Chemico-Biological Interactions 180 (2009) 327–339

Contents lists available at ScienceDirect

Chemico-Biological Interactions

journal homepage: www.elsevier.com/locate/chembioint

Mini review

Transport of lipids by ABC proteins: Interactions and implications for cellular toxicity, viability and function

Irving L.M.H. Aye [1], Ambika T. Singh [1], Jeffrey A. Keelan *

School of Women's and Infant's Health, University of Western Australia, King Edward Memorial Hospital, 374 Bagot Road, Subiaco, Perth, WA 6008, Australia

ARTICLE INFO

Article history:
Received 9 December 2008
Received in revised form 15 April 2009
Accepted 24 April 2009
Available online 6 May 2009

Keywords:
ABC transporters
Phospholipids
Sphingolipids
Ceramide
Cholesterol
Apoptosis

ABSTRACT

Members of the ATP-binding cassette (ABC) family of membrane-bound transporters are involved in multiple aspects of transport and redistribution of various lipids and their conjugates. Most ABC transporters localize to the plasma membrane; some are associated with liquid-ordered cholesterol-/sphingolipid-rich microdomains, and to a lesser extent the membranes of the Golgi and endoplasmic reticulum. Hence, ABC transporters are well placed to regulate plasma membrane lipid composition and the efflux and redistribution of structural phospholipids and sphingolipids during periods of cellular stress and recovery. ABC transporters can also modulate cellular sensitivity to extrinsic pro-apoptotic signals through regulation of sphingomyelin–ceramide biosynthesis and metabolism. The functionality of ABC transporters is, in turn, modulated by the lipid content of the microdomains in which they reside. Cholesterol, a major membrane microdomain component, is not only a substrate of several ABC transporters, but also regulates ABC activity through its effects on microdomain structure. Several important bioactive lipid mediators and toxic lipid metabolites are also effluxed by ABC transporters. In this review, the complex interactions between ABC transporters and their lipid/sterol substrates will be discussed and analyzed in the context of their relevance to cellular function, toxicity and apoptosis.

Contents

* Corresponding author. Tel.: +61 8 9340 1880; fax: +61 8 9381 3031.
E-mail address: jeff.keelan@uwa.edu.au (J.A. Keelan).
[1] Both authors contributed equally.

0009-2797/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.cbi.2009.04.012

1. Introduction

The mammalian ATP-binding cassette (ABC) superfamily consists of 49 individual transport proteins belonging to 7 sub-families (ABCA to ABCG) involved in translocating a wide range of substrates across cellular membranes [1–4]. While ABC proteins are typically localized in the plasma membrane, some are also expressed in intracellular membranes of the Golgi, mitochondria and endoplasmic reticulum [4–8]. ABC transporters mediate ATP-driven transmembrane efflux against a concentration gradient of a wide variety of amphiphilic ligands, including glycolipids, phospholipids, sterols and xenobiotics [4,9,10]. As such, they participate in diverse biological processes such as waste disposal and detoxification, cell signaling, lipid trafficking, membrane homeostasis, drug resistance and stem cell development [11,12].

Members of the ABC superfamily show extensive sequence homology and conservation of domain organization [13,14]. Functional ABC proteins typically comprise of two transmembrane domains and two ATP-binding domains. Substrate specificity is determined by 5 or 6 α-helices yielding anywhere between 5 and 17 transmembrane segments. While most ABC proteins exist as full transporters, several members (mainly from the G-subfamily) have only 1 transmembrane domain and 1 nucleotide binding fold and are therefore known as "half-transporters" [15]. These half-transporters form homo/hetero-oligomers to function [4–8].

Historically, research on ABC transporters focused originally on their role in xenobiotic transport (phase III metabolism) [10,16]. The major ABC xenobiotic transporters are ABCB1 (multidrug resistance protein 1; MDR1), ABCG2 (breast cancer resistance protein; BCRP) and ABCC1-3 (multidrug resistance associated protein [MRP] 1–3), all of which been shown to limit the accumulation of cytotoxic compounds in tumour cells [17–23] as well as healthy tissues [24–26]. ABCB1, which encodes the archetypal ABC transporter MDR1 (originally termed P-glycoprotein), is the most clinically important and pharmacologically active xenobiotic efflux transporter [10,27]; it is widely expressed and transports a wide variety of basic or neutral organic compounds. The related transporter, MDR3, transports a subset of MDR1 substrates, but has a more limited range of expression and activity than MDR1 [28,29]. ABCG2/BCRP and members of the MRP family also efflux a broad range of xenobiotic substrates including some clinically relevant drugs that are not MDR1 substrates [30].

2. Endogenous lipid substrates of ABC transporters

2.1. Mechanism of lipid efflux

Independent of their drug trafficking functions, ABC proteins are also involved in transport and regulation of a variety of endogenous compounds such as nucleotides, bile acid, porphyrins, steroids/steroid conjugates and phospho-/glyco-/sphingolipids [10,31–33]. ABC proteins actively participate in maintaining lipid asymmetry across cellular membranes, including the plasma membrane [34]. Hypothetically, all ABC transporters that are involved in trafficking of hydrophobic drugs have the ability to transport analogs of membrane lipids [35]. Following the identification of a role for the archetypal drug transporters MDR1 and MDR3 in phospholipid efflux [36,37], many of the aforementioned ABC drug transporters have also been implicated in lipid transport [35,38,39]. In addition, many of the more recently identified members, particularly from the ABCA and ABCG subfamilies, have been identified as key molecules in the regulation of cellular lipid transport and whole body lipid homeostasis (Table 1). What is more, evidence now suggests that the function of many of these proteins is, in turn, dependent on the membrane lipid milieu in which they reside.

The lipid bilayer of the plasma membrane is made up of asymmetrically arranged lipid species [40]. This asymmetric distribution is usually preserved throughout the cellular life but in certain circumstances, such as during cell differentiation or apoptosis, asymmetry is lost through facilitated phospholipid translocation or endo-/exocytosis and related processes. Transbilayer movement of lipids is actively orchestrated by three major groups of enzymes: P-type ATPases (flippases), ABC transporters (floppases) and scramblases/lipid translocases (Fig. 1) [41,42]. In addition, certain regulatory molecules have been postulated to co-exist with various lipid translocases to assist with their transport functions [43]. Consequently, disruption of the membrane equilibrium due to lateral movement of lipids across the membranes occurs; this is corrected when another lipid is either translocated back in the opposite direction or by expansion of one side of the membrane resulting in curvature [44]. The latter effect may be the underlying cause of endocytotic vesicle budding when lipids translocate towards the cytoplasmic surface [45,46].

In general, substrates for ABC transport must first diffuse into the membrane phospholipid bilayer before they can be effluxed [47]. Substrate binding typically occurs in the cytoplasmic side of the lipid bilayer, followed by translocation to the outer leaflet (floppase activity) prior to eventual efflux to an acceptor or, in the case of hydrophilic compounds, directly into the extracellular fluid (discussed in more detail below) [47,48]. However, no single model adequately explains ABC transporter efflux mechanism, and it is likely that different members and substrates employ distinct mechanisms. For many transporters, the "hydrophobic vacuum cleaner" and "flippase" models correspond with structural and experimental data [49]. The "hydrophobic vacuum cleaner" model postulates that ABC transporters efflux substrates which have diffused into the plasma membrane bilayer into the extracellular aqueous environment [50]. This model is commonly used to explain the drug–efflux function observed in those multidrug-resistant transporters. The alternative flippase model, which pertains more to phospholipid efflux, entails translocation of substrates from the inner to outer leaflet, or directly to the extracellular space [48]. A composite model has also been proposed where the transporter relocates the substrate to a region of intermediate hydrophobicity adjacent to the transporter in the extracellular leaflet of the plasma membrane [47]. This places the substrate in an activated state, thereby energetically favouring its binding and removal by an acceptor molecule/docking protein such as apolipoprotein-AI (apoA-I). These models are difficult to distinguish experimentally.

Table 1
Human ABC lipid transporters, their tissue expression, lipid substrates, modulators, acceptors and associated genetic diseases.

Gene Name	Major sites of expression	Lipid Substrates	Lipid Modulators	Acceptors	Associated genetic disorders	References
ABCA1 (ABC1)	Ubiquitous	Chol, PS SM, PC, S1P, 25-OH-chol	Cer (stimulates) LacCer (inhibits)	Apo-AI, AII, E, CI, CII, CIII, AIV	Tangier disease, familial hypoalphalipoproteinemia (ischemic heart disease)	[52,189,200,236,237]
ABCA2	Brain	Chol, SM, PS, PE			(Alzheimer's disease)	[63,66,133,238]
ABCA3	Lung, brain, heart, pancreas	Chol, SM, PC			Fetal/neonatal lung deficiency	[67,69,134,135,239]
ABCA4 (ABCR)	Retinal photoreceptors	*N*-retinyl-PE		(Cytosolic)	Fundus flavimaculatis; retinitis pigmentosum 19; cone-rod dystrophy (age-related macular degeneration)	[136]
ABCA7	Myelolymphatic system, brain, skin	Chol, PS, PC Cer		ApoA-I (ApoA-II?)		[156,159,240,241]
ABCA12	Skin keratinocytes	GluCer			Harlequin ichthyosis	[133,158]
ABCB1 (MDR1)	Brain, liver, kidneys, GI, placenta	SM, GluCer, sphingoid bases, PC PS, PE, Chol, PAF, corticosteroids, androgens, estrogens, progestins	Sph, Cer, S1P (stimulates) SM GluCer, GalCer (inhibits)			[34,37,104,120,148,170,197,242–244]
ABCB3 (TAP-2)	Ubiquitous	PS, PE, PC			(Immune deficiency)	[37,116,121,122]
ABCB4 (MDR3)	Liver, bile canilicular membrane, placenta	PC			Progressive familial intrahepatic cholestasis	[245–248]
ABCC1 (MRP1)	Brain, liver, kidneys, GI, placenta	LTC_4, GluCer, SM, PC, S1P, GSH, UGT, steroid conjugates				[105,109,127,150,193,249,250]
ABCG1	Ubiquitous	Chol, PC, SM, 7β-OH-chol, 7-keto-chol	SM (stimulates)	HDL (LDL?)		[83,94,225,251,252]
ABCG2 (BCRP)	Placenta, breast, liver, GI	PC, PS Sulphated steroids	Chol (stimulates)			[39,190,192,253,254]
ABCG4	Macrophage, brain, eye, spleen, liver	Chol				[93,95,97]
ABCG5 & ABCG8	Liver, GI	Plant sterols, Chol		HDL Bile salts	Sitosterolemia	[99,101–103,255]

Abbreviations: Apo, apolipoprotein; HDL, high density lipoproteins; LDL, low density lipoproteins; Chol, cholesterol; 7β-OH-chol, 7β-hydroxycholesterol; 25-OH-chol, 25-hydroxycholesterol; 7-keto-chol, 7-ketocholesterol; PC, phosphatidylcholine; PE, phosphatidyl-ethanolamine; PS, phosphatidylserine; *N*-retinyl-PE, *N*-rentinyl phosphatidylethanolamine; Cer, ceramide; GalCer, galactosylceramide; GluCer, glucosylceramide; LacCer, lactosylceramide; Sph, sphingosine; S1P, sphingosine-1-phosphate; SPK1, sphingosine kinase-1; LPA, lysophosphatidic acid; LTC_4, leukotriene C_4, PAF, platelet activating factor; GSH, glutathione; UGT, glucuronide; GI, gastrointestinal.? indicates uncertainty.

While some substrates (e.g. xenobiotics) can be expelled from the membrane directly into the extracellular fluid, many endogenous lipophilic substrates require docking of an acceptor protein or carrier macromolecule to create the energetically favourable conditions needed to promote dissociation of the lipid from the donor membrane and its subsequent efflux from the cell. Typically, carrier proteins such as apolipoproteins and albumin act as acceptors for the majority of cellular

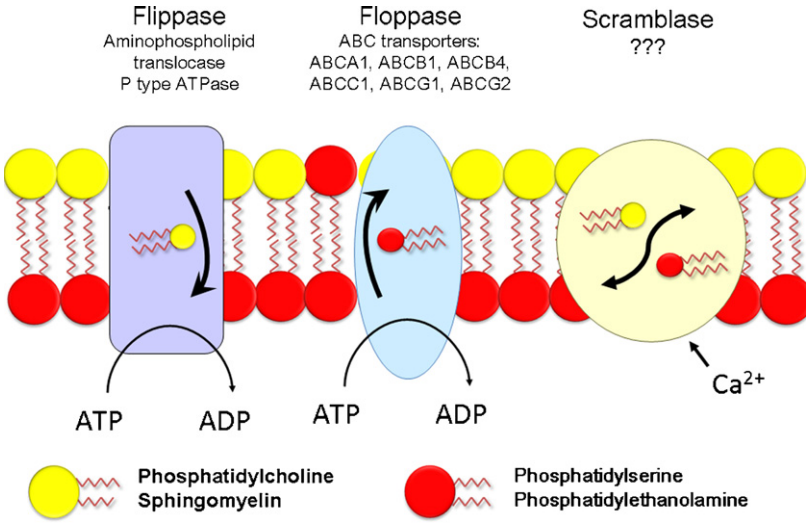

Fig. 1. Regulators of plasma membrane lipid asymmetry. Translocation of lipids is carried out by the flippases (active translocation to the cytoplasmic leaflet), floppases (active translocation to the exoplasmic leaflet) and scramblases (promote equilibrium through a Ca^{2+}-dependent mechanism).

