCF gene contains a pair of nucleotide-binding folds. The best characterized member, the *S. cerevisiae* GCN20 gene mediates the activation of eIF-2 α-kinase (Marton *et al*. 1997) and its human homolog, ABCF1, is associated with the ribosome and appears to have a similar role (Tyzack *et al*. 2000).

Conclusions

Study of ABC transporters is still in its infancy, but recent knowledge in this area has led to the elucidation of the cause of several significant inherited human diseases, and to new insights into possible treatments of cancer and drug pharmacokinetics.

Acknowledgements

This work was supported by IGA MHCR grant CEZ:L17/98:00023001.

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