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INVITED REVIEW

ABCA1, from pathology to membrane function

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Abstract The ABCA1 transporter is the prototype of the A class of mammalian adenosine triphosphate binding cassette transporters and one of the largest members of this family. ABCA1 has been originally identified as an engulfment receptor on macrophages and, more recently, it has been shown to play an essential role in the handling of cellular lipids. Indeed by promoting the effluxes of membrane phospholipids and cholesterol to lipid-poor apoprotein acceptors, ABCA1 controls the formation of high-density lipoproteins and thus the whole process of reverse cholesterol transport. A number of additional phenotypes have been found in the mouse model of invalidation of the ABCA1 gene. In spite of their clinical diversity, they all are extremely sensitive to variations in the physicochemical properties of the cell membrane, which ABCA1 controls as a lipid translocator.

Keywords ABC transporter · Lipid translocation · Tangier disease · Membrane vesiculation

Introduction

Protein-mediated lipid translocation on cellular membrane is one of the crucial biochemical mechanisms orchestrating organism physiology. Nevertheless, the main molecular actors and their role in lipid handling are still elusive.

Adenosine triphosphate binding cassette (ABC) transporters are one of the largest protein families ubiquitously conserved from bacteria to man [36]. In spite of their diversity in terms of substrate handling, they all share a similar "modus operandi", in that the hydrolysis of adenosine triphosphate provides the energy required for active transport of substrates across biological membranes. A significant number of ABC transporters are involved in the handling of cellular lipids [110]. The fact that the mutations in their genes are associated with pathological phenotypes or even clinically overt diseases related to lipid metabolism emphasises their crucial role in the homeostasis of cellular lipids. ABCA1 is a key playmaker as it controls, at the cell membrane, the initial steps leading to high-density lipoprotein (HDL) formation and, as a consequence, the whole process of reverse cholesterol transport from peripheral tissues to the liver [57, 109]. In this study, our aim is to review the functional impact of the ABCA1 transporter, highlighting the tight relation between the biochemical activity and the function. ABCA1 acts as a lipid translocator and, as such, modulates the lipid architecture at the membrane and its physicochemical properties. Lipid architecture indeed controls proper membrane functioning both as a physical barrier and as a signalling device. Understanding how it is orchestrated is thus a challenging but essential task.

Structural hints

The annotation of genomic databases led to the identification of 49 human ABC proteins classified into seven distinct subfamilies, ABC-A through ABC-G on the basis of similarity in gene structure, sequence or phylogenesis [36, 98]. In 1994, the identification of ABCA1 and its structural peculiarities led to the definition of a new subclass further named A [63]. The complete genomic

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sequence of the human and mouse ABCA1 genes, including their promoters and regulatory elements, has been determined in the late 1990s [51, 81, 89]. In terms of molecular architecture, ABCA1 is a full-sized ABC transporter, in that it shows a symmetrical structure with a transmembrane spanning domain (TMD) consisting of six transmembrane segments (TMS) and a nucleotide-binding domain (NBD), repeated in tandem. In the NBDs, all the diagnostic motifs can be found. ABCA1 possesses two extremely large extracellular loops, located between TMS1 and 2 and between TMS7 and 8 (Fig. 1). This is the most original feature of the A class of the ABC transporters shared by all the members [33]. Detailed topological studies have been performed in the case of ABCR (ABCA4) and ABCA1 and demonstrated a clear conservation of the topological arrangement [12]. This also holds true for ABCA7 and for the other members on the basis of sequence alignment and hydrophobicity plot comparisons [9, 44]. These extracellular loops show sequence hypervariability among the ABCA members and may thus participate directly to the functional specification of individual transporters in their appropriate expression compartment.

A precise description of the molecular function of ABCA1 as a membrane translocator is so far not achieved and most of the knowledge on the substrates that it may handle is actually rather indirect. The bottom line experiment would consist in the purification of the transporter and its functional reconstitution in artificial systems such as proteoliposomes. However, considering that ABCA1 is a polytopic membrane protein of very large size, "en masse" production and purification for reconstitution or crystallographic purposes is extremely demanding. Hence, alternative methods to approach the problem of its quaternary structure may be extremely valuable.