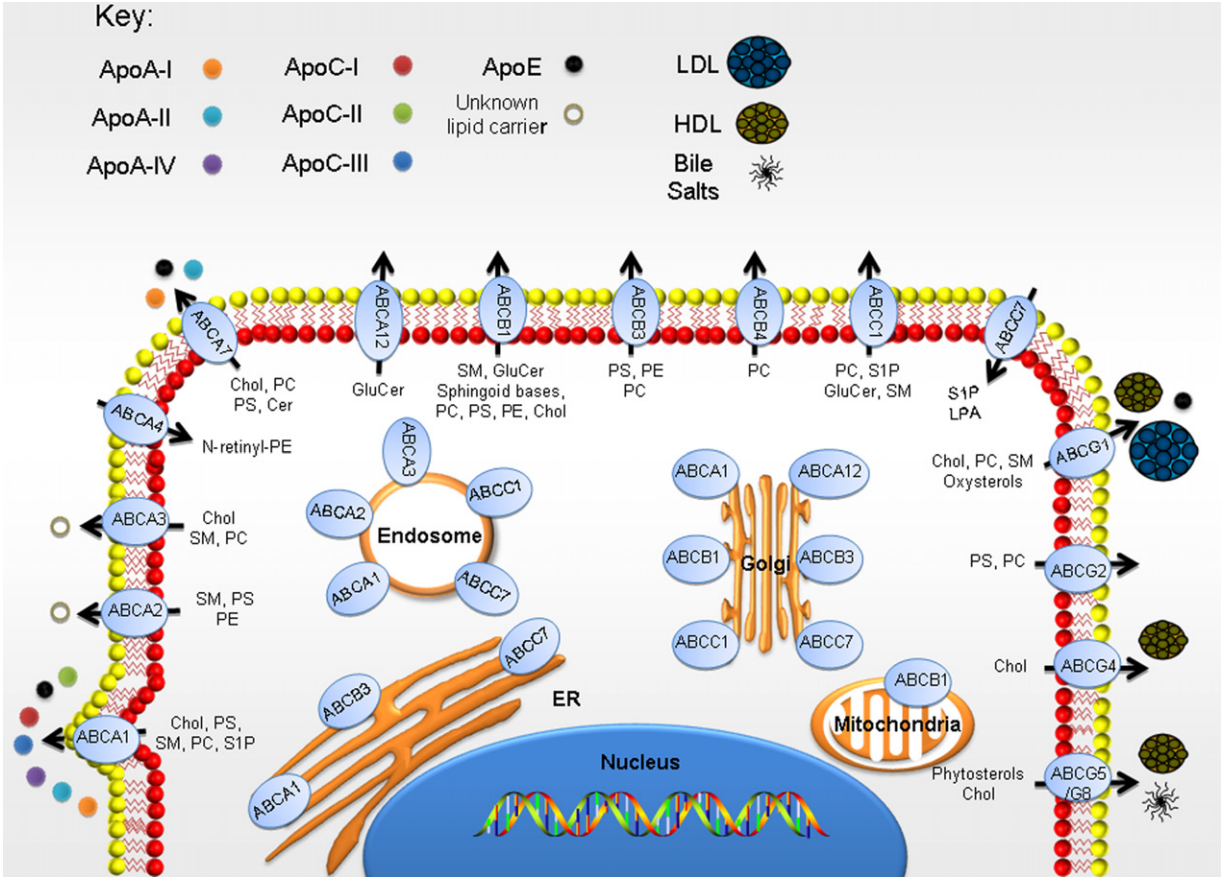

Fig. 2. Overview of ABC transporters involved in lipid efflux. Schematic representation of subcellular ABC transporter localization, known acceptors and direction of transport. Black arrows represent transport direction at the plasma membrane. Vectorial transport by intracellular transporters has not been firmly established. Apo, apolipoprotein; HDL, high density lipoproteins; LDL, low density lipoproteins; Chol, cholesterol; PC, phosphatidylcholine; PE, phosphatidylethanolamine; PS, phosphatidylserine; Cer, ceramide; *N*-retinyl-PE, *N*-rentinyl phosphatidylethanolamine; GluCer, glucosylceramide; S1P, sphingosine-1-phosphate; SM, sphingomyelin; LPA, lysophosphatidic acid.

sphingolipids and phospholipids that are ABC substrates [51,52] (Fig. 2).

2.2. ABC efflux of cholesterol and other sterols

2.2.1. ABCA family

Cholesterol efflux is primarily carried out by members of the ABCA and G families. A ubiquitously expressed protein, ABCA1 has been reported to be involved in disorders ranging from atherosclerosis and diabetes to Alzheimer's disease [53–55] (Table 1). A significant breakthrough in our understanding of the regulation of cholesterol disposition was uncovered by the identification of ABCA1 mutations as the cause of a rare lipid disorder known as Tangier disease [56–58]. Individuals with this disease often present with very low levels of high density lipoproteins (HDL) and apolipoprotein A-I (apoA-I) due to an impairment in ABCA1-dependent cholesterol translocation to these lipoproteins. On the other hand, overexpression of ABCA1 increases plasma HDL levels and protects against atherosclerosis in animal models [59]. Hepatic ABCA1 is a major regulator of plasma HDL production, whereas ABCA1 in macrophages has little influence on circulating HDL, but is critical in limiting macrophage cholesterol accumulation and subsequent pro-atherosclerotic activation [54,60]. Very recently, murine placental abca1 has also been shown to play an important role in trans-placental transfer of cholesterol to the fetus, together with the HDL-tethering protein sr-b1 [61]. Regulation of cholesterol distribution by other ABCA members has also been demonstrated by findings that ABCA2 over-expression in Chinese hamster ovary cells reduces trafficking of LDL-derived cholesterol to the endoplasmic reticulum [62,63]. High ABCA2 expression levels in the brain and co-localization with Alzheimer's disease markers suggest that ABCA2 may play an important role in neuronal lipid metabolism [62,64,65]. However, direct efflux to apolipoproteins from ABCA2 has not been able to be demonstrated [66] so the mechanistic explanation underlying these observations is not clear. ABCA3, which is expressed predominantly in the lungs [67], has also been demonstrated to efflux cholesterol in an alveolar cell line [68] and may be implicated in aspects of fetal lung surfactant production during lung maturation [69].

Cholesterol transport by ABCA1 is highly dependent on the presence of apoA-I, although transport to other lipoproteins (e.g. apoE) may also occur. An interaction between apoA-I and ABCA1 at the plasma membrane surface during cholesterol efflux has been confirmed through different approaches such as cross-linking [70,71], immunoprecipitation [72], biotinylation [73] and radiolabeling [74–76]. ABCA1-mediated cholesterol efflux has also been shown to have a dependence on plasma membrane ceramide content [77]. However, while some data suggest a direct interaction between ABCA1 and apoA-I at the plasma membrane surface [78], leading to lipidation of apoA-I and association with nascent HDL [52], only ~10% of cell associated apoA-I can be cross-linked to ABCA1 [79]. Moreover, structural studies have demonstrated that apoA-I binding and cholesterol efflux are dissociable [80,81]. Furthermore, ABCA1 significantly decreases plasma membrane rigidity independent of its interactions with apolipoproteins [82]. ABCA1 can also transport several species of sphingomyelin and PC, and

function co-ordinately in effluxing them together with cholesterol from peripheral cells [83]. In light of these data it has been proposed that ABCA1 may not act as a receptor for apoA-I *per se*, but instead generates high affinity binding sites for apoA-I by enriching the exofacial leaflet with cholesterol and phospholipids, modifying the lipid domain environment and facilitating apoA-I docking and cholesterol uptake without direct contact [52]. This may promote formation of apo-A1-containing exovesicles and solubilization of apo-A-I-bound phospholipids and cholesterol for incorporation into nascent HDL [51,84,85].

To complicate matters further, an alternative model has been proposed, whereby apoA-I is internalized via receptor-mediated endocytosis and endosomally acquires phospholipids and associated cholesterol from specific intracellular pools (lipid droplets) prior to re-secretion [86]. However, recent evidence suggests that this retroendocytotic pathway contributes less than 2% of lipidated HDL, and the plasma membrane is in fact the major site of apoA-I lipidation and efflux of cholesterol by ABCA1 [87,88]

2.2.2. ABCG family

All members of the human ABCG subfamily, with the exception of ABCG2/BCRP, function as cholesterol transporters [89]. ABCG1 displays the most widespread expression pattern, and is currently thought to be one of the major regulators of cellular cholesterol content in mammals [89,90]. In many aspects ABCG1 displays similarities to ABCA1, such as tissue expression patterns and regulatory pathways [52,91]. Unlike ABCA1, however, apoA-I does not act as an acceptor for cholesterol effluxed via ABCG1, but is instead dependent on HDL (specifically, HDL_2 and HDL_3), discoidal apoE and possibly LDL [92]. ABCG1-mediated cholesterol transfer to HDL does not require their direct interaction [93], and it has been proposed that ABCA1 and ABCG1 are responsible for redistributing cholesterol pools to different membrane domains accessible to either apoA-I or HDL [94]. ABCG4, which is highly homologous to ABCG1, also promotes cholesterol efflux to HDLs but not apolipoproteins [82,93]. It is likely that ABCA1, G1 and G4 act in concert to facilitate cholesterol efflux [95], where ABCA1 performs initial lipidation of apoA-I with cholesterol and PC to generate nascent HDL, which is then an acceptor for ABCG/4-transported cholesterol [96]. Unlike ABCG1, however, tissue expression of ABCG4 is much more restricted [97,98].

The ABCG5 and ABCG8 half transporters dimerize with each other in the endoplasmic reticulum before translocating to the cell surface. Largely present in the liver and intestines, ABCG5 and ABCG8 transport plant and shellfish sterols normally encountered in our diet. Mutations in these genes are linked to β-sitosterolemia, a rare disorder caused by accumulation of the phytosterol β-sitosterol [99,100]. In addition to plant sterols, β-sitosterolemics also display high levels of plasma cholesterol but very low levels of biliary cholesterol. This has led to the hypothesis that cholesterol may also be a substrate of ABCG5/G8. Indeed, mice models of abcg5/g8 knockouts and knock-ins confirm this hypothesis, and while intestinal expression is required to limit dietary sterol absorption, hepatic expression promotes secretion into the bile [101,102]. Interestingly, ABCG5/G8-mediated cholesterol efflux is dependent on bile salts as acceptors and not apolipoproteins or HDL [103].

2.2.3. Sterol transport by other ABC proteins

Besides the ABCA and ABCG subfamilies, active redistribution of cholesterol across the cell membrane by ABCB1/MDR1 has been described [104]. Additionally, intracellular trafficking of cholesterol has also been detected by MDR1 in an ATP-dependent manner, although some studies suggest that this may be a consequence of its sphingolipid effluxing function (see below), since cholesterol is known to interact with glucosylceramide [105]. Recently, efflux of a variety of other steroids by MDR1 has been demonstrated [106]. Overexpression of MDR1 human colon carcinoma cells reduces intracellular levels of glucocorticoids (cortisol, dexamethasone), mineralcorticoids (aldosterone, corticosterone), and, to a lesser extent, androgens (testosterone, dihydrotestosterone), estradiol and progestins (pregnenolone, 17 hydroxyprogesterone) [107]. Surprisingly, progesterone is not an MDR1 substrate, although both agonist and antagonist effects of progesterone on MDR1 activity have been reported [107,108]. There is also evidence of steroid transport by ABCC1/MRP1 and ABCG2/BCRP. Estradiol, eicosanoids and their glutathione conjugates are transported by MRP1 [109], while BCRP translocates sulphated conjugates of steroids such as dehydroepiandrosterone sulphate (DHEAS), 17β-estradiol-3-sulphate and estrone-3-sulphate [110,111]. The steroid efflux function suggests an involvement of some ABC transporters in endocrine function, although the lack of aberrant pathologies in knockout mice imply at most a secondary role of these transporters in steroid regulation [112,113]. Both ABCG1 and G4 are expressed in the testis, raising the possibility that they perform an endocrine/steroid efflux role in this tissue [114].

2.3. Phospholipid efflux

Several ABC transporters recognize and efflux the major phospholipids: phosphatidylcholine (PC), phosphatidylethanolamine (PE) and phosphatidylserine (PS). Using experimental lipid substrates labelled with the fluorophore nitrobenzoxadiazole (NBD), several studies have provided evidence of MDR1- and MDR3-dependent regulation of cellular PC, PE and PS distribution [37,115–122]. MDR3 is localized mainly to the liver, but has also been reported to be abundantly expressed in the placenta [123]. The clinical significance of PC transport by MDR3 is apparent in a genetic condition known as progressive familial intrahepatic cholestasis (PFIC), a disorder involving liver inflammation and fibrosis, which occurs as a consequence of an MDR3 functional mutation [124]. In addition, PC and PS also act as substrates for the other xenobiotic transporters BCRP [39] and MRP1 [38,125–127]. These findings are indicative of a role for lipid-effluxing ABC proteins in regulating membrane composition, asymmetry and stability via translocation of key membrane phospholipids.

ABCA1 and ABCG1 also regulate cellular phospholipid levels. Early evidence suggested that ABCA1 acts as a translocator of PC, PS and PE [74,81,128–130], while ABCG1 transports PC only [83,131]. As discussed above, the generation of nascent HDL particles requires ABCA1-mediated phospholipid efflux to apoA-I [128,132].

Abca2 and abca3 null mice display impaired phospholipid regulation: low levels of PE and PS in the brains of abca2 null mice [133], and low PC content in lamellar bodies of alveolar tissues in abca3 null animals [69,134]. Furthermore, abca3 mutations are associated with severe neonatal surfactant deficiency, illustrating the vital role that this transporter plays in pulmonary lipid transport [135]. ABCA4 on the other hand transports a retinal-specific phospholipid (*N*-retinylidene phosphatidylethanolamine) found in rod disc membranes of the eye [136,137]. Mutations in this gene have also been documented in several retinal degenerative disorders and current evidence suggests that this protein may be a retinal-specific transporter [138–140].

Members of the eicosanoid family of lipid mediators are also substrates for ABC proteins. Leukotriene C4 is effluxed by ABCC1/MRP1 [141–143], MRP2 [141] and MRP3 [117], whereas MRP4 is a transporter of prostaglandin E_1 and E_2 [144]. MRP4 may also transport other related eicosanoids such as PGA_2, $PGF_{2\alpha}$ and thromboxane A_2 [144]. The physiological importance of these transporters with respect to eicosanoid secretion remains to be determined.

2.4. Efflux and trafficking of sphingolipids

2.4.1. ABCB1/MDR1

Although sphingolipids (e.g. sphingomyelin, sphingosine, ceramide and glucosylceramide) are localized primarily in the plasma membranes, a significant fraction can be found in the Golgi and endoplasmic reticulum. In addition to cellular efflux, trafficking of sphingolipids between organelles is also an important and regulated process. Amongst the ABCB subfamily, MDR1 is rather promiscuous in the specificity of its sphingolipid substrates, although much of this evidence is based on transport of short chain, fluorescent sphingolipids and may not apply to natural substrates [145]. Nevertheless, Eckford and Sharom presented evidence that the ability of MDR1 to transport drugs and act as a sphingolipid floppase occur via the same mechanism [119]. MDR1 mediates translocation of sphingomyelin and glucosylceramide across the plasma membrane of drug-resistant and normal cells [120]. MDR1 also mediates translocation of glucosylceramide from the cytosolic to luminal surface of the Golgi, which is accompanied by an increase in glucosylceramide synthase activity and synthesis of complex glycosphingolipids [146,147]. Trafficking of sphingomyelin and glucosylceramide between the Golgi and plasma membrane may also be MDR1-dependent [120]. In cancer treatments studies using Caco-2 cells, MDR1 has been shown to prevent accumulation of cytotoxic plant and fungal sphingoid bases (except sphingosine) [148].

