Published in final edited form as:

Biochim Biophys Acta. 2010 August ; 1801(8): 824–830. doi:10.1016/j.bbaliip.2010.02.010.

The role of ATP-binding cassette transporter A1 in Alzheimer's disease and neurodegeneration

Radosveta Koldamova*, Nicholas F. Fitz, and Iliya Lefterov*

Department of Environmental and Occupational Health, University of Pittsburgh, Pittsburgh, PA 15219, USA

Abstract

ATP-binding cassette transporter A1 — ABCA1, is the most extensively studied transporter in human pathology. ABCA1 became a primary subject of research in many academic and pharmaceutical laboratories immediately after the discovery that mutations at the gene locus cause severe familial High Density Lipoprotein (HDL) deficiency and, in the homozygous form — Tangier disease. The protein is the major regulator of intracellular cholesterol efflux which is the initial and essential step in the biogenesis and formation of nascent HDL particles. The transcriptional regulation of *ABCA1* by nuclear Liver X Receptors (LXR) provided a starting point for drug discovery and development of synthetic LXR ligands/ABCA1 activators for treatment of arteriosclerosis. A series of reports that revealed the role of ABCA1 in A β deposition and clearance, as well as the possibility for association of some *ABCA1* genetic variants with risk for Alzheimer's disease (AD) brought a new dimension to ABCA1 research. The *LXR-ABCA1-APOE* regulatory axis is now considered a promising therapeutic target in AD, which includes the only proven risk factor for AD — APOE, at two distinct levels — transcriptional regulation by LXR, and ABCA1 controlled lipidation which can influence A β aggregation and amyloid clearance. This review will summarize the results of research on ABCA1, particularly related to AD and neurodegeneration.

Keywords

Alzheimer's disease; ABCA1; Liver X Receptor; Cell cholesterol transport; APOE; Animal model; Amyloid deposition; Cognitive impairment

1. Introduction

Human ATP-binding cassette transporter A1 — ABCA1, which belongs to subfamily A of a large superfamily of ABC transmembrane transporters, was identified and cloned in 1993 by Luciani et al. [1,2]. The cloning was accomplished by PCR in an approach based on the sequence similarity of regularly spaced motifs within the ATP cassette. The gene is mapped to the human chromosome 9q31. In the early studies the expression of ABCA1 was correlated spatially and temporally to areas of programmed cell death and initially a requirement for the engulfment of apoptotic bodies was the only, although not well characterized function of the protein [3]. Later, the role of ABCA1 in the optimal engulfment of apoptotic and necrotic cell corpses was connected to its function in membrane-lipid turnover and more specifically to transbilayer movement and redistribution

of phosphatidylserine, which is required for engulfment [4]. The complete human *ABCA1* gene sequence, was published in 2000 [5], after the discovery that *ABCA1* mutations, genetic variants and single nucleotide polymorphisms (SNPs) may have substantial impact on human pathology. *ABCA1* spans 149 kb and is comprised of 50 exons and the protein is 2261 amino acids long. It is an integral trans-membrane protein that consists of two halves of similar structure. Each half has a multispinning membrane domain containing six helices followed by a cytoplasmic nucleotide binding domain. A large extracellular loop connects the first transmembrane segment to the transmembrane domain in each half of the protein [6].

2. Supramolecular structure and normal function related to cholesterol efflux

An important step towards understanding and further exploring ABCA1 function was the discovery that mutations in their heterozygous forms cause familial hypoalphalipoproteinemia (high density lipoprotein — HDL, deficiency), and in their homozygous or compound heterozygous forms — Tangier disease (TD). Both conditions are functionally characterized by impaired cellular cholesterol efflux, highly inefficient reverse cholesterol transport (RCT), and therefore low levels of HDL particles [7–9]. Research on ABCA1 was dramatically reinforced after D. Mangelsdorf et al. found that *ABCA1* is under the transcriptional control of nuclear Liver X Receptors (LXR) [10].