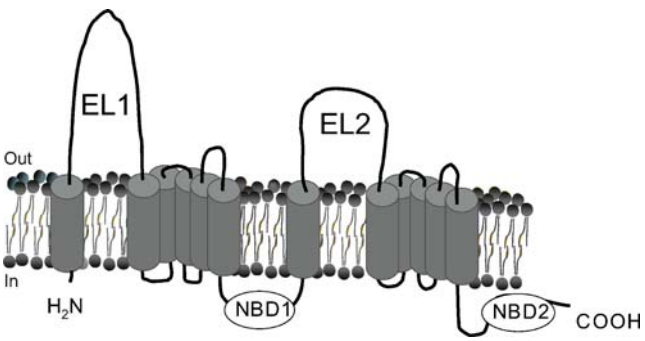

Fig. 1 Schematic view of the topological arrangement of ABCA1. ABCA1 is a full-length transporter with a $(TMD\text{-}NBD)_2$ arrangement. The distinctive and hypervariable extracellular loops between TMS1 and TMS2 and between TMS7 and TMS8 are indicated as *EL1* and *EL2*, respectively. *NBD*, nucleotide binding domain. The intracellular position of the N and C terminus is also indicated. The membrane orientation is indicated (*In and Out*)

Regulation of ABCA1 expression and activity

Transcriptional control

The essential role played by ABCA1 in reverse cholesterol transport and its identification as a protector against the risk of cardiovascular diseases provoked a profusion of studies to decipher how its expression is controlled both at the transcriptional and posttranscriptional level [90]. ABCA1 expression is highly regulated and implies a variety of molecular actors. For the sake of simplicity, we will discuss them in three major groups: cyclic adenosine monophosphate (cAMP) as an example of secondary messengers; nuclear orphan receptors, the principal controllers of ABCA1 expression; and cytokines, which can exert pleiotropic effects on ABCA1 expression. A schematic overview is given in Fig. 2 and in Table 1.

cAMP

Cyclic AMP is a ubiquitous second messenger involved in the control of a variety of metabolic events from muscle contraction to memory and in cellular functions such as vesicular secretion and cell growth [19, 38]. In the case of ABCA1, cAMP up-regulates its expression, by acting both at the transcriptional and translational level. Treatment of mouse macrophage cell lines (RAW 264.7 and J774) with cAMP analogues causes a huge increase in both ABCA1 mRNA and protein levels (estimated at 50- to 70-fold), whereas it has little or no effect on ABCA1 mRNA in human tissue, arguing for different regulation between cell types and species [22, 31, 74]. This effect has been linked to an increased stability of ABCA1 messenger RNA upon cAMP induction. However, the identification of a cAMP-responsive element essential for the induction of ABCA1 gene expression has been reported quite recently. This acts in conjunction with a nearby STAT3/4 element and is not conserved in the human ABCA1 gene, explaining the lack of cAMP stimulation on human ABCA1 gene [56].

Nuclear orphan receptors

Nuclear receptors are one of the largest groups of transcriptional factors, originally designated as "orphans" as, at that time, the specific ligands were unknown. Nuclear receptors are ligand-dependent transcription factors that regulate numerous aspects of development and homeostasis [6]. The family of nuclear receptors includes liver-X receptor (LXR α and β), retinoic-X receptor (RXR), peroxisome proliferator-activated receptor (PPAR α, β and γ), farnesoid-X receptor, pregnane-X receptor (PXR) and thyroid hormone receptor (TR). They are all structurally characterised by an amino-terminal domain responsible