2.4.2. ABCC1/MRP1

MRP1 is another ABC family member that has been reported to translocate fluorescent short-chain cholesterol and sphingolipids, such as sphingomyelin and glucosylceramide, similar to MDR1's floppase mechanism; however, its transport activity is across basolateral membranes as opposed to the apical membrane efflux of MDR1 [149]. However, similar to MDR1, the apparent inability of MRP1 to transport long-chain lipids throws doubt on the accuracy of the findings based on the use of short-chain analogs [105,149]. On the other hand, sphingomyelin and glucosylceramide transport can be prevented by MDR1 and MRP1 antagonists [120,149]. Furthermore, while many studies have reported MRP1-mediated transport of glutathione-conjugated substrates, others have reported no indication of any covalent glutathione–lipid conjugates amongst the short-chain sphingolipids transported by this protein [149]. The underlying causes of these discrepancies await clarification.

An important and specific role of MRP1 in sphingosine-1-phosphate (S1P) transport in mast cells has recently been identified [150]. S1P is a potent mitogen and HDL component that acts via binding to extracellular receptors; therefore, its secretion from the cell is vital to its ability to exert its actions [151–153]. Secretion of S1P in astrocytes is also inhibited by small interfering RNAs specific to ABCA1, implicating ABCA1 in the efflux of this bioactive sphingolipid [154]. Whether other sphingolipids are also transported by ABCA1 remains unknown.

2.4.3. ABCA family

Gene knockout models have also implicated ABCA2 and ABCA3 as transporters of sphingomyelin [133,155]. ABCA2 performs a vital role in murine sphingomyelin and ganglioside metabolism [133]. Sphingomyelin is also a substrate of ABCG1, which translocates this lipid to HDL particles [83]. Other ABCA subfamily members shown to mediate transport of phospholipids and glucosylceramide include ABCA3, ABCA7 and ABCA12 [156–158]. In keratinocytes, ABCA7 expression increases dramatically with differentiation, coinciding with the accumulation of ceramide [159]. A possible involvement between ABCA7 and ceramide was also suspected when overexpression of ABCA7 in cells produced elevated ceramide levels which eventually hampered cell viability [159]. In cultures of keratinocytes from harlequin ichthyosis patients (with mutations in the ABCA12 gene), there is an abnormality in glucosylceramide distribution which was restored by genetic correction of the ABCA12 gene [157,158]. ABCA12 may, therefore, also function as a ceramide transporter, although it should be noted that a direct interaction between sphingolipids and ABCA7 or ABCA12 was not reported in these cases.

3. Effects of membrane lipids on ABC transporter activity

3.1. Membrane microdomains (lipid rafts) and ABC activity

In addition to regulating membrane lipid composition and distribution, the activity of ABC transporters can in turn be modulated by the lipid environment in which they reside. The perception of the plasma membrane as a homogenous phospholipid bilayer is outmoded and has long been replaced by concepts of lateral, structural and compositional heterogeneity manifesting as membrane microdomains of variable size, composition and function in a state of constant flux [160–164]. Extensive studies have attempted to define the properties and functions of these specialized microdomains (historically called lipid rafts) [161,165,166]. Several different definitions of membrane microdomains, their composition and structure exist based on various methods of isolation. However, at a recent symposium they were collectively defined as "*small (10–200 nm), heterogeneous, highly dynamic, sterol- and sphingolipid-enriched domains that compartmentalize cellular processes, and at times stabilize to form larger platforms through protein–protein and protein–lipid interactions*" [161]. Terms that have widely been used to describe membrane microdomains such as "lipid rafts", "detergent resistant", "plasma membrane" and "liquid-ordered" are no longer considered accurate [161], although are still used in light of the lack of alternatives. In this review, we will use the term "membrane microdomain" as a general descriptor for liquid-ordered, cholesterol-/sphingolipid-rich regions of the plasma membrane, with more specific terminology employed where distinctions between isolation methodologies are necessary. Expression of a wide range of cell signaling proteins in membrane microdomains suggests the close involvement of these domains in signal transduction [167–169]. Studies have demonstrated roles for membrane microdomains in cellular signaling, viral and toxin entry, and protein and lipid trafficking [160–164]. ABC transporters MDR1, MRP1, ABCA1, ABCG1 and ABCG2/BCRP are amongst the various proteins expressed in membrane microdomains and their complex interactions with membrane lipids and/or proteins determine their overall cellular effects.

3.1.1. MDR1

Expression of MDR1 has been identified in various different kinds of membrane microdomain fractions with different functions based on its localization [170] and domain properties [171]. Originally about 30–40% of cellular MDR1 protein was thought to reside in "classical" Triton X100-resistant microdomains (TRMs) [172]. However, it is now thought that while a small proportion of MDR1 exists in these domains, the majority is localized to non-classical domains that are insoluble in other detergents such as Brij 96 and Lubrol WX (LRMs) [165,173]. Cholesterol depletion has little effect on MDR1-associated ATPase activity in these LRMs. Evidence of a correlation between expression of caveolin, an integral structural component originally identified as a raft-like domain (caveolae), and MDR1 has been observed in drug-resistant cells implicating a possible role for these membrane domains in MDR function [172]. In agreement with this work, Garrigues et al. proposed an

involvement of MDR1 in stabilization of cholesterol-enriched membrane microdomains and caveolae [104]. Furthermore, this transporter has also been shown to transport caveolae from the Golgi apparatus to the plasma membrane [34].

As membrane microdomains are highly enriched in sphingomyelin, ceramide and cholesterol, the activity of domain-associated proteins, including ABC transporters, is sensitive to variations in membrane content of these lipids [166,170]. Drug binding, transport and ATPase activity of MDR1 expressed in membrane microdomains have been shown to be influenced by cholesterol [71,174–176]. While some studies reported MDR1 function to be cholesterol-dependent, others argue that MDR1 is functional in the absence of cholesterol [170,177,178]. In contrast to MDR1, MRP1 has been localized to membrane microdomains with similar lipid/protein compositions exhibiting much less heterogeneity [165,173]. Moreover, reports show that only severe cholesterol depletion (<40%) was able to significantly reduce MRP1 activity [179,180].

3.1.2. ABCA1

ABCA1 was initially believed to be localized in lipid raft formations [181]. However, several studies have now reported that ABCA1 is not associated with the classic TRMs [182,183]. Instead, ABCA1 has been identified in the larger LRMs in macrophages [182]. Association in these domains is cell-type specific, since ABCA1 was not detected in either domain in fibroblasts. Furthermore, addition of apoA-I resulted in depletion of cholesterol and phospholipids from LRMs, while addition of HDL_3 depleted the cholesterol content of TRMs. While this study implicates ABCA1 localization in LRMs, HDL_3-specific removal of lipids from TRMs indicates that ABCG1 may be also involved. There is some evidence that ABCA1 may also be associated with caveolar-rafts [184]. However, this may again be cell-type specific, since no such interaction was observed in hepatocytes [185]. Despite the lack of association with classical TRMs, ABCA1 activity may nevertheless disrupt membrane microdomains assemblies. Overexpression of ABCA1 results in a marked reduction in the amount of cholesterol and sphingomyelin in TRMs [186]. Altering ABCA1 levels also impairs Akt signaling which is known to be regulated by microdomain composition and structure. On the other hand, mutations in the ATP binding domain of ABCA1 fail to induce cholesterol or sphingomyelin redistribution, and do not impair Akt signaling. [183]

3.1.3. ABCG family

Evidence of involvement of ABCG1 in membrane microdomains is suggested by reports that alteration of sphingomyelin levels affects ABCG1 function [94], although it should be noted that unlike ABCA1, ABCG1 has not been directly isolated from membrane microdomains. Studies have described cholesterol translocation to the extracellular leaflet of the plasma membrane by both ABCA1 and ABCG1 in macrophages in an apoA-I-dependent and/or -independent manner, a process which seems to be dependent on sphingomyelin content in the plasma membrane [93,187]. Ceramide, a major microdomain component, is also a regulator of cholesterol efflux via enhancement of plasma membrane-bound apoA-I [188]. Paradoxically, while reduced sphingomyelin levels enhance efflux of cholesterol by ABCA1, it may decrease ABCG1-mediated cholesterol efflux [189]. Cholesterol efflux is preferentially accompanied by flopping PC and sphingomyelin by ABCA1 and ABCG1, respectively [83,189].

Storch et al. have shown in canine kidney epithelial cells that BCRP activity is regulated by the cholesterol content of membrane microdomains [190]. BCRP expression was detected mainly in membrane microdomains, but interestingly, localization remained unaffected following cholesterol depletion [171,190]. In agreement with these findings, studies on human and insect membrane vesicles demonstrate variable BCRP stimulation depending on cholesterol loading and depletion [191,192]. Given the pivotal role of BCRP in the absorption, distribution and excretion of xenobiotics, recognizing the significance of cholesterol in modulating its activity could have important pharmacotherapeutic implications.

3.2. Sphingolipid regulation of ABC transporter function

Besides being substrates of ABC transporters, membrane lipids may in turn affect the functional activity and/or expression of these membrane proteins as they are an integral part of the plasma membrane [37,193]. The lipid environment may affect membrane proteins in several ways: by determining the concentration of various exogenous/endogenous substrates and controlling their transport rates; by determining suitability of endogenous lipids as substrate; by affecting their catalytic activity; and by providing a platform for substrate loading [170].

A considerable amount of evidence suggests that components of the sphingolipid biosynthetic and metabolic pathways are regulators of ABC function. Veldman et al. in MDR expressing ovarian carcinoma cells demonstrated inhibition of MDR1 activity by short chain sphingolipids sphingomyelin, glucosylceramide and galactosylceramide, while the opposite (stimulation) was observed with sphingosine [22]. However, since sphingosine inhibits protein kinase C (PKC) activity, and MDR1 activity is affected by PKC-mediated phosphorylation, it is possible that the stimulatory effects of sphingosine on MDR1 activity were indirect [194]. Nevertheless, trafficking of MDR1 to the canicular plasma membrane and induction of MDR1 expression has been shown to be directly dependent on glucosylceramide [195,196]. These effects of exogenous sphingolipids on MDR1 activity do not appear to be due to non-specific membrane perturbations, since other short chain lipids failed to have any effect. It is likely that MDR1 activity is modulated by these specific sphingolipids through interactions with domains of the proteins in the outer leaflet of the plasma membrane [22]. In contrast to these findings, upregulation of MDR1 expression by short-chain ceramide and glucosylceramide has been described in human breast cancer cell lines [196]. Modulation of MDR1 activity by natural long chain glucosylceramide in the Golgi has also been reported, conflicting with the popular assumption that the effects of sphingolipids on ABC transporters are restricted to short chain analogs [147].

Pilorget et al. described the regulation of MDR1 function by sphingosine kinase and S1P in endothelial cells of the blood brain barrier [197]. From their MDR1 substrate efflux studies they concluded that sphingosine kinase increases MDR1 expression through the generation of extra- and intracellular S1P. Interestingly, although S1P mediates the stimulation of MDR1 activity, on its own S1P had no effect on the expression of MDR1 [197].

Sphingolipids may also regulate cholesterol efflux via ABCA1. Ceramide enhances cholesterol efflux by increasing cell surface expression of ABCA1, thereby promoting increased apoA-I binding [198]. C_2-dihydroceramide, which lacks any apoptotic activity, was also shown to promote ABCA1 function [198,199]. In contrast, glycosphingolipids may reduce cholesterol efflux via the ABCA1/apoA-I pathway, as enhanced accumulation of lactosyl ceramide or other glycosphingolipids (as occurs in patients with glycosphingolipid storage disorder) reduces ABCA1 mRNA expression [200]. These findings support earlier studies indicating that cellular cholesterol efflux is inhibited by SM accumulation and accelerated when SM is depleted [201,202]. Collectively these studies suggest that glycosphingolipid synthesis and accumulation reduces ABCA1 levels, through an unknown mechanism, opposite to the actions of ceramide.

4. Transport of pro-apoptotic lipids by ABC transporters

4.1. MDR1

Under normal physiological conditions, MDR1 helps to maintain cell viability through efflux-mediated cellular detoxification [23,106]. However, as effluxers of bioactive lipids, these transporters may also prevent cell death through alternative mechanisms involving modulation of lipid distribution and actions. MDR1, for example, exhibits anti-apoptotic effects in various cell types in response to different apoptotic stimuli that are both dependent and independent of its role as a drug effluxer [203–206]. Elevated levels of MDR transporters in drug-resistant cells are associated with altered membrane content of cholesterol, sphingomyelin, glucosylceramide and other glycosphingolipids [22,190,193,207] and it has been postulated that MDR1 may impart protection by modulating the plasma membrane pool of sphingomyelin, a precursor of ceramide. Ceramide acts as an intracellular signaling molecule during apoptosis and is liberated through rapid activation of acid sphingomyelinase and clustering of membrane microdomains in response to TNF-α, CD95/Fas ligand and UV irradiation, agents known to induce apoptosis [208–212]. MDR1 promotes sphingomyelin externalization, resulting in lower levels of sphingomyelin available for ceramide synthesis on the intracellular side of the plasma membrane [213]. In response to treatment with the MDR1 inhibitor, PSC833, inner plasma membrane sphingomyelin levels increase together with enhanced sphingomyelinase activity and ceramide synthesis [214], although there is concern over the interpretation of these studies since the effects of PSC833 may be MDR1-independent [206].

MDR1 is also expressed in the mitochondria of drug-resistant cells, where it may interfere with aspects of apoptosis in response to anticancer drugs via blocking the release of cytochrome *c* into the cytosol [5]. Mitochondrial expression of MDR1 was found to be absent in drug-sensitive cells, supporting the involvement of this transporter in multidrug resistance and apoptosis at the mitochondrial level [5]. Moreover, MDR1 is also localized to the Golgi, where it can prevent ceramide induced cell death by facilitating its glycosylation to glucosylceramide [146] and subsequent translocation from the cytosolic surface of the Golgi to the lumen [147,215]; MDR1 is also an effluxer of glucosylceramide [119]. MDR1 may also exert protective effects by inhibiting the activation of caspase-3 [204]. Interestingly, caspase-3-mediated cleavage of MDR1 occurs during apoptosis resulting in reduced MDR1 activity [216]. These findings highlight the potential for MDR1 to regulate drug resistance both directly, by effluxing cytotoxic drugs, and indirectly by translocating sphingomyelin to the outer leaflet of the plasma membrane thereby inhibiting ceramide release.

