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Review

The ABCA subclass of mammalian transporters

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Abstract

We describe here a subclass of mammalian ABC transporters, the ABCA subfamily. This is a unique group that, in contrast to any other human ABC transporters, lacks a structural counterpart in yeast. The structural hallmark of the ABCA subfamily is the presence of a stretch of hydrophobic amino acids thought to span the membrane within the putative regulatory (R) domain. As for today, four ABCA transporters have been fully characterised but 11 ABCA-encoding genes have been identified. ABCA-specific motifs in the nucleotide binding folds can be detected when analysing the conserved sequences among the different members. These motifs may reveal functional constraints exclusive to this group of ABC transporters.

Keywords: ABCA subclass; ABC1; ABCR; Consensus motif; Gene family

Contents

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1. Introduction

The family of ABC transporters is one of the largest family of proteins. In genomes whose sequence has been completed they represent between 2–5% of the whole coding regions [1–4] An arbitrary extrapolation to the human genome which is estimated to contain 60–70 000 genes, will lead to an expected number of ABC transporters of more than 1000, which is likely to be by far an overestimation. Since a comprehensive list is present in the ABC transporter web page (http://www.med.rug.nl/mdl/humanabc.htm), and the ABC transporters in various organisms are reviewed in detail in this special issue, we concentrate here only on the ABCA subfamily.

The structural archetype of a full size ABC transporters encoded by a single gene is the P-glycoprotein which possesses a canonical 6×2 transmembrane spanners paired in tandem to the nucleotide binding domains (NBD). However, several subfamilies can be identified on the basis of structural features. Our aim here is to discuss the distinctive structural features of the ABCA subfamily, which appears to be restricted to multicellular organisms. Indeed, the class of mammalian ABC1-like proteins, or, according to the novel nomenclature proposed by the genome project ABCA proteins, lacks a yeast structural ortholog [5–7]. Interestingly, however, transporters sharing similar features can be found in other evolutionarily distant organisms (see below).

2. Features of the ABCA class of ABC transporters

When analysing the prototype of this class, ABCA1 (formerly ABC1), we reported the presence of a regulatory domain reminiscent of the R domain in CFTR. However, here this domain is split into two halves by a highly hydrophobic segment, which we called HH1 [8]. Based on secondary structure predictions, which predicted HH1 as a transmembrane segment but favoured a β conformation, and from analogy to similarly structured domains in K^+ channels [8–11], we proposed the topological model shown in Fig. 1, panel A. The experimental support to this model comes from the analysis of the protease sensitivity of a number of Myc-tagged ABC1 chimeras, transcripted and translated in vitro in the presence of microsomal membranes (Hamon and Chimini, unpublished) and immunoprecipitated with the anti-myc monoclonal antibody 9E10 [12]. The validity of the model was also examined by a specific antibody reacting with the first NBD of ABC1 [13]. These experiments allowed to define the position of the extracellular loop between TM5 and TM6, which contains a glycosylated asparagine, to confirm the intracellular location of the two ABC domains, as well as the cytosolic location of the second half of the regulatory domain. However, as it is frequently the case with polytopic membrane proteins, alternative topologies cannot be excluded. An example is shown in Fig. 1, panel B, where the HH1 domain is represented as spanning the membrane once from inside to outside. This prediction includes a large extracellular loop of 260 residues, corresponding in the former model to the second half of the R domain. We are currently testing these models by analyzing the reactivity of surface-exposed transporters with a panel of antisera, generated against predicted extracellular loops. For the following discussion we will refer to the topology model shown in panel A.

3. The ABCA gene family

In 1994 we reported the identification of ABCA1 and its structural peculiarities among ABC transporters [8]. It soon became apparent that ABC1 was not a unique example and a large group of transporters shared similar features [8,14–17] (Table 1). Indeed, so far four ABCA genes have been fully sequenced, namely ABCA1, ABCA2, ABCA3 or C and ABCR, either in mouse, man or other mammals. We have recently identified a fifth transporter conserved in mouse and man (tentatively called ABCA7 or ABCX (Broccardo et al. submitted and Dean and Allikments, personal communication). and have evidence for the presence of at least five other individual ABCA genes. Recently, the analysis of osteoclast-specific transcripts has also allowed the identifications of partial sequences (named OCA), closely related to the ABCA family (Wagstaff, personal communication). Their relationship to known ABCA transporters, however, is still unknown.