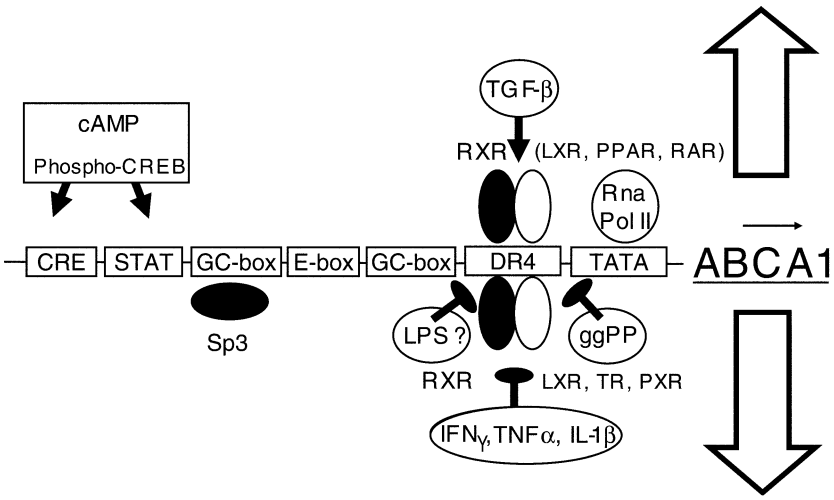

Fig. 2 Transcriptional regulation at the ABCA1 promoter. The diagram schematises the structure of ABCA1 promoter. The factors up-regulating the transcription of ABCA1 gene are indicated *above* it, whereas *below* are indicated those down-regulating its expression. For simplicity, the *boxes* and their positioning along the sequence are not drawn to scale (see Table 1 and [14] for further details)

for transcriptional activation and DNA binding and by a carboxy-terminal ligand-binding domain. Among them, LXRs emerge as major regulators of lipid homeostasis. LXRs form obligate heterodimers with RXR and, in this configuration, recognise specific DNA response elements consisting of two direct hexanucleotide repeats separated by four nucleotides (DR4 elements) [26]. Two LXR isoforms exist, LXR α and β, encoded by different genes. In contrast to LXR β, which is ubiquitously expressed, the α isoform has a prominent activity in macrophages and liver. The LXR target genes are involved in the whole spectrum of steps crucial in lipid metabolic pathways, from absorption of dietary cholesterol to cellular cholesterol effluxes and reverse cholesterol transport to the metabolism of lipoproteins and the synthesis and esterification of fatty acids [60]. The regulation of cholesterol homeostasis is particularly relevant in macrophages as these cells accumulate massive amounts of cholesterol during the development of atherosclerosis [59]. ABCA1 identification as a sterol sensitive gene is well assessed, both in human and mouse systems, and most of the inductive transcriptional effect of natural or synthetic lipid appears to be mediated via LXRs [20, 90, 103]. The activation of LXR/RXR dimers by physiologically occurring oxysterols, retinoids or their agonists stimulates, via the DR4 element in ABCA1 promoter, the transcription of the gene. This, in turn, leads to an increase in the ABCA1-dependent phospholipid and cholesterol efflux to ApoA-I [21, 52, 70, 111].

The PPAR class of nuclear hormone receptors (α and γ) also participates in the up-regulation of ABCA1 expression and reverse cholesterol transport indirectly via enhanced transcription of LXR α [14–16]. The down-regulation of ABCA1 transcription can be achieved through promiscuous PXRs activated by a wide variety of compounds including natural and synthetic androgens in prostate cancer cells [90, 96] or through TR/RXR dimers and geranylgeranyl pyrophosphate (ggPP), an intermediate in the endogenous mevalonate pathway [29]. All of these factors act via the DR4 element in the ABCA1 promoter [90].

Crosstalks with immune regulatory pathways

Cytokines have been shown to exert pleiotropic and antinomic effects on ABCA1 transcription. As a general rule, pro-inflammatory cytokines, tumor necrosis factor α (TNF), interleukin-1β (IL-1β) and interferon-γ down-regulate the LXR-mediated enhancement of ABCA1 transcription and protein expression [64, 76], whereas transforming growth factor β (TGF β) has the reverse effect and induces ABCA1 expression [77]. These results reinforce the recent findings of multiple crossroads between cellular handling of cholesterol and inflammatory responses mostly mediated at the LXR level. The activation of LXR indeed exerts a global anti-inflammatory effect and promotes macrophage survival [13, 41]. Though this is likely to depend on the coordinate activation of multiple sets of genes, it may be worth to investigate whether ABCA1, as a lipid transporter, is directly instrumental in modulating macrophage responsiveness to activation stimuli [27, 40, 108].