4.2. ABCG2

MDR1 is not the only ABC transporter with anti-apoptotic functions; ABCG2/BCRP has also been suggested to play an important role in cellular survival. In placental trophoblast cells, which express BCRP at high levels, silencing of BCRP expression or pharmacological blockade of its activity renders the cells susceptible to stress-induced apoptosis. This can occur as a result of cell–cell fusion during the differentiation process [217], or in response to activation of the extrinsic apoptosis pathway by TNF-α and interferon-γ (IFN-γ) [218]. However, while BCRP silencing was associated in this study with increased susceptibility to ceramide-induced apoptosis, and increased intracellular ceramide levels, it should be noted that evidence of transport of ceramide by BCRP was not provided.

4.3. Oxysterol transport

Recent evidence suggests that in addition to cholesterol, ABCA1 and ABCG1 may prevent the accumulation of cytotoxic cholesterol-derived oxysterols in cells. Oxidized LDLs (oxLDL) contain oxysterols such as 25-hydroxy- and 7-keto-cholesterol which can induce apoptosis in several cell types [219,220] by increasing levels of Fas and Fas ligand [221], promote cytochrome *c* release [222], and trigger an increase in intracellular calcium concentrations [223]. 25-Hydroxycholesterol is transported by ABCA1 with a relatively high affinity [224], while ABCG1 is an effluxer of 7-ketocholesterol [225,226], the second most abundant oxysterol found in atherosclerotic plaques (the most abundant being 27-hydroxycholesterol) [227]. Interestingly, oxysterols are also endogenous ligands of the liver X receptor (LXR), a nuclear transcription factor which regulates genes involved in cholesterol metabolism, including ABCA1 and ABCG1 [228]; hence, oxysterols may also contribute to the regulation of their own elimination [229]. However, the extent to which cellular oxysterols levels are dependent on ABCA1 and ABCG1 efflux activity is questionable, as their physicochemical properties allow ample passive diffusion across cell membranes [230].

4.4. Phagocytosis

In mammals PS externalization acts as a signal to initiate phagocytosis. Studies in *Caenorhabditis elegans* (*C. elegans*) have shown that the phagocytic receptor CED1 interacts with CED7 [231] the insect orthologue of ABCA1 [232]. Macrophages deficient in ABCA1 fail to phagocytose apoptotic cells, while transfectants acquire phagocytic behaviour [233]. At the *in vivo* level, in ABCA1 null mice transient accumulation of apoptotic corpses in limb buds can be seen during embryonic development [233]. The mechanism through which ABCA1 interacts with the phagocytic process is unclear. However, following phagocytosis of apoptotic cells, cholesterol efflux is enhanced in an ABCA1-dependent manner [234]. This phenomenon is specific to apoptosis, since necrotic cells fail to induce cholesterol efflux. Indeed, cholesterol efflux may depend on PS externalization, since PS vesicles are able to stimulate efflux. Although increased apoA-I binding is observed in apoptotic cells, phosphatidylserine efflux is not dependent on apoA-I since annexin V, a phosphatidylserine binding protein, neither competes with the apolipoprotein for ABCA1 nor inhibits cholesterol efflux to apoA-I [129]. In addition to ABCA1, the homologous protein ABCA7 has also recently been implicated in phagocytosis, since abrogation of Abca7 expression in mice leads to reduced phagocytosis of apoptotic cells [235]. Interestingly, in this study an Abca1-dependent phagocytic function could not be demonstrated, possibly due to strain differences or methodological issues related to phagocytosis assays. Hence, it appears that while ABCA1 and ABCA7 may be involved in the phagocytic process, their precise role remains obscure.

5. Summary and conclusions

Evolution has made extensive use of the efflux capacity of ABC transporters to accomplish a wide and diverse range of activities related to cytoprotection and homeostasis. Their structure and function dictates an intimate association with the constituents of the plasma membrane lipid bilayer. Not surprisingly, some ABC transporters show preferential localization to membrane microdomains and, like other domain-associated proteins, their activity is affected by their surrounding lipid environment. Hence, they are well placed to regulate the efflux and redistribution of lipids during periods of cellular division, stress and recovery, and in turn to be regulated by alterations in membrane lipid composition. ABC proteins are also able to transport ceramides,

sphingolipids and glycosphingolipids, major constituents of membrane microdomains which play important and fundamental roles in cellular signaling, endocytosis, differentiation and apoptosis.

Cholesterol, the other major constituent of membrane microdomains, is also a substrate for several ABC transporters. A variety of models explaining the mechanism of ABC-mediated cholesterol efflux to acceptor proteins have been proposed, but the complexity and diversity of the process has so far thwarted attempts to gain an in-depth understanding of the entire process. Efflux of cholesterol by ABC transporters plays a critical role in whole body cholesterol homeostasis and prevention of undesirable accumulation of cholesterol esters, in addition to several tissue-specific functions. Whether or not the cholesterol content of membrane microdomains can also be regulated by ABC-mediated efflux is unknown. Several other sterol species are also effluxed by ABC transporters, including toxic oxysterols as well as inactive steroid metabolites, consistent with the view that ABC proteins function to prevent build up of toxins and waste products.

ABC transporters are not only located on the plasma membrane, but are also expressed in the Golgi and endoplasmic reticulum, where they perform important functions with respect to distribution of sphingolipids between intracellular organelles. Through regulation of ceramide/sphingosine levels in various cellular compartments, and the availability of sphingomyelin for conversion to ceramide by sphingomyelinase, ABC transporters are able to influence cellular sensitivity to apoptotic signals. This can be either in response to cytotoxic drugs, or extrinsic activators such as cytokines and death ligands. ABC transporters are therefore able to act as anti-stress/anti-toxicity proteins, consistent with their well-established role in multidrug resistance through prevention of cellular accumulation of cytotoxic drugs.

Further clarification of the mechanism of transfer of lipid substrates by ABC transporters, their regulation at both the transcriptional and activity levels by lipid substrates, and their interaction with microdomain components should be forthcoming in the near future. This will enhance our appreciation of the importance of ABC transporters in a wide variety of cellular processes and functions, shed further light on their role in various lipid storage disorders and pathologies, and open up new avenues for targeted intervention.

Conflict of interest

None.

Acknowledgements

The authors gratefully acknowledge the funding support of the Women and Infants Research Foundation at King Edward Memorial Hospital, Perth, the Raine Medical Research Foundation and the University of Western Australia. Irving Aye and Ambika Singh are both Australian Postgraduate Award recipients.

References

[1] C. Higgins, ABC transporters: from microorganisms to man, Annu. Rev. Cell Biol. 8 (1992) 67–113.
[2] S. Childs, V. Ling, The MDR superfamily of genes and its biological implications, Important Adv. Oncol. (1994) 21–36.
[3] M. Dean, R. Allikmets, Evolution of ATP-binding casette transporter genes, Curr. Opin. Genet. Dev. 5 (1995) 779–785.
[4] M. Dean, Y. Hamon, G. Chimini, The human ATP-binding cassette (ABC) transporter superfamily, J. Lipid Res. 42 (2001) 1007–1017.
[5] M. Solazzo, O. Fantappie, N. Lasagna, C. Sassoli, D. Nosi, R. Mazzanti, P-gp localisation in mitochondria and its functional characterisation in multiple drug-resistant cell lines, Exp. Cell Res. 312 (2006) 4070–4078.
[6] A. Rajagopal, S. Simon, Subcellular localisation and activity of multidrug resistance proteins, Mol. Biol. Cell 14 (2003) 3389–3399.
[7] I. Ifergan, G. Jansen, Y. Assaraf, Cytoplasmic confinement of Breast Cancer Resistance Protein (BCRP/ABCG2) as a novel mechanism of adaptation to short-term folate deprivation, Mol. Pharmacol. 67 (2005) 1349–1359.
[8] M. Tsuchida, Y. Emi, Y. Kida, M. Sakaguchi, Human ABC transporter isoform B6 (ABCB6) localizes primarily in Golgi apparatus, Biochem. Biophys. Res. Commun. 369 (2008) 369–375.
[9] G.R. Briggs, R.K. Freeman, S.J. Yaffe, Drugs in Pregnancy and Lactation, 7th ed., Lippincott Williams & Wilkins (LWW), Philadelphia, 2005, p. 2000.
[10] A. Schinkel, J. Jonker, Mammalian drug efflux transporters of the ATP binding cassette (ABC) family: an overview, Adv. Drug Deliv. Rev. 55 (2003) 3–29.
[11] P. Jones, A. George, The ABC transporter structure and mechanism: perspectives on recent research, Cell. Mol. Life Sci. 61 (2004) 682–699.
[12] K. Linton, Structure and function of ABC transporters, Physiology 22 (2007) 122–130.
[13] M. Dean, T. Annilo, Evolution of the ATP-binding cassette (ABC) transporter superfamily in vertebrates, Annu. Rev. Genomics Hum. Genet. 6 (2005) 123–142.
[14] W. Saurin, M. Hofnung, E. Dassa, Getting in or out: early segregation between importers and exporters in the evolution of ATP-binding cassette (ABC) transporters, J. Mol. Evol. 48 (1999) 22–41.
[15] S.C. Hyde, P. Emsley, M.J. Hartshorn, M.M. Mimmack, U. Gileadi, S.R. Pearce, M.P. Gallagher, D.R. Gill, R.E. Hubbard, C.F. Higgins, Structural model of ATP-binding proteins associated with cystic fibrosis, multidrug resistance and bacterial transport, Nature 346 (1990) 362–365.
[16] G. Szakacs, J. Annereau, S. Lababidi, U. Shankavaram, A. Arciello, K. Bussey, W. Reinhold, Y. Guo, G. Kruh, M. Reimers, J. Weinstein, M. Gottesman, Predicting drug sensitivity and resistance: profiling ABC transporter genes in cancer cells, Cancer Cell 6 (2004) 129–137.
[17] R. Juliano, V. Ling, A surface glycoprotein modulating drug permeability in Chinese hamster ovary cell mutants, Biochim. Biophys. Acta 455 (1976) 152–162.
[18] S. Mirski, J. Gerlach, S. Cole, Multidrug resistance in a human small cell lung cancer cell line selected in adriamycin, Cancer Res. 47 (1987) 2594–2598.
[19] L. Doyle, W. Yang, L. Abruzzo, T. Krogmann, Y. Gao, A. Rishi, D. Ross, A multidrug resistance transporter from human MCF-7 breast cancer cells, Proc. Natl. Acad. Sci. U.S.A. 95 (1998) 15665–15670.
[20] M. Kool, M. de-Haas, G. Scheffer, R. Scheper, M. van-Eijk, J. Juijn, F. Baas, P. Borst, Analysis of expression of cMOAT (MRP2), MRP3, MRP4, and MRP5, homologues of the multidrug resistance-associated protein gene (MRP1), in human cancer cell lines, Cancer Res. 57 (1997) 3537–3547.
[21] S. Cole, G. Bhardwaj, J. Gerlach, J. Mackie, C. Grant, K. Almquist, A. Stewart, E. Kurz, A. Duncan, R. Deeley, Overexpression of a transporter gene in a multidrug-resistant human lung cancer cell line, Science 258 (1992) 1650–1654.
[22] R.J. Veldman, H. Sietsma, K. Klappe, D. Hoekstra, J.W. Kok, Inhibition of P-glycoprotein activity and chemosensitization of multidrug-resistant ovarian carcinoma 2780AD cells by hexanoylglucosylceramide, Biochem. Biophys. Res. Commun. 266 (1999) 492–496.
[23] M.M. Gottesman, Mechanisms of cancer drug resistance, Annu. Rev. Med. 53 (2002) 615–627.
[24] F. Thiebaut, T. Tsuruo, H. Hamada, M. Gottesman, I. Pastan, M. Willingham, Cellular localization of the multidrug-resistance gene product P-glycoprotein in normal human tissues, Proc. Natl. Acad. Sci. U.S.A. 84 (1987) 7735–7738.
[25] A. Ayrton, P. Morgan, Role of transport proteins in drug absorption, distribution and excretion, Xenobiotica 31 (2001) 469–497.
[26] E. Leslie, R. Deeley, S. Cole, Multidrug resistance proteins: role of P-glycoprotein, MRP1, MRP2, and BCRP (ABCG2) in tissue defence, Toxicol. Appl. Pharmacol. 204 (2005) 216–237.
[27] M. Nagashige, F. Ushigome, N. Koyabu, K. Hirata, M. Kawabuchi, T. Hirakawa, S. Satoh, K. Tsukimori, H. Nakano, T. Uchimi, M. Kuwano, H. Ohtani, Y. Sawada, Basal membrane localization of MRP1 in human placental trophoblast, Placenta 24 (2003) 951–958.
[28] J. Marin, O. Briz, M. Serrano, A review of the molecular mechanisms involved in the placental barrier of drugs, Curr. Drug Deliv. 1 (2004) 275–289.
[29] G. Nagel, Differential function of the two nucleotide binding domains on cystic fibrosis transmembrane conductance regulator, Biochim. Biophys. Acta 1461 (1999) 263–274.
[30] G. Leonard, T. Fojo, S. Bates, The role of ABC transporters in clinical practice, Oncologist 8 (2003) 411–424.
[31] T. Litman, T.E. Druley, W.D. Stein, S.E. Bates, From MDR to MXR: new understanding of multidrug resistance systems, their properties and clinical significance, Cell. Mol. Life Sci. 58 (2001) 931–959.
[32] G. Kruh, M. Belinsky, The MRP family of drug efflux pumps, Oncogene 22 (2003) 7537–7552.
[33] A. Bodo, E. Bakos, F. Szeri, A. Varadi, B. Sarkadi, The role of multidrug transporters in drug availability, metabolism and toxicity, Toxicol. Lett. 140–141 (2003) 133–143.
[34] H. Sietsma, R. Veldman, J. Kok, The involvement of sphingolipids in multidrug resistance, J. Membr. Biol. 181 (2001) 153–162.
[35] P. Borst, N. Zelcer, A. van Helvoort, ABC transporters in lipid transport, Biochim. Biophys. Acta 1486 (2000) 128–144.
[36] J. Smit, A. Schinkel, R.O. Elferink, A. Groen, E. Wagenaar, L. van Deemter, C. Mol, R. Ottenhoff, N. van der Lugt, M. van Roon, Homozygous disruption of the murine mdr2 P-glycoprotein gene leads to a complete absence of phospholipid from bile and to liver disease, Cell 75 (1993) 451–462.
[37] A. Van Helvoort, A. Smith, H. Sprong, I. Fritzsche, A. Schinkel, P. Borst, G. van Meer, MDR1 P-glycoprotein is a lipid translocase of broad specificity, while