A pairwise comparison of the published full nucleotide sequences for ABCA cDNAs shows an over-

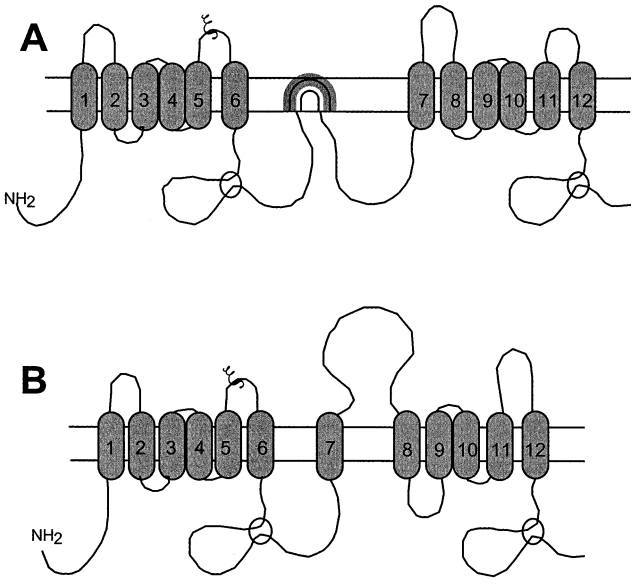

Fig. 1. Predictive topology of ABCA1 as a prototype of the ABCA subclass of transporters. (A) Topological model proposed by the authors with two symmetrical halves interrupted by an R-domain. The highly hydrophobic segment (HH1) is drawn as a hairpin crossing the membrane twice. Each half is composed of a set of six transmembrane spanners and an ATP binding cassette. (B) Alternative topological prediction, with HH1 spanning the membrane once, from the inside to the outside. This leads to an asymmetric structure with a large extracellular loop followed by an odd number of transmembrane spanners in the second half of the transporter.

all identity of around 60% among the different genes, irrespectively of the pairs analysed. Cross-species conservation of individual genes is extremely high, exceeding 85% identity. This allows to design member-specific probes, detecting unique transcripts in Northern blots (Fig. 2). Indeed, although the length of each transcript is around 7 kb, slight differences in size can be seen when the RNAs are separated on agarose gels, as shown in panel A. In addition, when a panel of tissues and cell lines is used to hybridise, all these genes appear to be expressed ubiquitously at low levels. Still, a preferential and non-redundant territory of expression can be assigned to individual members. ABCA1 is 10-fold overexpressed in the uterus of pregnant women [8], followed by the expression levels in liver, adrenals and normal uterus, whereas ABCA2 is overexpressed in the adult brain, and ABCA3 in the liver, lung and kidney (Fig. 2). The most recently recognised member, ABCA7 or ABCX, is preferentially expressed in the spleen and more generally in lymphoid organs (not shown, Broccardo et al., in preparation). ABCR was not included in this analysis, since its expression has been reported to be restricted to the retina [18,19].

The currently estimated number of ABCA genes is at least 11, based on the analysis of dbEST by Dean and co-workers (personal communication). A similar estimation was obtained in our laboratory, by a genomic amplification assay with degenerate primers targeting ABCA-specific consensus motifs, which flank conserved introns in the NBDs (see below and Broccardo et al., unpublished observation).