Posttranscriptional modulation of ABCA1 activity

Posttranscriptional regulation plays an important role in the modulation of ABCA1 function by controlling either protein stability and turnover or its activity [62]. The basal regulation of the cellular levels of ABCA1 transporter is

Table 1 Transcriptional regulation of ABCA1 gene

Substances	Cell types/tissues	Factors	ABCA1 expression	References
Secondary messengers				
Nucleotide analogs	RAW 264.7 J774	cAMP	+	[22, 31, 56, 74]
Lipids				
Oxysterols LXR agonists	Macrophages, intestine, liver, Sertoli cells, neuronal cells	LXR α, LXR β	+	[20, 25, 50, 67]
Retinoids	Macrophages	RXR α, RAR γ, LXR α	+	[21, 52, 101, 112]
PPAR α-agonists	Macrophages, intestine	PPAR α	+	[16, 48]
PPAR γ-agonists	Macrophages	PPAR γ	+	[14, 16, 61]
PPAR δ-agonists	THP-1	PPAR δ	+	[72]
PXR-agonist	HepG2 rat hepatocytes	Rifampicin, LCA, PCN	+	[90, 96]
Unsaturated fatty acids	J774, RAW 264.7	?	−	[114, 116]
Cholesterol depletion	HUVEC	SREBP2	−	[121]
Geranylgeranylpyrophosphate	THP-1, CaCo-2	ggPP, Rho	−	[29]
Hormones				
Estrogen	Liver, intestine	ER α	+	[97]
Androgen	LNCaP	?	−	[28]
Thyroid hormone	Fibroblast, 293T	TR α	−	[39]
Cytokines				
TNF α	J774	?	−	[47]
IL-1 β	J774	?	−	[47]
LPS	RAW 264.7 J774	NFκB	−	[5, 47]
IFN γ	Macrophages	STAT1	−	[77, 115]
TGF β	Macrophages	?	+	[77]
Oncostatin M	HepG2	?	+	[53]
Drugs				
Aa2 receptor agonist	THP-1	cAMP	+	[80]
Niacin	MonoMac6	cAMP, PPAR γ	+	[85]
Statins	Macrophages RAW 264.7, THP-1	LXR α	+/−	[95, 118, 120]
Verapamil	RAW 264.7	?	+	[100]
Bisphosphanate	Macrophages	?	+	[99]
Others				
Hypoxia	HUVEC	HIF1 α/ARNT	+	[66]

controlled by calpain-mediated degradation [106], whereas its activity is under the control of diverse protein kinases. Protein kinase A is an effector system that responds to changes in intracellular cAMP. ABCA1 is constitutively phosphorylated by protein kinase A at specific Ser 2054 in the second NBD, in RAW 264.7 macrophages and in transfected human embryonic kidney cell lines. ABCA1 phosphorylation directly modulates its activity and the downstream efflux of phospholipids and cholesterol to the acceptor ApoA-I [92]. It has also been reported that ApoA-I docking at the cell surface may be instrumental in the induction of ABCA1 phosphorylation, through the cAMP/protein-kinase-A-dependent pathway [32]. Protein kinase CK2 conversely acts as a down-regulator of ABCA1 activity by phosphorylating amino acid residues located downstream of the first NBD [83]. Other regulatory kinases have been reported to contribute to ABCA1-dependent effluxes by acting, however, on targets other than the transporter itself [104].

Expression pattern and intracellular distribution

Establishing precisely the cellular localisation of ABCA1 and the most relevant functional sites is critical to understand its physiological function. However, the lack of valuable antibodies has prevented a detailed immunohistological description of the ABCA1 expression pattern in the living animal so far. A number of studies in tissues and cell lines have analysed the expression pattern of ABCA1 transcript in human, mouse or baboon via Northern blot, reverse transcriptase-polymerase chain reaction, dot blot or

in situ hybridisation analysis [8, 17, 44, 51, 54, 63, 117]. There is a general consensus toward a wide distribution of ABCA1 mRNA with variation in abundance in specific sites. The highest mRNA expression levels are detected in placenta, pregnant uterus, liver, lung, adrenal glands, heart, small intestine and fetal tissues; the lowest expression is found in pancreas, skeletal muscle, ovary, colon, prostate, mammary glands and bone marrow. The discrepancies concern mainly the level of expression rather than the presence or absence of the transcript.

Wellington et al. [117] have proposed an extensive review of the distribution pattern of mouse ABCA1, taking into account both transcript and protein levels. According to this work, the level of transcript may not accurately predict protein abundance, notably in tissue with intermediate to low abundance of ABCA1 transcript. In conclusion, liver, adrenal glands, testis, pregnant uterus and placenta appear as the major sites of ABCA1 expression. At the cellular level, tissue macrophages as well as macrophage-like cell lines of mouse or human origin are consistently expressing high levels of the transporter. Expression in both liver and macrophage appears of extreme physiological relevance. The expression of ABCA1 on the basolateral membrane of hepatocytes has been shown to indeed contribute significantly to the maintenance of circulating HDL level, in agreement with the prevailing view that the liver is the major site responsible for HDL biogenesis [42, 43]. On the other hand, despite the ubiquitous expression of ABCA1, the accumulation of cholesterol in both human and mouse models of ABCA1 dysfunction occurs principally in macrophages. However, the global amount of lipid efflux from these cells provides only a minimal contribution to circulating HDL levels. The progression of foam cell formation and the atheroma development are consistently significantly influenced by the ABCA1 expression on macrophages but largely independent of the levels of circulating HDL [1, 2, 30].