MDR3 P-glycoprotein specifically translocates phosphatidylcholine, Cell 87 (1996) 507–517.
[38] D. Dekkers, P. Comfurius, A. Schroit, E. Bevers, R. Zwaal, Transbilayer movement of NBD-labeled phospholipids in red blood cell membranes: outward-directed transport by the multidrug resistance protein 1 (MRP1), Biochemistry (Mosc) 37 (1998) 14833–14837.
[39] H. Woehlecke, A. Pohl, N. Alder Baerens, H. Lage, A. Herrmann, Enhanced exposure of phosphatidylserine in human gastric carcinoma cells overexpressing the half-size ABC transporter BCRP (ABCG2), Biochem. J. 376 (2003) 489–495.
[40] A. Zachowski, Phospholipids in animal eukaryotic membranes: transverse asymmetry and movement, Biochem. J. 294 (1993) 1–14.
[41] E.M. Bevers, P. Comfurius, D.W. Dekkers, R.F. Zwaal, Lipid translocation across the plasma membrane of mammalian cells, Biochim. Biophys. Acta 1439 (1999) 317–330.
[42] P. Williamson, R.A. Schlegel, Transbilayer phospholipid movement and the clearance of apoptotic cells, Biochim. Biophys. Acta 1585 (2002) 53–63.
[43] M. Ikeda, A. Kihara, Y. Igarashi, Lipid asymmetry of the eukaryotic plasma membrane: functions and related enzymes, Biol. Pharm. Bull. 29 (2006) 1542–1546.
[44] M.P. Sheetz, S.J. Singer, Biological membranes as bilayer couples. A molecular mechanism of drug–erythrocyte interactions, Proc. Natl. Acad. Sci. U.S.A. 71 (1974) 4457–4461.
[45] P. Devaux, Static and dynamic lipid asymmetry in cell membranes, Biochemistry (Mosc) 30 (1991) 1163–1173.
[46] E. Farge, D. Ojcius, A. Subtil, A. Dautry-Varsat, Enhancement of endocytosis due to aminophospholipid transport across the plasma membrane of living cells, Am. J. Physiol. Cell Physiol. 276 (1999) C725–C733.
[47] G. Van Meer, D. Halter, H. Sprong, P. Somerharju, M. Egmond, ABC lipid transporters: extruders, flippases, or flopless activators? FEBS Lett. 580 (2006) 1171–1177.
[48] C. Higgins, M. Gottesman, Is the multidrug transporter a flippase? Trends Biochem. Sci. 17 (1992) 18–21.
[49] M. Hennessy, J. Spiers, A primer on the mechanics of P-glycoprotein the multidrug transporter, Pharmacol. Res. 55 (2007) 1–15.
[50] H. Bolhuis, H. Van Veen, D. Molenaar, B. Poolman, A. Driessen, W. Konings, Multidrug resistance in Lactococcus lactis: evidence for ATP-dependent drug extrusion from the inner leaflet of the cytoplasmic membrane, EMBO J. 15 (1996) 4239–4245.
[51] C. Vedhachalam, P. Duong, M. Nickel, D. Nguyen, P. Dhanasekaran, G. Rothblat, S. Lund-Katz, M. Phillips, Mechanism of ATP-binding cassette transporter A1 mediated cellular lipid efflux to apolipoprotein A-I and formation of high density lipoprotein particles, J. Biol. Chem. 282 (2007) 25123–25130.
[52] C. Cavelier, I. Lorenzi, L. Rohrer, A. von Eckardstein, Lipid efflux by the ATP-binding cassette transporters ABCA1 and ABCG1, Biochim. Biophys. Acta 1761 (2006) 655–666.
[53] C. Salinas, I. Cruz-Bautista, R. Mehta, M. Villarreal-Molina, F. Perez, M. Tusie-Luna, S. Canizales-Quinteros, The ATP-binding cassette transporter subfamily A member 1 (ABC-A1) and type 2 diabetes: an association beyond HDL cholesterol, Curr. Diabetes Rev. 3 (2007) 264–267.
[54] A. Attie, ABCA1: at the nexus of cholesterol, HDL and atherosclerosis, Trends Biochem. Sci. 32 (2007) 172–179.
[55] E. Rodriguez-Rodriguez, I. Mateo, J. Llorca, C. Sanchez-Quintana, J. Infante, I. Garcia-Gorostiaga, P. Sanchez-Juan, J. Berciano, O. Combarros, Association of genetic variants of ABCA1 with Alzheimer's disease risk, Am. J. Med. Genet. B. Neuropsychiatr. Genet. 144B (2007) 964–968.
[56] M. Bodzioch, E. Orso, J. Klucken, T. Langmann, A. Bottcher, W. Diederich, W. Drobnik, S. Barlage, C. Buchler, M. Porsch-Ozcurumez, W. Hahmann, K. Oette, G. Rothe, C. Aslanidis, K. Lackner, G. Schmitz, The gene encoding ATP-binding cassette transporter 1 is mutated in Tangier disease, Nat. Genet. 22 (1999) 347–351.
[57] A. Brooks-Wilson, M. Marcil, S. Clee, L. Zhang, K. Roomp, M. van Dam, L. Yu, C. Brewer, J. Collins, H. Molhuizen, O. Loubser, B. Ouelette, K. Fichter, K. Ashbourne-Excoffon, C. Sensen, S. Scherer, S. Mott, M. Denis, D. Martindale, J. Frohlich, K. Morgan, B. Koop, S. Pimstone, J.G. Kastelein Jr., M. Hayden, Mutations in ABC1 in Tangier disease and familial high-density lipoprotein deficiency, Nat. Genet. 22 (1999) 336–345.
[58] S. Rust, M. Rosier, H. Funke, J. Real, Z. Amoura, J. Piette, J. Deleuze, H. Brewer, N. Duverger, P. Denefle, G. Assmann, Tangier disease is caused by mutations in the gene encoding ATP-binding cassette transporter 1, Nat. Genet. 22 (1999) 352–355.
[59] C. Joyce, L. Freeman, H.B. Brewer Jr., S. Santamarina-Fojo, Study of ABCA1 function in transgenic mice, Arterioscler. Thromb. Vasc. Biol. 23 (2003) 965–971.
[60] S. Yokoyama, Assembly of high-density lipoprotein, Arterioscler. Thromb. Vasc. Biol. 26 (2006) 20–27.
[61] M.L. Lindegaard, C.A. Wassif, B. Vaisman, M. Amar, E.V. Wasmuth, R. Shamburek, L.B. Nielsen, A.T. Remaley, F.D. Porter, Characterization of placental cholesterol transport: ABCA1 is a potential target for in utero therapy of Smith–Lemli–Opitz syndrome, Hum. Mol. Genet. 17 (2008) 3806–3813.
[62] G. Schmitz, W. Kaminski, ABCA2: a candidate regulator of neural transmembrane lipid transport, Cell. Mol. Life Sci. 59 (2002) 1285–1295.
[63] J. Mack, V. Beljanski, K. Tew, D. Townsend, The ATP-binding cassette transporter ABCA2 as a mediator of intracellular trafficking, Biomed. Pharmacother. 60 (2006) 587–592.
[64] Z.J. Chen, B. Vulevic, K.E. Ile, A. Soulika, W. Davis Jr., P.B. Reiner, B.P. Connop, P. Nathwani, J.Q. Tronjanowski, K.D. Tew, Association of ABCA2 expression with determinants of Alzheimer's disease, FASEB J. 18 (2004) 1129–1131.
[65] M. Nishimura, S. Naito, Tissue-specific mRNA expression profiles of human ATP binding cassette and solute carrier transporter superfamilies, Drug Metab. Pharmacokinet. 20 (2005) 452–477.
[66] W.S. Kim, C.S. Weickert, B. Garner, Role of ATP-binding cassette transporters in brain lipid transport and neurological disease, J. Neurochem. 104 (2008) 1145–1166.
[67] G. Yamano, H. Funahashi, O. Kawanami, L. Zhao, N. Ban, Y. Uchida, T. Morohoshi, J. Ogawa, S. Shioda, N. Inagaki, ABCA3 is a lamellar body membrane protein in human lung alveolar type II cells, FEBS Lett. 508 (2001) 221–225.
[68] Y. Matsumura, H. Sakai, M. Sasaki, N. Ban, N. Inagaki, ABCA3-mediated choline-phospholipids uptake into intracellular vesicles in A549 cells, FEBS Lett. 581 (2007) 3139–3144.
[69] N. Ban, Y. Matsumura, H. Sakai, Y. Takanezawa, M. Sasaki, H. Arai, N. Inagaki, ABCA3 is a lipid transporter in pulmonary surfactant biogenesis, J. Biol. Chem. 282 (2007) 9628–9634.
[70] M. Denis, B. Haidar, M. Marcil, M. Bouvier, L. Krimbou, J. Genest Jr., Molecular and cellular physiology of apolipoprotein A-I lipidation by the ATP-binding cassette transporter A1 (ABCA1), J. Biol. Chem. 279 (2004) 7384–7394.
[71] E. Wang, C.N. Casciano, R.P. Clement, W.W. Johnson, Cholesterol interaction with the daunorubicin binding site of P-glycoprotein, Biochem. Biophys. Res. Commun. 276 (2000) 909–916.
[72] M. Fitzgerald, A. Morris, A. Chroni, A. Mendez, V. Zannis, M. Freeman, ABCA1 and amphipathic apolipoproteins form high-affinity molecular complexes required for cholesterol efflux, J. Lipid Res. 45 (2004) 287–294.
[73] J. Oram, R. Lawn, M. Gavin, D. Wade, ABCA1 is the cAMP-inducible apolipoprotein receptor that mediates cholesterol secretion from macrophages, J. Biol. Chem. 275 (2000) 34508–34511.
[74] G. Francis, R. Knopp, J. Oram, Defective removal of cellular cholesterol and phospholipids by apolipoprotein A-I in Tangier disease, J. Clin. Invest. 96 (1995) 78–87.
[75] E. Neufeld, A. Remaley, S. Demosky, J. Stonik, A. Cooney, M. Comly, N. Dwyer, M. Zhang, J. Blanchette-Mackie, S. Santamarina-Fojo, H. Brewer Jr., Cellular localisation and trafficking of the human ABCA1 transporter, J. Biol. Chem. 276 (2001) 27584–27590.
[76] N. Wang, D. Silver, P. Costet, A. Tall, Specific binding of apoA-I, enhanced cholesterol efflux, and altered plasma membrane morphology in cells expressing ABC1, J. Biol. Chem. 275 (2000) 33053–33058.
[77] A. Ghering, W. Davidson, Ceramide structural features required to stimulate ABCA1-mediated cholesterol efflux to apolipoprotein A-I, J. Lipid Res. 47 (2006) 2781–2788.
[78] A. Chroni, G. Koukos, A. Duka, V. Zannis, The carboxy-terminal region of apoA-I is required for the ABCA1-dependent formation of alpha-HDL but not prebeta-HDL particles in vivo, Biochemistry (Mosc) 46 (2007) 5697–5708.
[79] C. Vedhachalam, A. Ghering, W. Davidson, S. Lund-Katz, G. Rothblat, M. Phillips, ABCA1-induced cell surface binding sites for ApoA-I, Arterioscler. Thromb. Vasc. Biol. 27 (2007) 1603–1609.
[80] N. Mukhamedova, Y. Fu, M. Bukrinsky, A. Remaley, D. Srividov, The Role of Different Regions of ATP-Binding Cassette Transporter A1 in cholesterol efflux, Biochemistry (Mosc) 46 (2007) 9388–9398.
[81] V. Rigot, Y. Hamon, O. Chambenoit, M. Alibert, N. Duverger, G. Chimini, Distinct sites on ABCA1 control distinct steps required for cellular release of phospholipids, J. Lipid Res. 43 (2002) 2077–2086.
[82] A. Vaughan, J. Oram, ABCA1 redistributes membrane cholesterol independent of apolipoprotein interactions, J. Lipid Res. 44 (2003) 1373–1380.
[83] A. Kobayashi, Y. Takanezawa, T. Hirata, Y. Shimizu, K. Misasa, N. Kioka, H. Arai, K. Ueda, M. Matsuo, Efflux of sphingomyelin, cholesterol, and phosphatidylcholine by ABCG1, J. Lipid Res. 47 (2006) 1791–1802.
[84] C.J. Fielding, P.E. Fielding, Cellular cholesterol efflux, Biochim. Biophys. Acta (BBA) Mol. Cell Biol. Lipids 1533 (2001) 175–189.
[85] I.C. Gelissen, M. Harris, K.A. Rye, C. Quinn, A.J. Brown, M. Kockx, S. Cartland, M. Packianathan, L. Kritharides, W. Jessup, ABCA1 and ABCG1 synergize to mediate cholesterol export to apoA-I, Arterioscler. Thromb. Vasc. Biol. 26 (2006) 534–540.
[86] E.B. Neufeld, J.A. Stonik, S.J. Demosky Jr., C.L. Knapper, C.A. Combs, A. Cooney, M. Comly, N. Dwyer, J. Blanchette-Mackie, A.T. Remaley, S. Santamarina-Fojo, H.B. Brewer Jr., The ABCA1 transporter modulates late endocytic trafficking: insights from the correction of the genetic defect in Tangier disease, J. Biol. Chem. 279 (2004) 15571–15578.
[87] M. Denis, Y. Landry, X. Zha, ATP-binding cassette A1-mediated lipidation of apolipoprotein A-I occurs at the plasma membrane and not in the endocytic compartments, J. Biol. Chem. 283 (2008) 16178–16186.
[88] L. Faulkner, S. Panagotopulos, J. Johnson, L. Woollett, D. Hui, S. Witting, J. Maiorano, W. Davidson, An analysis of the role of a retroendocytosis pathway in ABCA1-mediated cholesterol efflux from macrophages, J. Lipid Res. 49 (2008) 1322–1332.
[89] H. Kusuhara, Y. Sugiyama, ATP-binding cassette, subfamily G (ABCG family), Pflugers Arch. 453 (2007) 735–744.
[90] G. Schmitz, T. Langmann, S. Heimerl, Role of ABCG1 and other ABCG family members in lipid metabolism, J. Lipid Res. 42 (2001) 1513–1520.
[91] G. Schmitz, T. Langmann, Transcriptional regulatory networks in lipid metabolism control ABCA1 expression, Biochim. Biophys. Acta 1735 (2005) 1–19.
[92] S. Sankaranarayanan, J.F. Oram, B.F. Asztalos, A.M. Vaughan, S. Lund-Katz, M.P. Adorni, M.C. Phillips, G.H. Rothblat, Effects of acceptor composition and mechanism of ABCG1-mediated cellular free cholesterol efflux, J. Lipid Res. 50 (2009) 275–284.