All the fully identified ABCA genes map in synthenic regions in the mouse and human genome, respectively, and there is no evidence of gene clustering (Table 1). This suggests an evolutionary origin of

Table 1
The family of ABCA transporters

Name	Symbol	Chromosome human	Chromosome mouse	RNA	Amino acid	Exons	Accession
ABC1	ABCA1	9q22-q31	4A5-B3	6.9	2259	48	AJ012376
ABC2	ABCA2	9q34	2A2-B	6.7	>2174	>42	U18235
ABC3 (ABC-C)	ABCA3	16p13.3	17B	6.5	1704	?	U78735
ABCR	ABCA4	1p22	?	7.3	2273	50	NM000350
ABC4	ABCA7	19p13.3	10B4-C1	6.6	>1840	>37	–
EST90625	ABCA5	17q21-q24	?	?	?	38	U66672
EST155051	ABCA6	17q21	?	7	?	38	U66680
KIAA0822	ABCA8	17q24	?	5.7	1581	38	AB020629
EST640918	ABCA9	17q24	?	?	?	38	–
EST698739	ABCA10	17q24	?	?	?	38	–
EST1133530	ABCA11	4p16-pter	?	?	?	?	–

For yet unpublished results the sources are Broccardo et al., (ABCA7) and Dean et al. (ABCA5-6 and 8-11). KIAA0822 [45]

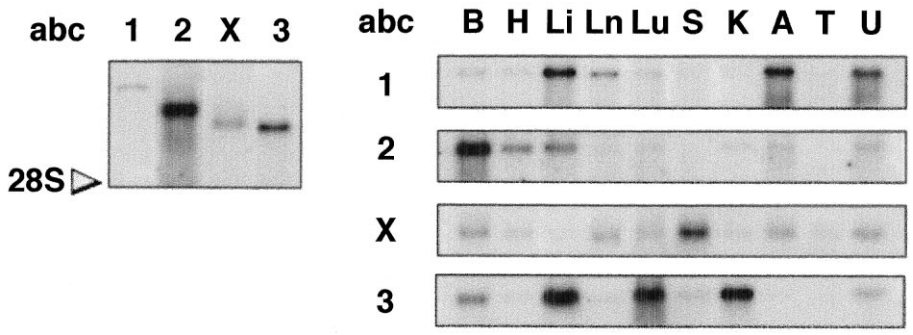

Fig. 2. Expression of ABCA transcripts. (A) Northern blot analysis of brain RNA with ABCA member-specific probes highlights small, but detectable differences in size. ABCA1 transcript is the largest one, followed by ABCA2, ABCA7 and ABCA3. (B) Northern blot analysis of a panel of RNAs from adult mouse tissues, hybridised with member-specific probes shows that all ABCA transcripts are detected ubiquitously at low levels. Non-redundant member-specific territories of preferential expression are nonetheless detectable. 1: ABCA1, 2: ABCA2, X: ABCA7, 3: ABCA3, B: brain, H: heart, Li: liver, Ln: lymph nodes, Lu: lung, K: kidney, A: adrenals, T: thymus, U: uterus.

individual members, predating speciation. Dean and co-workers have recently identified an additional ABCA gene on chromosome 4p16-pter, and a cluster of tandemly linked ABC genes on chromosome 17q24, apparently sharing similarities to the ABCA class (Dean, personal communication). A more detailed analysis and a final hypothesis about their evolutionary relationships will have to wait for the complete sequences and the mapping of the orthologs in the mouse genome.