At the cellular level, ABCA1 is predominantly located on the plasma membrane. It is currently thought that this localisation is necessary and sufficient for its function as a promoter of lipid effluxes. On the other hand, ABCA1–EGFP chimeras also decorate the endo-lysosomal compartment [34, 82, 88] from where they can actively shuttle to the plasma membrane [71, 88]. This may be relevant for the control of cellular lipid handling considering the endocytic recycling of cell-bound apoproteins. Takahashi and Smith [102] reported that uptake and resecretion of ApoA-I indeed occur via endocytic vesicles (retroendocytosis) where ApoA-I and ABCA1–EGFP could co-localise. Thus, in line with these results, it may be envisioned that ABCA1 not only mediates lipid desorption at the cell surface but, upon internalisation, may also pump lipids into the vesicular lumen. Those would associate with the endocytosed apoproteins there and be further released as mature HDL particles upon fusion of the vesicle with the plasma membrane [7] (Fig. 3).

ABCA1 and disease: human genetic and mouse models

The mutations in the ABCA1 transporter gene have been identified as the molecular defect responsible for Tangier disease, an autosomic recessive disorder of lipid metabolism [10, 55, 86, 87]. The clinical hallmarks of Tangier disease include the virtual absence of circulating HDL and ApoA-I. These are associated to a whole spectrum of signs, from orange tonsils, peripheral neuropathy, splenomegaly to thrombocytopenia and increased incidence of cardiovascular disease, whose clinical penetrance is however extremely variable [4]. Seminal to these signs is an impairment of cellular effluxes of phospholipids and cholesterol to lipid-poor apolipoproteins, diagnostic of Tangier disease among the other forms of hypoalphalipoproteinemias [4]. The mutations of ABCA1 have also been detected in a nosographically distinct disorder of HDL deficiency, familial HDL deficiency, that is clinically superimposable to Tangier disease but is transmitted as a dominant trait. This discrepancy may find its origin in the recent notion that ABCA1 assembly into oligomeric structures is required for full functional competence. We have indeed recently applied biophysical methods such as intermolecular fluorescence resonance energy transfer [46] and biochemical methods such as electrophoretic analysis in native condition (native polyacrylamide gel electrophoresis) [78] to the study of ABCA1 molecular assembly.

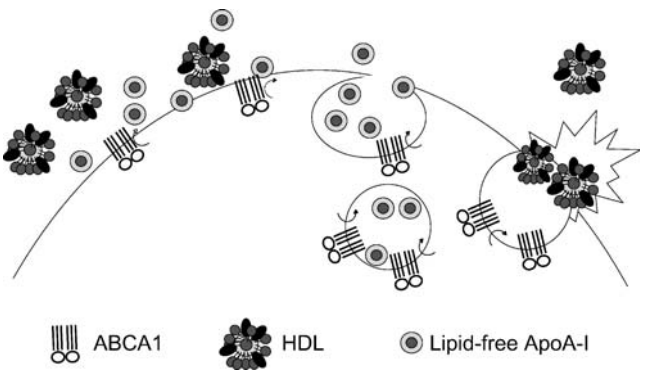

Fig. 3 Retroendocytosis as a source of newly formed HDL particles. Surface bound-ApoA-I is endocytosed and meets ABCA1 in recycling endosomes. From there, a retrograde secretion, reminiscent of receptor-ligand retroendocytosis, takes place. The ABCA1-dependent lipid desorption generates, in the vesicular lumen, lipidated ApoA-I particles and then fully mature HDL. The latter particles are secreted by vesicular fusion with the plasma membrane. *Arrows* schematise the lipid translocator function of ABCA1

These studies have provided evidence that ABCA1 is predominantly expressed as a dimer and that the transition between oligomeric states is part of its enzymatic cycle (Trompier et al., submitted for publication). Thus, the mutations specifically impairing oligomerisation would show a transdominant negative effect and the associated phenotypic abnormalities would be transmitted genetically as dominant traits.