[93] N. Wang, D. Lan, W. Chen, F. Matsuura, A. Tall, ATP-binding cassette transporters G1 and G4 mediate cellular cholesterol efflux to high-density lipoproteins, Proc. Natl. Acad. Sci. U.S.A. 101 (2004) 9774–9779.
[94] O. Sano, A. Kobayashi, K. Nagao, K. Kumagai, N. Kioka, K. Hanada, K. Ueda, M. Matsuo, Sphingomyelin-dependence of cholesterol efflux mediated by ABCG1, J. Lipid Res. 48 (2007) 2377–2384.
[95] A. Vaughan, J. Oram, ABCA1 and ABCG1 or ABCG4 act sequentially to remove cellular cholesterol and generate cholesterol-rich HDL, J. Lipid Res. 47 (2006) 2433–2443.
[96] W. Jessup, I.C. Gelissen, K. Gaus, L. Kritharides, Roles of ATP binding cassette transporters A1 and G1, scavenger receptor BI and membrane lipid domains in cholesterol export from macrophages, Curr. Opin. Lipidol. 17 (2006) 247–257.
[97] S. Oldfield, C. Lowry, J. Ruddick, S. Lightman, ABCG4: a novel human white family ABC-transporter expressed in the brain and eye, Biochim. Biophys. Acta 1591 (2002) 175–179.
[98] P.T. Tarr, P.A. Edwards, ABCG1 and ABCG4 are co-expressed in neurons and astrocytes of the CNS and regulate cholesterol homeostasis through SREBP-2, J. Lipid Res. 49 (2008) 169–182.
[99] M. Lee, K. Lu, S. Hazard, H. Yu, S. Shulenin, H. Hidaka, H. Kojima, R. Allikmets, N. Sakuma, R. Pegoraro, A. Srivastava, G. Salen, M. Dean, S. Patel, Identification of a gene, ABCG5, important in the regulation of dietary cholesterol absorption, Nat. Genet. 27 (2001) 79–83.
[100] S. Patel, G. Salen, H. Hidaka, P. Kwiterovich, A. Stalenhoef, T. Miettinen, S. Grundy, M. Lee, J. Rubenstein, M. Polymeropoulos, M. Brownstein, Mapping a gene involved in regulating dietary cholesterol absorption. The sitosterolemia locus is found at chromosome 2p21, J. Clin. Invest. 102 (1998) 1041–1044.
[101] L. Yu, R. Hammer, J. Li-Hawkins, K.D.L. Von Bergmann, J. Cohen, H. Hobbs, Disruption of Abcg5 and Abcg8 in mice reveals their crucial role in biliary cholesterol secretion, Proc. Natl. Acad. Sci. U.S.A. 99 (2002) 16237–16242.
[102] L. Yu, J. Li-Hawkins, R. Hammer, K. Berge, J. Horton, J. Cohen, H. Hobbs, Overexpression of ABCG5 and ABCG8 promotes biliary cholesterol secretion and reduces fractional absorption of dietary cholesterol, J. Clin. Invest. 110 (2002) 671–680.
[103] C. Vrins, E. Vink, K. Vandenberghe, R. Frijters, J. Seppen, A. Groen, The sterol transporting heterodimer ABCG5/ABCG8 requires bile salts to mediate cholesterol efflux, FEBS Lett. 581 (2007) 4616–4620.
[104] A. Garrigues, A.E. Escargueil, S. Orlowski, The multidrug transporter, P-glycoprotein, actively mediates cholesterol redistribution in the cell membrane, Proc. Natl. Acad. Sci. U.S.A. 99 (2002) 10347–10352.
[105] R.J. Raggers, T. Pomorski, J.C. Holthuis, N. Kalin, G. van Meer, Lipid traffic: the ABC of transbilayer movement, Traffic 1 (2000) 226–234.
[106] T. Mizutani, M. Masuda, E. Nakai, K. Furumiya, H. Togawa, Y. Nakamura, Y. Kawai, K. Nakahira, S. Shinkai, K. Takahashi, Genuine functions of P-glycoprotein (ABCB1), Curr. Drug Metab. 9 (2008) 167–174.
[107] K.M. Barnes, B. Dickstein, G.B. Cutter Jr., T. Fojo, S.E. Bates, Steroid treatment, accumulation, and antagonism of P-glycoprotein in multidrug-resistant cells, Biochemistry 35 (1996) 4820–4827.
[108] W. Kim, L. Benet, P-glycoprotein (P-gp/MDR1)-mediated efflux of sex-steroid hormones and modulation of P-gp expression in vitro, Pharm. Res. 21 (2004) 1284–1293.
[109] E. Bakos, L. Homolya, Portrait of multifaceted transporter, the multidrug resistance-associated protein 1 (MRP1/ABCC1), Pflugers Arch. 453 (2007) 621–641.
[110] M. Grube, S. Reuther, H. Meyer-zu-Schwabedissen, K. Kock, K. Draber, C.A. Ritter, C. Fusch, G. Jedlitschky, H.K. Kroemer, Organic anion transporting polypeptide 2B1 and breast cancer resistance protein interact in the transepithelial transport of steroid sulfates in human placenta, Drug Metab. Dispos. 35 (2007) 30–35.
[111] Y. Imai, S. Asada, S. Tsukahara, E. Ishikawa, T. Tsuruo, Y. Sugimoto, Breast cancer resistance protein exports sulfated estrogens but not free estrogens, Mol. Pharmacol. 64 (2003) 610–618.
[112] C. Chen, X. Liu, B. Smith, Utility of Mdr1-gene deficient mice in assessing the impact of P-glycoprotein on pharmacokinetics and pharmacodynamics in drug discovery and development, Curr. Drug Metab. 4 (2003) 272–291.
[113] G. Rappa, R. Finch, A. Sartorelli, A. Lorico, New insights into the biology and pharmacology of the multidrug resistance (MRP) from gene knockout models, Biochem. Pharmacol. 58 (1999) 557–562.
[114] S. Koshiba, T. Ito, A. Shiota, K. Wakabayashi, M. Ueda, H. Ichinose, T. Ishikawa, Development of polyclonal antibodies specific to ATP-binding cassette transporters human ABCG4 and mouse Abcg4: site-specific expression of mouse Abcg4 in brain, J. Exp. Ther. Oncol. 6 (2007) 321–333.
[115] I. Bosch, K. Dunussi-Joannopoulos, R. Wu, S. Furlong, J. Croop, Phosphatidylcholine and phosphatidylethanolamine behave as substrates of the human MDR1 P-glycoprotein, Biochemistry (Mosc) 36 (1997) 5685–5694.
[116] C. Frijters, C. Tuijn, R. Ottenhoff, B. Zegers, A. Groen, R. Elferink, The role of different P-glycoproteins in hepatobiliary secretion of fluorescently labeled short-chain phospholipids, J. Lipid Res. 40 (1999) 1950–1958.
[117] Y. Romsicki, F. Sharom, Phospholipid flippase activity of the reconstituted P-glycoprotein multidrug transporter, Biochemistry (Mosc) 40 (2001) 6937–6947.
[118] A. Pohl, H. Lage, P. Muller, T. Pomorski, A. Herrmann, Transport of phosphatidylserine via MDR1 (multidrug resistance 1)P-glycoprotein in a human gastric carcinoma cell line, Biochem. J. 365 (2002) 259–268.
[119] P. Eckford, F. Sharom, The reconstituted P-glycoprotein multidrug transporter is a flippase for glucosylceramide and other simple glycosphingolipids, Biochem. J. 389 (2005) 517–526.
[120] A. Van Helvoort, M. Giudici, M. Thielemans, G. Van Meer, Transport of sphingomyelin to the cell surface is inhibited by brefeldin A and in mitosis, where C6-NBD-sphingomyelin is translocated across the plasma membrane by a multidrug transporter activity, J. Cell Sci. 110 (1997) 75–83.
[121] A. Smith, J. Timmermans-Hereijgers, B. Roelofsen, K. Wirtz, W. van Blitterswijk, J. Smit, A. Schinkel, P. Borst, The human MDR3 P-glycoprotein promotes translocation of phosphatidylcholine through the plasma membrane of fibroblasts from transgenic mice, FEBS Lett. 354 (1994) 263–266.
[122] S. Ruetz, P. Gros, Phosphatidylcholine translocase: a physiological role for the mdr2 gene, Cell 77 (1994) 1071–1081.
[123] D.A. Evseenko, J.W. Paxton, J.A. Keelan, ABC drug transporter expression and functional activity in trophoblast-like cell lines and differentiating primary trophoblast, Am. J. Physiol. Regul. Integr. Comp. Physiol. 290 (2006) R1357–R1365.
[124] J. de Vree, E. Jacquemin, E. Strum, D. Cresteil, P. Bosma, J. Aten, J. Deleuze, M. Desrochers, M. Burdelski, O. Bernard, R. Oude Elferink, M. Hadchouel, Mutations in the MDR3 gene cause progressive familial intrahepatic cholestasis, Proc. Natl. Acad. Sci. U.S.A. 95 (1998) 282–287.
[125] D. Dekkers, P. Comfurius, R. van Gool, E. Bevers, R. Zwaal, Multidrug resistance protein 1 regulates lipid asymmetry in erythrocyte membranes, Biochem. J. 350 (2000) 531–535.
[126] Z. Huang, X. Chang, J. Riordan, Y. Huang, Fluorescent modified phosphatidylcholine floppase activity of reconstituted multidrug resistance-associated protein MRP1, Biochim. Biophys. Acta 1660 (2004) 155–163.
[127] D. Kamp, C. Haest, Evidence for a role of the multidrug resistance protein (MRP) in the outward translocation of NBD-phospholipids in the erythrocyte membrane, Biochim. Biophys. Acta 1372 (1998) 91–101.
[128] L. Liu, A. Bortnick, M. Nickel, P. Dhanasekaran, P. Subbaiah, S. Lund-Katz, G. Rothblat, M. Phillips, Effects of apolipoprotein A-I on ATP-binding cassette transporter A1-mediated efflux of macrophage phospholipid and cholesterol: formation of nascent high density lipoprotein particles, J. Biol. Chem. 278 (2003) 42976–42984.
[129] J. Smith, C. Waelde, A. Horwitz, P. Zheng, Evaluation of the role of phosphatidylserine translocase activity in ABCA1-mediated lipid efflux, J. Biol. Chem. 277 (2002) 17797–17803.
[130] N. Alder-Baerens, P. Muller, A. Pohl, T. Korte, Y. Hamon, G. Chimini, T. Pomorski, A. Herrmann, Headgroup-specific exposure of phospholipids in ABCA1-expressing cells, J. Biol. Chem. 280 (2005) 26321–26329.
[131] J. Klucken, C. Buchler, E. Orso, W. Kaminski, M. Porsch-Ozcurumez, G. Liebisch, M. Kapinsky, W. Diederich, W. Drobnik, M. Dean, R. Allikmets, G. Schmitz, ABCG1 (ABC8), the human homolog of the Drosophila white gene, is a regulator of macrophage cholesterol and phospholipid transport, Proc. Natl. Acad. Sci. U.S.A. 97 (2000) 817–822.
[132] H. Hassan, M. Denis, D. Lee, I. Iatan, D. Nyholt, I. Ruel, L. Krimbou, J. Genest, Identification of an ABCA1-dependent phospholipid-rich plasma membrane apolipoprotein A-I binding site for nascent HDL formation: implications for current models of HDL biogenesis, J. Lipid Res. 48 (2007) 2428–2442.
[133] H. Sakai, Y. Tanaka, M. Tanaka, N. Ban, K. Yamada, Y. Matsumura, D. Watanabe, K. Sasaki, T. Kita, N. Inagaki, ABCA2 deficiency results in abnormal sphingolipid metabolism in mouse brain, J. Biol. Chem. 282 (2007) 19692–19699.
[134] N. Cheong, H. Zhang, M. Madesh, M. Zhao, K. Yu, C. Dodia, A. Fisher, R. Savani, H. Shuman, ABCA3 is critical for lamellar body biogenesis in vivo, J. Biol. Chem. 282 (2007) 23811–23817.
[135] S. Shulenin, L. Nogee, T. Annilo, S. Wert, J. Whitsett, M. Dean, ABCA3 gene mutations in newborns with fatal surfactant deficiency, N. Engl. J. Med. 350 (2004) 1296–1303.
[136] S. Beharry, M. Zhong, R. Molday, N-retinylidene-phosphatidylethanolamine is the preferred retinoid substrate for the photoreceptor-specific ABC transporter ABCA4 (ABCR), J. Biol. Chem. 279 (2004) 53972–53979.
[137] M. Illing, L. Molday, R. Molday, The 220-kDa rim protein of retinal rod outer segments is a member of the ABC transporter superfamily, J. Biol. Chem. 272 (1997) 10303–10310.
[138] J. Rozet, S. Gerber, E. Souied, I. Perrault, S. Chatelin, I. Ghazi, C. Leowski, J. Dufier, A. Munnich, J. Kaplan, Spectrum of ABCR gene mutations in autosomal recessive macular dystrophies, Eur. J. Hum. Genet. 6 (1998) 291–295.
[139] J. Weng, N. Mata, S. Azarian, R. Tzekov, D. Birch, G. Travis, Insights into the function of Rim protein in photoreceptors and etiology of Stargardt's disease from the phenotype in abcr knockout mice, Cell 98 (1999) 13–23.
[140] A. Yatsenko, N. Shroyer, R. Lewis, J. Lupski, Late-onset Stargardt disease is associated with missense mutations that map outside known functional regions of ABCR (ABCA4), Hum. Genet. 108 (2001) 346–355.
[141] G. Jedlitschky, D. Keppler, Transport of leukotriene C4 and structurally related conjugates, Vitam. Horm. 64 (2002) 153–184.
[142] P. Wu, C.J. Oleschuk, Q. Mao, B.O. Keller, R.G. Deeley, S.P. Cole, Analysis of human multidrug resistance protein 1 (ABCC1) by matrix-assisted laser desorption ionization/time of flight mass spectrometry: toward identification of leukotriene C4 binding sites, Mol. Pharmacol. 68 (2005) 1455–1465.
[143] R.G. Deeley, S.P. Cole, Substrate recognition and transport by multidrug resistance protein 1 (ABCC1), FEBS Lett. 580 (2006) 1103–1111.
[144] G. Reid, P. Wielinga, N. Zelcer, I.v.d. Heijden, A. Kuil, M.d. Haas, J. Wijnholds, P. Borst, The human multidrug resistance protein MRP4 functions as a prostaglandin efflux transporter and is inhibited by nonsteroidal antiinflammatory drugs, Proc. Natl. Acad. Sci. U.S.A. 100 (2003) 9244–9249.
[145] S. Neumann, G. van Meer, Sphingolipid management by an orchestra of lipid transfer proteins, Biol. Chem. 389 (2008) 1349–1360.