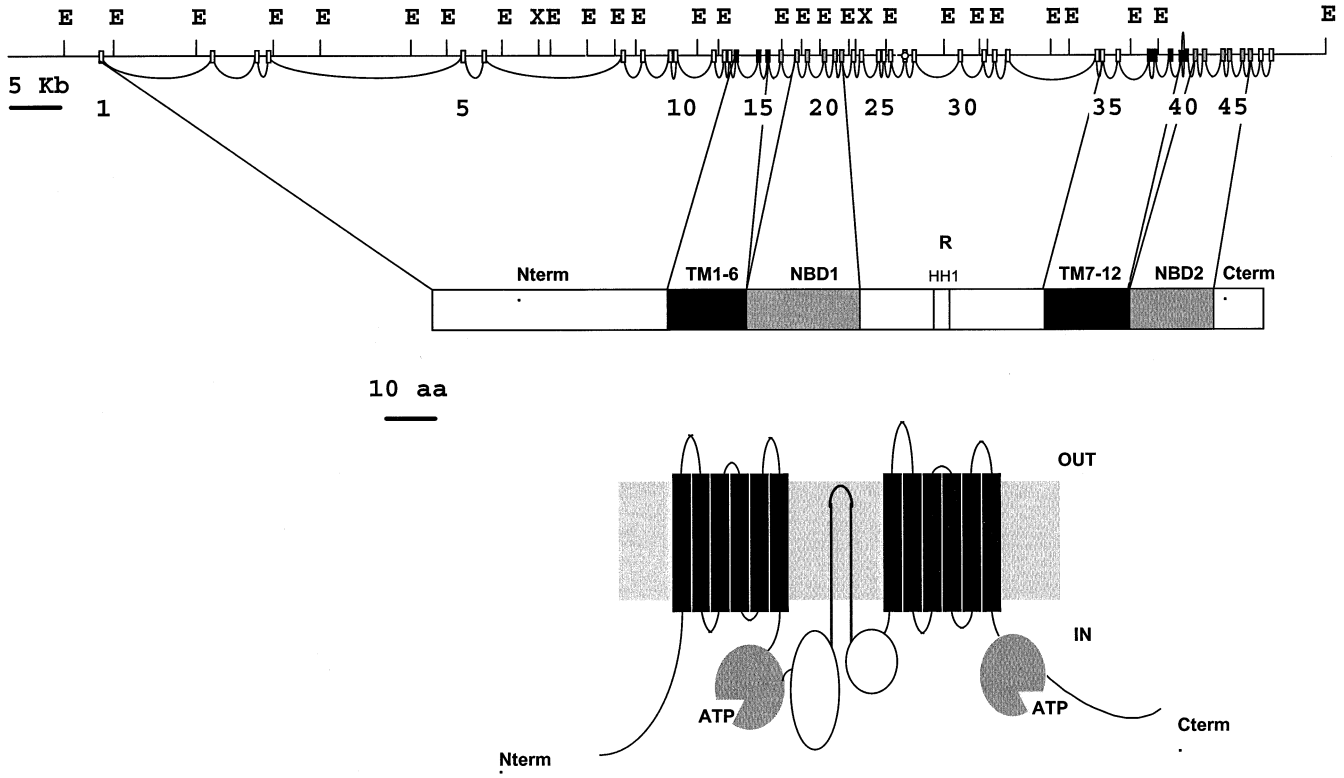

Fig. 3. Correspondence between genomic structure of the ABCA1 gene and protein domains. (Top panel) Exon-intron structure of the ABCA1 gene on mouse chromosome 4. Exons are shown as filled boxes. The positions of *Eco*RI (E) and *Xho*I (X) restriction sites are given. (Middle and bottom panel) Exon-encoded protein domains are highlighted by graphic motifs, either in the linear representation or in the predicted protein. TM: transmembrane helix, NBD: nucleotide binding domain, R: regulatory domain.

4. Gene organisation

A full genomic organisation has been published for human ABCR [20,21]. That of the mouse ABCA1 gene is schematically shown in Fig. 3 and has been deposited in the databases. The mouse ABCA1 gene spans more than 100 kb on chromosome 4A5-B3, and is split into 49 exons (Broccardo et al., personal communication). The overall exon organisation and the correspondence between exons and the encoded protein domains are shown in Fig. 3. It has to be noted that a striking conservation of the gene structure organisation is present among the different members of the ABCA subclass. Most of the splice junctions are indeed perfectly conserved among the different genes, for instance 42 out of the 48 introns of ABCA1 are perfectly conserved in ABCR, both in position and type [20]. No clusters of introns of the same type can be evidenced, however, in any of the analysed genes.