An investigation on the relationship between discrete mutation and phenotype may also be instrumental in understanding what governs the variable penetrance of clinical signs in Tangier pedigrees. As direct genotype/phenotype correlations are impossible due to the rarity of the disease (60 pedigrees reported as for now) [94], alternative approaches such as the generation of appropriate animal models exclusively expressing informative ABCA1 mutants have to be envisioned. Finally, as ABCA1 can be considered one of the most clearly identified therapeutic targets in the prevention of cardiovascular disease [58, 73], several efforts have arisen in the aim of predicting how and whether genetic polymorphism may contribute to differences in phenotypic traits [11, 79].

The generation of knockout mice irrevocably demonstrated that ABCA1 dysfunction is sufficient to generate hypolipidemic profiles [17, 34, 68, 75]. These mice faithfully reproduce the human syndrome; however, a few traits appear limited to the mouse models. First, the engulfment of cells dying by apoptosis is clearly impaired during embryonic development in the mice [34]. This defect, which is devoid of major developmental consequences, has obviously not been investigated in humans. In addition, ABCA1−/− females are infertile due to impaired placental development, a phenotype related to the high expression level of ABCA1 in the pregnant uterus [17, 75]. A similar sign is lacking in human Tangier patients though an increased incidence of spontaneous abortions has been informally recorded.

The availability of animal models carrying the invalidation of ABCA1 gene has prompted a large body of work to be targeted at the definition of the protective role of the transporter in the development of atheroma lesion. Though the results globally confirm the predicted protective effect, a number of inconsistencies can be observed [42]. These are likely to originate from the heterogeneity of genetic backgrounds used in the different experimental setups. Though the alterations in metabolic profile and most phenotypes related to ABCA1 loss of function appear robust and background-insensitive, exquisite differences in the ABCA1 expression indeed exist between the various mouse strains (Trompier, unpublished results) [65]. This together with the well-known genetically determined differences in the cytokine regime and the activation of immunoregulatory pathways may well contribute to blur the experimental results obtained from heterogeneous sources.

The invalidation of ABCA1 gene in mice leads also to clinically relevant phenotypes unrelated to lipid metabolism; these span from aberrant responses to malaria infection to increased development of Alzheimer's related degenerative lesions. In ABCA1−/− mice, generated in the pure DBA1/J background, the infection with *Plasmodium berghei* ANKA indeed leads to a robust resistance to the development of fatal cerebral malaria [18]. This can be traced to a reduced activation of macrophages in response to *Plasmodium* antigens as very low levels of circulating TNF α and plasma microparticles were observed. Modified macrophages polarisation, consequent to the ABCA1 deletion, may hence be envisioned and is indeed supported by the exquisite responses of ABCA1−/− myelomonocytic lineages to inflammatory stimuli and cytokine activation (Broccardo, unpublished results). The development of crosses between ABCA1 deleted mice and Alzheimer's prone models, in heterogeneous genetic backgrounds, more recently revealed that the absence of the transporter induces an aggravation of fibrillar amyloid deposit [35, 49, 113]. This may be related directly not only to the ABCA1 function as a provider of lipid to nascent HDL-like particles in the brain but also to the fact that cholesterol content/distribution in ABCA1−/− membranes is greatly altered. It is known that the amyloidogenic proteolysis of Alzheimer's precursor protein is indeed largely determined by its partitioning in/out membrane microdomains [37].

In this respect, it may be worth mentioning that the sorting of ABCA1 in specialised membrane domains is still a controversial issue. In our hands and at odds with previous results [23, 69], the experimental evidence indicates that a substantial fraction of the transporter is located in Lubrol WX and Brij 98 insoluble membrane domains while largely excluded from the classical "core microdomains" defined as Triton X-100 insoluble (Zarubica, unpublished observation). This finding has been quite recently supported by the lipidomic analysis of ABCA1-generated membrane microvesicles, clearly indicating that a conspicuous proportion derives from membrane microdomains [24]. Thus, irrespective of the transporter partitioning in the liquid-ordered or liquid-disordered membrane phases, its ability to facilitate desorption of membrane phospholipids and cholesterol may be expected to have consequences on the lateral arrangement of membrane lipids and on the sorting of proteins [84].