[146] M.F. De Rosa, D. Sillence, C. Ackerley, C. Lingwood, Role of multiple drug resistance protein 1 in neutral but not acidic glycosphingolipid biosynthesis, J. Biol. Chem. 279 (2004) 7867–7876.
[147] J. Turzanski, M. Grundy, S. Shang, N. Russell, M. Pallis, P-glycoprotein is implicated in the inhibition of ceramide-induced apoptosis in TF-1 acute myeloid leukemia cells by modulation of the glucosylceramide synthase pathway, Exp. Hematol. 33 (2005) 62–72.
[148] T. Sugawara, M. Kinoshita, M. Ohnishi, T. Tsuzuki, T. Miyazawa, J. Nagata, T. Hirata, M. Saito, Efflux of sphingoid bases by P-glycoprotein in human intestinal Caco-2 cells, Biosci. Biotechnol. Biochem. 68 (2004) 2541–2546.
[149] R. Raggers, A. Van Helvoort, R. Evers, G. Van Meer, The human multidrug resistance protein MRP1 translocates sphingolipid analogs across the plasma membrane, J. Cell Sci. 112 (1999) 415–422.
[150] P. Mitra, C. Oskeritzian, S. Payne, M. Beavan, S. Milstien, S. Spiegel, Role of ABCC1 in export of sphingosine-1-phosphate from mast cells, Proc. Natl. Acad. Sci. U.S.A. 103 (2006) 16394–16399.
[151] S. Pyne, S.C. Lee, J. Long, N.J. Pyne, Role of sphingosine kinases and lipid phosphate phosphatases in regulating spatial sphingosine 1-phosphate signalling in health and disease, Cell Signal. 21 (2009) 14–21.
[152] Y.A. Hannun, L.M. Obeid, Principles of bioactive lipid signalling: lessons from sphingolipids, Nat. Rev. Mol. Cell. Biol. 9 (2008) 139–150.
[153] S.E. Alvarez, S. Milstien, S. Spiegel, Autocrine and paracrine roles of sphingosine-1-phosphate, Trends Endocrinol. Metab. 18 (2007) 300–307.
[154] K. Sato, E. Malchinkhuu, Y. Horiuchi, C. Mogi, H. Tomura, M. Tosaka, Y. Yoshimoto, A. Kuwabara, F. Okajima, Critical role of ABCA1 transporter in sphingosine 1-phosphate release from astrocyte, J. Neurochem. 103 (2007) 2610–2619.
[155] N. Cheong, M. Madesh, L. Gonzales, M. Zhao, K. Yu, P. Ballard, H. Shuman, Functional and trafficking defects in ATP binding cassette A3 mutants associated with respiratory distress syndrome, J. Biol. Chem. 281 (2006) 9791–9800.
[156] S. Abe-Dohmae, Y. Ikeda, M. Matsuo, M. Hayashi, K. Okuhira, K. Ueda, S. Yokoyama, Human ABCA7 supports apolipoprotein-mediated release of cellular cholesterol and phospholipid to generate high density lipoprotein, J. Biol. Chem. 279 (2004) 604–611.
[157] M. Akiyama, Y. Sugiyama-Nakagiri, K. Sakai, J. McMillan, M. Goto, K. Arita, Y. Tsuji-Abe, N. Tabata, K. Matsuoka, R. Sasaki, D. Sawamura, H. Shimizu, Mutations in lipid transporter ABCA12 in harlequin ichthyosis and functional recovery by corrective gene transfer, J. Clin. Invest. 115 (2005) 1777–1784.
[158] C. Lefevre, S. Audebert, F. Jobard, B. Bouadjar, H. Lakhdar, O. Boughdene-Stambouli, C. Blanchet-Bardon, R. Heilig, M. Foglio, J. Weissenbach, M. Lathrop, J. Prud'homme, J. Fischer, Mutations in the transporter ABCA12 are associated with lamellar ichthyosis type 2, Hum. Mol. Genet. 12 (2003) 2369–2378.
[159] D. Kielar, W. Kaminski, G. Liebisch, A. Piehler, J. Wenzel, C. Mohle, S. Heimerl, T. Langmann, S. Friedrich, A. Bottcher, S. Barlage, W. Drobnik, G. Schmitz, Adenosine triphosphate binding cassette (ABC) transporters are expressed and regulated during terminal keratinocyte differentiation: a potential role for ABCA7 in epidermal lipid reorganization, J. Invest. Dermatol. 121 (2003) 465–474.
[160] A. Cremesti, F. Goni, R. Kolesnick, Role of sphingomyelinase and ceramide in modulating rafts: do biophysical properties determine biologic outcome? FEBS Lett. 531 (2002) 47–53.
[161] L.J. Pike, Rafts defined: a report on the Keystone Symposium on lipid rafts and cell function, J. Lipid Res. 47 (2006) 1597–1598.
[162] E. Ikonen, R.G. Parton, Caveolins and cellular cholesterol balance, Traffic 1 (2000) 212–217.
[163] I.R. Nabi, P.U. Le, Caveolae/raft-dependent endocytosis, J. Cell Biol. 161 (2003) 673–677.
[164] R.G. Parton, A.A. Richards, Lipid rafts and caveolae as portals for endocytosis: new insights and common mechanisms, Traffic 4 (2003) 724–738.
[165] G. Radeva, J. Perabo, F. Sharom, P-glycoprotein is localised in intermediate-density membrane microdomains distinct from classical lipid rafts and caveolar domains, FEBS J. 272 (2005) 4924–4937.
[166] L. Pike, Lipid rafts: heterogeneity on the high seas, Biochem. J. 378 (2004) 281–292.
[167] E.J. Smart, G.A. Graf, M.A. McNiven, W.C. Sessa, J.A. Engelman, P.E. Scherer, T. Okamoto, M.P. Lisanti, Caveolins, liquid-ordered domains, and signal transduction, Mol. Cell. Biol. 19 (1999) 7289–7304.
[168] K. Simons, D. Toomre, Lipid rafts and signal transduction, Nat. Rev.: Mol. Cell Biol. 1 (2000) 31–41.
[169] L. Pike, Lipid rafts: bringing order to chaos, J. Lipid Res. 44 (2003) 655–667.
[170] Z. Bacso, H. Nagy, K. Goda, L. Bene, F. Fenyvesi, J. Matko, G. Szabo, Raft and cytoskeleton associations of an ABC transporter: P-glycoprotein, Cytometry A 61 (2004) 105–116.
[171] S. Dos Santos, C. Weber, C. Franke, W. Muller, G. Eckert, Cholesterol: Coupling between membrane microenvironment and ABC transporter activty, Biochem. Biophys. Res. Commun. 354 (2007) 216–221.
[172] Y. Lavie, G. Fiucci, M. Liscovitch, Up-regulation of caveolae and caveolar constituents in multidrug-resistant cancer cells, J. Biol. Chem. 273 (1998) 32380–32383.
[173] J. Hinrichs, K. Klappe, I. Hummel, J. Kok, ATP-binding cassette transporters are enriched in non-caveolar detergent-insoluble glycosphingolipid-enriched membrane domains (DIGs) in human multidrug-resistant cancer cells, J. Biol. Chem. 279 (2004) 5734–5738.
[174] Y. Romsicki, F.J. Sharom, The membrane lipid environment modulates drug interactions with the P-glycoprotein multidrug transporter, Biochemistry 38 (1999) 6887–6896.
[175] A. Rothnie, D. Theron, L. Soceneantu, C. Martin, M. Traikia, G. Berridge, C.F. Higgins, P.F. Devaux, R. Callaghan, The importance of cholesterol in maintenance of P-glycoprotein activity and its membrane perturbing influence, Eur. Biophys. J. 30 (2001) 430–442.
[176] T. Saeki, A.M. Shimabuku, K. Ueda, T. Komano, Specific drug binding by purified lipid-reconstituted P-glycoprotein: dependence on the lipid composition, Biochim. Biophys. Acta 1107 (1992) 105–110.
[177] P. Lu, R. Liu, F.J. Sharom, Drug transport by reconstituted P-glycoprotein in proteoliposomes. Effect of substrates and modulators, and dependence on bilayer phase state, Eur. J. Biochem. 268 (2001) 1687–1697.
[178] Y. Romsicki, F.J. Sharom, The ATPase and ATP-binding functions of P-glycoprotein—modulation by interaction with defined phospholipids, Eur. J. Biochem. 256 (1998) 170–178.
[179] K. Klappe, J. Hinrichs, B. Kroesen, H. Sietsma, J. Kok, MRP1 and glucosylceramide are coordinately over expressed and enriched in rafts during multidrug resistance acquisition in colon cancer cells, Int. J. Cancer 110 (2004) 511–522.
[180] C. Marbeuf-Gueye, V. Stierle, P. Sudwan, M. Salerno, A. Garnier-Suillerot, Perturbation of membrane microdomains in GLC4 multidrug-resistant lung cancer cells—modification of ABCC1 (MRP1) localization and functionality, FEBS J. 274 (2007) 1470–1480.
[181] G. Schmitz, W. Kaminski, E. Orso, ABC transporters in cellular lipid trafficking, Curr. Opin. Lipidol. 11 (2000) 493–501.
[182] W. Drobnik, H. Borsukova, A. Bottcher, A. Pfeiffer, G. Liebisch, G.J. Schutz, H. Schindler, G. Schmitz, Apo AI/ABCA1-dependent and HDL3-mediated lipid efflux from compositionally distinct cholesterol-based microdomains, Traffic 3 (2002) 268–278.
[183] A. Mendez, G. Lin, D. Wade, R. Lawn, J. Oram, Membrane lipid domains distinct from cholesterol/sphingomyelin-rich rafts are involved in the ABCA1-mediated lipid secretory pathway, J. Biol. Chem. 276 (2001) 3158–3166.
[184] Y. Lin, C. Ma, W. Hsu, H. Lo, V. Yang, Molecular interaction between caveolin-1 and ABCA1 on high-density lipoprotein-mediated cholesterol efflux in aortic endothelial cells, Cardiovasc. Res. 75 (2007) 575–583.
[185] Y. Fu, A. Hoang, G. Escher, R.G. Parton, Z. Krozowski, D. Sviridov, Expression of caveolin-1 enhances cholesterol efflux in hepatic cells, J. Biol. Chem. 279 (2004) 14140–14146.
[186] Y. Landry, M. Denis, S. Nandi, S. Bell, A. Vaughan, X. Zha, ATP-binding cassette transporter A1 expression disrupts raft membrane microdomains through its ATPase-related functions, J. Biol. Chem. 281 (2006) 36091–36101.
[187] A.M. Vaughan, J.F. Oram, ABCG1 redistributes cell cholesterol to domains removable by high density lipoprotein but not by lipid-depleted apolipoproteins, J. Biol. Chem. 280 (2005) 30150–30157.
[188] S. Witting, J. Maiorano, W. Davidson, Ceramide enhances cholesterol efflux to apolipoprotein A-I by increasing the cell surface presence of ATP-binding cassette transporter A1, J. Biol. Chem. 278 (2003) 40121–40127.
[189] K. Nagao, K. Takahashi, K. Hanada, N. Kioka, M. Matsuo, K. Ueda, Enhanced apoA-I-dependent cholesterol efflux by ABCA1 from sphingomyelin deficient Chinese hamster ovary cells, J. Biol. Chem. 282 (2007) 14868–14874.
[190] C. Storch, R. Ehehalt, W. Haefeli, J. Weiss, Localisation of the human breast cancer resistance protein (BCRP/ABCG2) in lipid rafts/caveolae and modulation of its activity by cholesterol in vitro, J. Pharmacol. Exp. Ther. 323 (2007) 257–264.
[191] A. Pal, D. Mehn, E. Molnar, S. Gedey, P. Meszaros, T. Nagy, H. Glavinas, T. Janaky, O. von Richter, G. Bathori, L. Szente, P. Krajcsi, Cholesterol potentiates ABCG2 activity in a heterologous expression system-improved in vitro model to study function of human ABCG2, J. Pharmacol. Exp. Ther. 321 (2007) 1085–1094.
[192] A. Telbisz, M. Muller, C. Ozvegy-Lackzka, L. Homolya, L. Szente, A. Varadi, B. Sakardi, Membrane cholesterol selectively modulates the activity of the human ABCG2 multidrug transporter, Biochim. Biophys. Acta 1768 (2007) 2698–2713.
[193] J.W. Kok, R.J. Veldman, K. Klappe, H. Koning, C.M. Filipeanu, M. Muller, Differential expression of sphingolipids in MRP1 overexpressing HT29 cells, Int. J. Cancer 87 (2000) 172–178.
[194] C.W. Sachs, L.M. Ballas, S.W. Mascarella, A.R. Safa, A.H. Lewin, C. Loomis, F.I. Carroll, R.M. Bell, R.L. Fine, Effects of sphingosine stereoisomers on P-glycoprotein phosphorylation and vinblastine accumulation in multidrug-resistant MCF-7 cells, Biochem. Pharmacol. 52 (1996) 603–612.
[195] K.A. Wojtal, E. de Vries, D. Hoekstra, S.C. van Ijzendoorn, Efficient trafficking of MDR1/P-glycoprotein to apical canalicular plasma membranes in HepG2 cells requires PKA-RIIalpha anchoring and glucosylceramide, Mol. Biol. Cell 17 (2006) 3638–3650.
[196] V. Gouaze-Andersson, J.Y. Yu, A.J. Kreitenberg, A. Bielawska, A.E. Giuliano, M.C. Cabot, Ceramide and glucosylceramide upregulate expression of the multidrug resistance gene MDR1 in cancer cells, Biochim. Biophys. Acta 1771 (2007) 1407–1417.
[197] A. Pilorget, M. Demeule, S. Barakat, J. Marvaldi, J. Luis, R. Beliveau, Modulation of P-glycoprotein function by sphingosine kinase-1 in brain endothelial cells, J. Neurochem. 100 (2007) 1203–1210.
[198] S.R. Witting, J.N. Maiorano, W.S. Davidson, Ceramide enhances cholesterol efflux to apolipoprotein A-I by increasing the cell surface presence of ATP-binding cassette transporter A1, J. Biol. Chem. 278 (2003) 40121–40127.
[199] A. Ghering, W. Davidson, Ceramide structural features required to stimulate ABCA1-mediated cholesterol efflux to apoliprotein A-I, J. Lipid Res. 47 (2006) 2781–2788.
[200] E.N. Glaros, W.S. Kim, C.M. Quinn, J. Wong, I. Gelissen, W. Jessup, B. Garner, Glycosphingolipid accumulation inhibits cholesterol efflux via the ABCA1/