A cross-gene analysis of the intron-exon organisation reveals the highest conservation among members in the regions encoding the NBDs and the transmembrane anchors (Fig. 4 and 5). In contrast, a comparison of the structure of the N- and C-terminal halves of a single gene shows that equivalent domains do not share a similar genomic organisation. This suggests an independent evolution, which is not unusual among ABC transporters. It does once again corroborate the evolutionary hypothesis of the origin of multidomain transporters from fusion of independently evolved individual domains, as opposed to internal duplication events giving rise to an ancestral transporter. A comparison of the structural organisation of the ABCA gene subclass with other structural classes, like MDR, MRP, CFTR or SUR transporters, shows class-specific diversifications and, again, corroborates the autonomous evolutionary history of each class of genes [22–26].

Finally, and in contrast to the NBD and TD encoding regions, the genomic fragment encoding the regulatory domain shows an extreme variability in the positions of splicing sites among individual transporters and in the number of exons (10 exons in ABCA2 and ABCA7, 13 for ABCA1 and ABCR). This variability is reflected down to the amino acid level, since this domain shows the least conservation in primary sequence. Its main characteristics, however, like the richness in charged residues, the presence of several putative phosphorylation sites, and the presence of the highly hydrophobic spanner, are constantly present. In spite of the invariable detec-

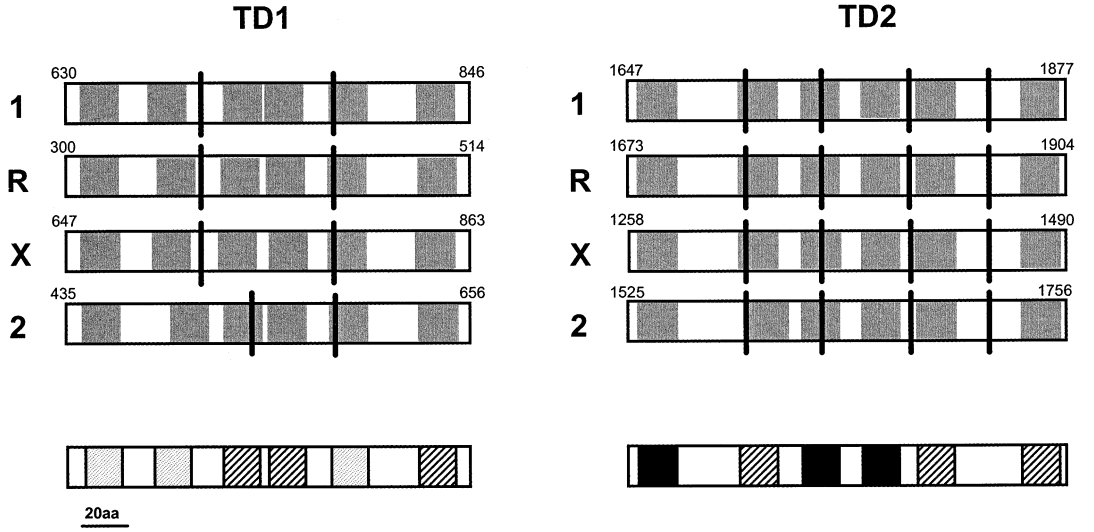

Fig. 4. Conservation of the gene structure across four different ABCA transporters. Transmembrane Domains (TD1 = N-terminal, TD2 = C-terminal). The amino acid positions, taken as borders, are indicated. For simplicity, the limit of each domain corresponds to the limits of the exons. The predicted TM spanners are shown in grey. The bottom rectangle shows the percentage of sequence identity across members for each spanner. Symbols: black solid square: 40–60%, thick hatched squares: 20–40%, thin hatched squares: 0–20% of identity. Exon-introns boundaries are shown by vertical bars. 1: ABCA1, 2: ABCA2, X: ABCA7, R: ABCAR.