ABC transporters in lipid homeostasis

The shedding of lipid from cell membranes is a ubiquitous event. In most cases, it concerns the transport of a specific

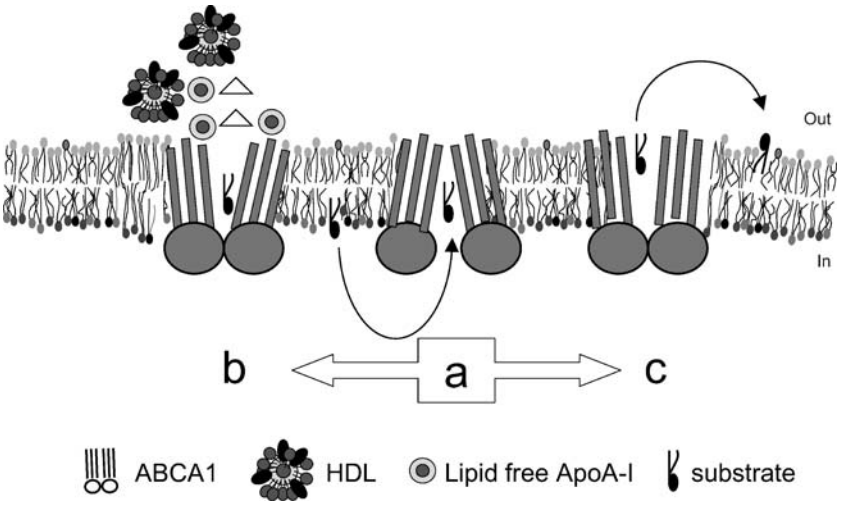

Fig. 4 Bimodal functioning of ABCA1 as a lipid translocator. **a** The ABCA1 substrate (*black*) is translocated, at minimal energetic expense, in the internal core of the transporter. No rotation of the lipid headgroup is required. The lipid can now either be desorbed in the same orientation on the acceptor ApoA-I (**b**) and follow the routing to HDL formation (*arrowheads*) or, in the absence of the acceptor, be flipped to the external membrane leaflet (**c**) [110]. The movements of the lipid substrate are schematised by the *arrows*. The inner and outer leaflets of the membrane are indicated

monomer form of lipid from one leaflet of the membrane to the other or to an external acceptor. Many human diseases have been related to defective desorption of lipids from cell membranes and, in nearly all cases, members of the ABC transporter family appear at the origin of defect [110]. In their vast majority, they belong to the A, D and G classes [3, 36] and dedicated reviews in this issue]. The D class includes half-transporters localised at the membrane of the peroxisome and involved in peroxisome biogenesis and/or in the transport of fatty acids across the membrane of these organelles [105]. Apart from ABCA1, most of the A class members are supposed to transport lipid substrates from the cytosol to either the exofacial leaflet of the membrane or the extracellular space or onto specialised membranes in intracellular organelles [45, 93, 107]. Four out the ABCG hemitransporters have been implicated in the transport of sterols, either in the intestine where ABCG5 and ABCG8 pump back absorbed sterols into the gut lumen [119] or in macrophages and liver cells where ABCG1 and ABCG4 work in concert with ABCA1 to actively transport cholesterol to mature HDL [91].

In all of these cases, the direct evidence addressing the transport itself and the substrate specificity is relatively limited, though the latter one seems to be quite diverse among the different members. How this is controlled and more generally how transport occurs in mechanistic terms are still open questions. Several models have been suggested: from the classical flippase model to the refined variation recently proposed by van Meer et al. [110] (Fig. 4). This latter proposal suggests that the lipids could be translocated without undergoing reorientation of their headgroups, from the inner membrane leaflet to the internal core of the transporter. From there, it can either be released onto an external acceptor or, in its absence, be reoriented, at energetic expenses, in the exofacial membrane leaflet. In other words, for example in our case, ABCA1 could either pump the phospholipid substrates onto apoprotein acceptors docked in its close proximity or flip them into the external leaflet of the membrane. This model has the distinctive advantage to solve some of the incongruence of the more classical flippase model, such as the evident need for acceptors or the energetic demand required for release of lipid substrates into aqueous medium. In addition, this bimodal and non-exclusive model can easily accommodate molecular partners acting as regulators of extrusion vs membrane flipping.

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