apolipoprotein A-I pathway: 1-phenyl-2-decanoylamino-3-morpholino-1-propanol is a novel cholesterol efflux accelerator, J. Biol. Chem. 280 (2005) 24515–24523.
[201] A.R. Leventhal, W. Chen, A.R. Tall, I. Tabas, Acid sphingomyelinase-deficient macrophages have defective cholesterol trafficking and efflux, J. Biol. Chem. 276 (2001) 44976–44983.
[202] J. Ito, Y. Nagayasu, S. Yokoyama, Cholesterol–sphingomyelin interaction in membrane and apolipoprotein-mediated cellular cholesterol efflux, J. Lipid Res. 41 (2000) 894–904.
[203] R.W. Johnstone, E. Cretney, M.J. Smyth, P-glycoprotein protects leukemia cells against caspase-dependent, but not caspase-independent, cell death, Blood 93 (1999) 1075–1085.
[204] M.J. Smyth, E. Krasovskis, V.R. Sutton, R.W. Johnstone, The drug efflux protein, P-glycoprotein, additionally protects drug-resistant tumor cells from multiple forms of caspase-dependent apoptosis, Proc. Natl. Acad. Sci. U.S.A. 95 (1998) 7024–7029.
[205] L.J. Robinson, W.K. Roberts, T.T. Ling, D. Lamming, S.S. Sternberg, P.D. Roepe, Human MDR 1 protein overexpression delays the apoptotic cascade in Chinese hamster ovary fibroblasts, Biochemistry 36 (1997) 11169–11178.
[206] M. Pallis, N. Russell, P-glycoprotein plays a drug–efflux-independent role in augmenting cell survival in acute myeloblastic leukemia and is associated with modulation of a sphingomyelin–ceramide apoptotic pathway, Blood 95 (2000) 2897–2904.
[207] Y. Lavie, H. Cao, S.L. Bursten, A.E. Giuliano, M.C. Cabot, Accumulation of glucosylceramides in multidrug-resistant cancer cells, J. Biol. Chem. 271 (1996) 19530–19536.
[208] E. Gulbins, H. Grassme, Ceramide and cell death receptor clustering, Biochim. Biophys. Acta 1585 (2002) 139–145.
[209] H. Grassme, A. Cremesti, R. Kolesnick, E. Gulbins, Ceramide-mediated clustering is required for CD95-DISC formation, Oncogene 22 (2003) 5457–5470.
[210] J.A. Rotolo, J. Zhang, M. Donepudi, H. Lee, Z. Fuks, R. Kolesnick, Caspase-dependent and -independent activation of acid sphingomyelinase signaling, J. Biol. Chem. 280 (2005) 26425–26434.
[211] E. Gulbins, P. Li, Physiological and pathophysiological aspects of ceramide, Am. J. Physiol. Regul. Integr. Comp. Physiol. 290 (2006) R11–R26.
[212] L. Thon, H. Mohlig, S. Mathieu, A. Lange, E. Bulanova, S. Winoto-Morbach, S. Schutze, S. Bulfone-Paus, D. Adam, Ceramide mediates caspase-independent programmed cell death, FASEB J. 19 (2005) 1945–1956.
[213] C. Bezombes, N. Maestre, G. Laurent, T. Levade, A. Bettaieb, J.P. Jaffrezou, Restoration of TNF-alpha-induced ceramide generation and apoptosis in resistant human leukemia KG1a cells by the P-glycoprotein blocker PSC833, FASEB J. 12 (1998) 101–109.
[214] J. Klostergaard, E. Auzenne, E. Leroux, Characterization of cytotoxicity induced by sphingolipids in multidrug-resistant leukemia cells, Leuk. Res. 22 (1998) 1049–1056.
[215] J. Shabbits, L. Mayer, P-glycoprotein modulates ceramide-mediated sensitivity of human breast cancer cells to tubulin-binding anticancer drugs, Mol. Cancer Ther. 1 (2002) 205–213.
[216] I. Mantovani, A. Cappellini, P.L. Tazzari, V. Papa, L. Cocco, A.M. Martelli, Caspase-dependent cleavage of 170-kDa P-glycoprotein during apoptosis of human T-lymphoblastoid CEM cells, J. Cell. Physiol. 207 (2006) 836–844.
[217] D. Evseenko, J. Paxton, J. Keelan, The xenobiotic transporter ABCG2 plays a novel role in differentiation of trophoblast-like BeWo cells, Placenta 21 (2007) S116–S120.
[218] D. Evseenko, P. Murthi, J. Paxton, G. Reid, B.S. Emerald, K. Mohankumar, P. Lobie, S. Brennecke, B. Kalionis, J. Keelan, The ABC transporter BCRP/ABCG2 is a placental survival factor, and its expression is reduced in idiopathic human fetal growth restriction, FASEB J. 21 (2007) 3592–3605.
[219] M. Lyons, A. Brown, 7-Ketocholesterol, Int. J. Biochem. Cell Biol. 31 (1999) 369–375.
[220] S. Panini, M. Sinensky, Mechanisms of oxysterol-induced apoptosis, Curr. Opin. Lipidol. 12 (2001) 529–533.
[221] T. Lee, L. Chau, Fas/Fas ligand-mediated death pathway is involved in oxLDL-induced apoptosis in vascular smooth muscle cells, Am. J. Physiol. Cell Physiol. 280 (2001) C709–C718.
[222] D. Walter, J. Haendeler, J. Galle, A. Zeiher, S. Dimmeler, Cyclosporin A inhibits apoptosis of human endothelial cells by preventing release of cytochrome c from mitochondria, Circulation 98 (1998) 1153–1157.
[223] I. Escargueil-Blanc, O. Meilhac, M. Pieraggi, J. Arnal, R. Salvayre, A. Negre-Salvayre, Oxidized LDLs induce massive apoptosis of cultured human endothelial cells through a calcium-dependent pathway. Prevention by aurintricarboxylic acid, Arterioscler. Thromb. Vasc. Biol. 17 (1997) 331–339.
[224] S. Tam, L. Mok, G. Chimini, M. Vasa, R. Deeley, ABCA1 mediates high-affinity uptake of 25-hydroxycholesterol by membrane vesicles and rapid efflux of oxysterol by intact cells, Am. J. Physiol. Cell Physiol. 291 (2006) C490–C502.
[225] T. Engel, F. Kannenberg, M. Fobker, J. Nofer, G. Bode, A. Lueken, G. Assmann, U. Seedorf, Expression of ABCG1 prevents cell death by transporting cytotoxic 7beta-hydroxycholesterol, FEBS Lett. 581 (2007) 1673–1680.
[226] N. Terasaka, N. Wang, L. Yven-Charvet, A. Tall, High-density lipoprotein protects macrophages from oxidised low-density lipoprotein-induced apoptosis by promoting efflux of 7-ketocholesterol via ABCG1, Proc. Natl. Acad. Sci. U.S.A. 104 (2007) 15093–15098.
[227] A. Brown, S. Leong, R. Dean, W. Jessup, 7-Hydroperoxycholesterol and its products in oxidized low density lipoprotein and human atherosclerotic plaque, J. Lipid Res. 38 (1997) 1730–1745.
[228] P. Edwards, M. Kennedy, P. Mark, LXRs: oxysterol-activated nuclear receptors that regulate genes controlling lipid homeostasis, Vascul. Pharmacol. 38 (2002) 249–256.
[229] S. Gill, R. Chow, A. Brown, Sterol regulators of cholesterol homeostasis and beyond: the oxysterol hypothesis revisited and revised, Prog. Lipid Res. 47 (2008) 391–404.
[230] I. Bjorkhem, Crossing the barrier: oxysterols as cholesterol transporters and metabolic modulators in the brain, J. Intern. Med. 260 (2006) 493–508.
[231] Z. Zhou, E. Hartwieg, H. Horvitz, CED-1 is a transmembrane receptor that mediates cell corpse engulfment in *C. elegans*, Cell 104 (2001) 43–56.
[232] Y. Wu, H. Horvitz, The *C. elegans* cell corpse engulfment gene ced-7 encodes a protein similar to ABC transporters, Cell 93 (1998) 951–960.
[233] Y. Hamon, C. Broccardo, O. Chambenoit, M. Luciani, F. Toti, S. Chaslin, J. Freyssinet, P. Devaux, J. McNeish, D. Marguet, G. Chimini, ABC1 promotes engulfment of apoptotic cells and transbilayer redistribution of phosphatidylserine, Nat. Cell Biol. 2 (2000) 399–406.
[234] R. Kiss, M. Elliott, Z. Ma, Y. Marcel, K. Ravichandran, Apoptotic cells induce a phosphatidylserine-dependent homeostatic response from phagocytes, Curr. Biol. 16 (2006) 2252–2258.
[235] A. Jehle, S. Gardai, S. Li, P. Linsel-Nitschke, K. Morimoto, W. Janssen, R. Vandivier, N. Wang, S. Greenberg, B. Dale, C. Qin, P. Henson, A. Tall, ATP-binding cassette transporter A7 enhances phagocytosis of apoptotic cells and associated ERK signaling in macrophages, J. Cell Biol. 174 (2006) 547–556.
[236] R. Frikke-Schmidt, B. Nordestgaard, G. Jensen, R. Steffensen, A. Tybjaerg-Hansen, Genetic variation in ABCA1 predicts ischemic heart disease in general population, Arterioscler. Thromb. Vasc. Biol. 28 (2008) 180–186.
[237] A. Zarubica, D. Trompier, G. Chimini, ABCA1, from pathology to membrane function, Pflugers Arch. 453 (2007) 569–579.
[238] S. Mace, E. Cousin, S. Ricard, E. Genin, E. Spanakis, C. Lafargue-Soubigou, B. Genin, R. Fournel, S. Roche, G. Haussy, S. Soubigou, G. Brefort, P. Benoit, A. Brice, D. Campion, M. Hollis, L. Pradier, J. Benavides, J. Deleuze, ABCA2 is a strong genetic risk factor for early-onset Alzheimer's disease, Neurobiol. Dis. 18 (2005) 119–125.
[239] J. Bullard, S. Wert, L. Nogee, ABCA3 deficiency: neonatal respiratory failure and interstitial lung disease, Semin. Perinatol. 30 (2006) 327–334.
[240] N. Wang, D. Lan, M. Gerbod-Giannone, P. Linsel-Nitschke, A. Jehle, W. Chen, L. Martinez, A. Tall, ATP-binding cassette transporter A7 (ABCA7) binds apolipoprotein A-I and mediates cellular phospholipid but not cholesterol efflux, J. Biol. Chem. 278 (2003) 42906–42912.
[241] W. Kaminski, E. Orso, W. Diederich, J. Klucken, W. Drobnik, G. Schmitz, Identification of a novel human sterol-sensitive ATP-binding cassette transporter (ABCA7), Biochem. Biophys. Res. Commun. 273 (2000) 532–538.
[242] K. Tainton, M. Smyth, J. Jackson, J. Tanner, L. Cerruti, S. Jane, P. Darcy, R. Johnstone, Mutational analysis of P-glycoprotein: suppression of caspase activation in the absence of ATP-dependent drug efflux, Cell Death Differ. 11 (2004) 1028–1037.
[243] M.A. Johnson, K.H. Moore, G.J. Yuen, A. Bye, G.E. Pakes, Clinical pharmacokinetics of lamivudine, Clin. Pharmacokinet. 36 (1999) 41–66.
[244] P. Lala, S. Ito, C.A. Lingwood, Retroviral transfection of Madin-Darby canine kidney cells with human MDR1 results in a major increase in globotriaosylceramide and 10(5)- to 10(6)-fold increased cell sensitivity to verocytotoxin. Role of p-glycoprotein in glycolipid synthesis, J. Biol. Chem. 275 (2000) 6246–6251.
[245] T. Lang, M. Haberl, D. Jung, A. Drescher, R. Schlagenhaufer, A. Keil, E. Mornhinweg, B. Steiger, G. Kullak-Ublick, R. Kerb, Genetic variability, haplotype structures, and ethnical diversity of hepatic transporters MDR3 (ABCB4) and BSEP (ABCB11), Drug Metab. Dispos. 34 (2006) 1582–1599.
[246] R.P. Oude Elferink, C.C. Paulusma, Function and pathophysiological importance of ABCB4 (MDR3 P-glycoprotein), Pflugers Arch. 453 (2007) 601–610.
[247] M. Kano, J. Shoda, R. Sumazaki, K. Oda, Y. Nimura, N. Tanaka, Mutations identified in the human multidrug resistance P-glycoprotein 3 (ABCB4) gene in patients with primary hepatolithiasis, Hepatol. Res. 29 (2004) 160–166.
[248] I. Aye, J. Paxton, D. Evseenko, J. Keelan, Expression, Localisation and activity of ATP binding cassette (ABC) family of drug transporters in human amnion membranes, Placenta 28 (2007) 868–877.
[249] R. Raggers, I. Vogels, G. Van Meer, Upregulation of the expression of endogenous Mdr1 P-glycoprotein enhances lipid translocation in MDCK cells transfected with human MRP2, Histochem. Cell Biol. 117 (2002) 181–185.
[250] S.F. Zhou, L.L. Wang, Y.M. Di, C.C. Xue, W. Duan, C.G. Li, Y. Li, Substrates and inhibitors of human multidrug resistance associated proteins and the implications in drug development, Curr. Med. Chem. 15 (2008) 1981–2039.
[251] J. Smith, Insight into ABCG1-mediated cholesterol efflux, Arterioscler. Thromb. Vasc. Biol. 26 (2006) 1198–1200.
[252] S. Lorkowski, M. Kratz, C. Wenner, R. Schmidt, B. Weitkamp, M. Fobker, J. Reinhardt, J. Rauterberg, E. Galinski, P. Cullen, Expression of the ATP-binding cassette transporter gene ABCG1 (ABC8) in Tangier disease, Biochem. Biophys. Res. Commun. 283 (2001) 821–830.
[253] F. Staud, P. Pavek, Breast cancer resistance protein (BCRP/ABCG2), Int. J. Biochem. Cell Biol. 37 (2005) 720–725.
[254] M. Suzuki, H. Suzuki, Y. Sugimoto, Y. Sugiyama, ABCG2 transports sulfated conjugates of steroids and xenobiotics, J. Biol. Chem. 278 (2003) 22644–22649.
[255] S. Hazard, S. Patel, Sterolins ABCG5 and ABCG8: regulators of whole body dietary sterols, Pflugers Arch. 453 (2007) 745–752.