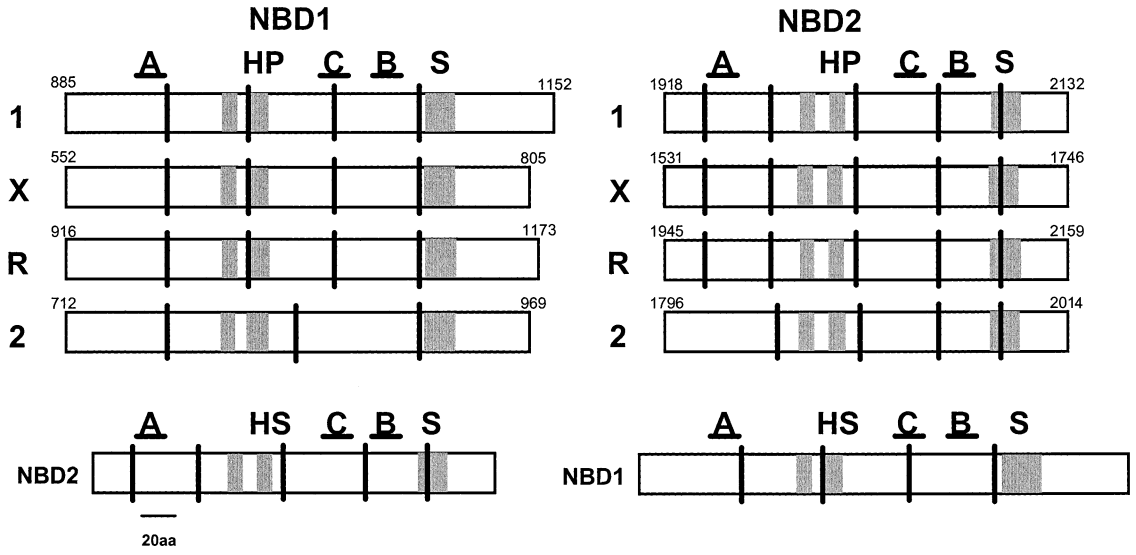

Fig. 5. Conservation of the gene structure across four different ABCA transporters. (NBD1 = N-terminal, NBD2 = C-terminal). The comparative genomic structures of four ABCA transporters are shown. The boundaries of the domains are indicated and correspond to the exons of interest. Introns are indicated by black bars. Conserved motifs are indicated by shaded bars. HS: hot spot, S: switch region, A: Walker A, B: Walker B, C: active transport signature. The bottom rectangle shows for comparison the organisation of a typical ABCA NBD2 or NBD1. 1: ABCA1, 2: ABCA2, X: ABCA7, R: ABCR.

tion of HH1, its position varies largely in each member; this leads to member-specific configurations of the R domain.

5. Sequence conservation and ABCA signatures

At the amino acid level, the known ABCA transporters show an identity from 45–66% along the whole sequence. The comparative analysis of their hydrophobicity plots also reveals highly similar profiles, leading to close, but unfortunately, still ambiguous predictions of topology.

For the sake of simplicity, the following discussion on ABCA sequence conservation will be articulated according to a conventional segmentation in domains. The border of each domain has been fixed according to exon limits. We define TD as the group of transmembrane helices and their intervening loops. This corresponds in ABCA1 to residues 630–846 for the N terminal TM 1–6 (exon 14–16) and from 1647–1877 for the C terminal set of membrane spanners (TM 7–12; exon 36–40). In the figure presented we label these limits for each of the analysed transporters.

An analysis of the sequences of TDs across the individual ABCAs demonstrates a higher degree of conservation in the second set of spanners (illustrated schematically in Fig. 4), in spite of a relatively low degree of primary sequence conservation, compared to that in the NBDs (average identity score of 44% for TD1 and 53% for TD2). This is particularly strik-

Table 2
ABCA specific signatures can be highlighted in the extended NBDs

	Walker A - #1	#50	Hot spot	ATS/C	Walker B	Switch #162
NBD1	**G**Q••••L**G**HN**GAGK**TTT	G•CP**Q**•N	LTV•EH••FY	L**SGG**M•RK	L**D**EPT•G•**D**P	L•T**H**•MDEA••LGDR
NBD2	**G**ECFGLL**G**VN**GAGK**STT	GYCP**Q**FD	LTGRE•L	Y**SGG**•KRK	L**D**EPTTGM**D**P	LTS**H**SMEECEALC•R

For simplicity the position of Walker A is numbered as +1. Residues in bold are conserved in all subclasses of the ABC transporter family. Normal face residues are conserved at 80% in ABCAs, whereas • corresponds to variable residues. NBD1 or NBD2 corresponds to the N or C-terminal NBD.

ing for the TM VII, IX and X, which all show identities higher than 50%. In addition, according to model A, the first and last extracellular loops in both sets of transmembrane regions show a divergent behaviour in term of sequence conservation. Whereas the 21 amino acid long loop between transmembrane helices I-II and the 36 amino acid long loop between TM VII-VIII are extremely conserved, the last extracellular loop (V-VI; 26 amino acids and XI-XII; 32 amino acids) can be considered hypervariable among the individual transporters.

The NBD corresponds to the extended nucleotide binding domain, i.e. in ABCA1 it spans from amino acid 885–1152 for the N-terminal one (NBD1: exon 18–22) and 1918–2132 for the C-terminal one (NBD2, exon 42–47). An overall analysis of sequence conservation at the NBDs shows an identity from 55 to 61% (average 59%) for NBD1, which increases to 57–69% (average 65%) at the NBD2. As already noted for the exon organisation, an intramolecular comparison of the two NBDs leads to a lesser degree of conservation, with an average value of 34,4%. This is definitely higher than the identity score between corresponding NBDs in ABC transporters belonging to different structural classes. These values range from 21 to 26% when comparing CFTR, MDR or TAP NDBs with the corresponding domains in ABCA1. A comparison of the two NBDs in other ABCs leads to variable results. For instance, in the case of CFTR, the identity score is 24%, while for MDRs and the two TAPS the score is 57 or 55%, respectively.

A closer analysis of NBD conservation leads to the definition of motifs unique to the ABCA family. These are summarised in Table 2 and detailed below. As required to belong to the family of ABC transporters, all ABCA proteins show in the NBDs the classical consensus Walker A, B and C, or ATS motifs (see [27]). Nonetheless, as it is the case for the different structural subgroups in yeast, specific signatures can be highlighted. First, at the level of the Walker motifs, a high conservation of residues surrounding either the conserved glycines in Walker A or the aspartate in Walker B can be documented. It is of note that similar conservations are found both in NBD1 and NBD2.

At least three other ABCA motifs can be defined. The so called 'switch' region, around the key histidine residue, downstream to Walker B, is highly conserved. Similarly, the cluster of residues surrounding the glutamine +50 from Walker A, and the 'hot spot' region, that roughly corresponds to the position of DF508 in CFTR [6,27,28] are conserved. In ABCAs the histidine is close to a highly acidic sequence, whereas the glutamine is invariably preceded by the doublet cysteine-proline. In the MDR/TAP subfamily there is no evidence for an acidic stretch of residues nearby the histidine, whereas both the histidine and the charged stretch are lacking in the CFTR/MRP cluster. All these consensus motifs are detectable in both NBDs, in spite of minor differences. An additional characteristic of the ABCA proteins is the symmetrical presence, downstream to both NBDs (+100–130 amino acids from Walker B), a conserved stretch of amino acids (T • EE•FL • V•E for the NBD1 and D•SV•Q• •L E/D N/Q VF), whose significance is so far unknown.

6. ABCAs in invertebrates

In order to estimate the reliability of the above described motifs, we scanned the ABC sequences in the databases from different genomes. This resulted in the identification of potential ABCA transporters in plants, insects and lower organisms. For instance, in *Arabidopsis thaliana*, several sequences encoding partial ABCA transporters could be detected. After eliminating redundancy and overlapping clones, we concluded that at least two full size ABCA sequences have been already sequenced in *Arabidopsis*, namely AC002339 in chromosome II, and AL049746 on chromosome III. Similarly, in *Dictyostelium discoideum*, the abcA sequence (U66526) shows high similarity to the ABCA subfamily, and again, all the above described motifs are present. In contrast to the mammalian ABCAs, however, AbcA possesses a unique NBD. Three ABCA full size transporters can be found in the *Caenorhabditis elegans* genome. One corresponds to ced-7 [29], which can be considered the functional ortholog of ABC1 in the nematode (see below), the two others share an identity higher than 40% at the amino acid level and correspond to AF10131 and AF003146 [30]. From a scan of the *Drosophila* genome project, three genomic sequences, potentially translating into ABCA trans-

porters with a full-size multidomain structure, were detected (AF034856, AC004321, AC004348). Preliminary information from F. Gamarro (personal communication) indicates that ABCA-encoding sequences, identifiable by the presence of these diagnostic motifs, exist also in parasites like *Trypanosoma cruzi* and *Leishmania tropica*.

7. ABCA1 and ced-7: the engulfment of apoptotic corpses

Among the members of the ABCA subgroup of transporters, ABCA1 has been functionally associated to the process of the engulfment of cells dying by apoptosis [13]. Several lines of evidence support the hypothesis. The first derives from the analysis of the ABCA1 expression pattern during mouse embryonic development. This analysis showed a direct spatio-temporal relationship between the expression of ABCA1 transcript and the areas of programmed cell death. In these areas the locally recruited macrophages, known to express ABC1, are actively engaged in the clearance of cell corpses. Consistently, in an 'in vitro' situation, the inhibition of ABCA1 function by a specific antibody greatly reduces the ability of peritoneal macrophages to phagocytose apoptotic thymocytes. This antibody has no effect on their ingestion of yeast, thus functionally linking ABC1 to the process of apoptotic engulfment. Last but not least comes the recent demonstration that an ABCA transporter of *C. elegans*, sharing around 30% identity with ABCA1, is able to complement ced-7 mutants [29]. Ced-7 belongs to one of the two epistatic groups of genes controlling the clearance of corpses generated by cell death during the development of the nematode. Altogether, these results strongly suggest that ABC1 and ced-7 are orthologs in these two evolutionary distant species.

It has to be noted, however, that although the similarities between ced-7 and ABC1 are quite high, in the absence of functional data it would have been extremely difficult to select the best candidate as an ortholog among the mammalian members of the ABCA class of transporters. Indeed, an exclusive analysis of sequence comparisons reveals roughly equivalent identities, ranging from 27 to 32% between ced-7 and each of the individual ABCA transporters. The precise molecular function exerted by an ABC transporter during the engulfment is, however, still an open question. Recent and preliminary results suggest an involvement of ABCA1 in the control of membrane lipid composition. Indeed, both in ABCA1 null mice and in overexpressing transfectants, an altered membrane mobility of phospholipids can be assessed (Broccardo et al., submitted). This might well fit the recently proposed concept that the engulfment of apoptotic bodies is an exquisite form of phagocytosis, since it requires the transbilayer movements of lipids on the surface of the phagocytes (Marguet et al., in press). Along the same line, mutations in the human gene encoding ABCA1 have been detected in patients affected by Tangier disease [31–34], a rare autosomal recessive disorder of lipid metabolism [35,36] whose locus indeed has been mapped to human chromosome 9q31 [37].

8. ABCR and chorioretinal degeneration

Frequently ABC transporters have been associated to diseases. In the group of ABCAs, so far only ABCR has been associated unambiguously to the pathogenesis of degenerative eye diseases [38–40]. In fact it has been reported by several groups that mutations in the ABCR coding regions can be detected in a large panel of degenerative illnesses of the retina, from Stargardt disease to recessive retinitis pigmentosa or cone-rod dystrophy [19,38,41]. A thorough discussion on the complex genetics of ABCR mutations and eye diseases is out of the scope of this article and can be found in [38]. No evidence on the molecular function of ABCR as a transporter has been provided, with the exception of the report that retinal activates its ATPase activity [42]. This makes retinal a good candidate as a substrate for ABCR-mediated transport, in analogy with the case of P-gp, whose enzymatic function can be stimulated by specific substrates [42–44].

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