Using cross-linking, native and SDS PAGE, wild type and mutant forms of ABCA1 derived from normal individuals or TD patients, J. Genest group demonstrated that ABCA1 exists as an oligomeric complex [11]. The formation of the complex is independent of lipoprotein or lipid binding to ABCA1 and the majority of the molecules form tetramers. The study was the first one to formulate the concept that the homo-tetrameric ABCA1 complex constitutes the smallest functional unit required for the biogenesis of HDL particles. The supra-molecular dynamics of ABCA1 multimeric structures — the assembly of dimeric structures and transition into higher order — tetramers, during the ATP catalytic cycle, which is a basic and crucial parameter in ABCA1 function, was revealed by Chimini's group using FRET and biochemical methods [12]. The organization of the homo-dimeric subunits, which are predominantly present in cells, is likely to be maintained by disulfide bonds. There is no evidence, however, that disulfide bonds are involved in the generation of homo-dimeric, or homo-tetrameric structures of higher order [11,12]. Importantly, in both studies it was demonstrated that mutations within the extracellular loops do not prevent the formation of tetrameric units and the formation of homo- and hetero-dimeric subunits comprised of mutant and wild type molecules is equally possible.

While the fact that ABCA1 plays a critical role in the biogenesis of HDL particles and in mediating cellular cholesterol efflux is indisputable, the mechanisms by which ABCA1 achieves these effects are not fully understood. A model, however, that explains the principal activity of ABCA1: regulation of apolipoprotein A-I (ApoA-I) binding to cells and the compositions of the discoidal HDL particles that are subsequently produced has been suggested [13,14]. In essence, according to the model, the initial binding of a small pool of ApoA-I to the largest extracellular loop of ABCA1 exerts a regulatory effect, which stabilizes the transporter at the cell surface, upregulates its activity, modulates its phosphorylation and inhibits its caspase mediated degradation. The increased translocase activity of ABCA1 and thus translocation of membrane phospholipids from the cytoplasmic to exofacial leaflet leads to lateral compression of the phospholipid molecules in the exofacial leaflet and expansion of those in the cytoplasmic leaflet. The unequal molecular packing density across the membrane is relieved in the second step by bending of the membrane and formation of exovesiculated domain to which ApoA-I binds with high

affinity. During the third step there is spontaneous solubilization of membrane phospholipids and cholesterol in the exovesiculated domain by the bound ApoA-I followed by formation of discoidal HDL particles with two, three, or four ApoA-I molecules per particle. It is believed that the lipidation of ApoE follows similar mechanism at the cell surface of astrocytes in the CNS. While it is the most popular model to explain ABCA1 mediated cholesterol efflux from macrophages, a second one has also been proposed. According to that, ApoA-I binds ABCA1 at the cell surface and is subsequently internalized and targeted to late endosomes, where ApoA-I picks up lipids and the apolipoprotein–lipid complexes are then resecreted from the cell by exocytosis [15]. Sufficient evidence exists that these two mechanisms are distinct and not mutually exclusive, but there is a controversy with regard to which one is dominant in ABCA1-mediated cholesterol efflux from macrophages to ApoA-I. Regardless of the debate, there is an unquestionable critical role of ABCA1 in ApoA-I and ApoE lipidation as well as in reverse cholesterol transport — a metabolic pathway whereby excess cholesterol in peripheral tissues is removed and transported to the liver, with a profound effect on human pathology.

The existence of multimeric ABCA1 structures and the above mechanisms for discoidal HDL formation have two important implications: on one side they help to explain substantially different clinical presentations associated with certain homozygous or compound heterozygous ABCA1 mutations, but without history or phenotypic abnormalities associated with Tangier disease [16,17]. On the other side, it is reasonable to predict that other molecular partners of ABCA1, excluding ABCA1 itself, may exist, which act as regulators, modulators or functional effectors in a much bigger multi-molecular complex. The identification of those molecules is crucial to understanding ABCA1 function as a receptor and thus to revealing downstream signaling pathways which may become active upon ABCA1–ApoA-I binding.

In this review, we will summarize the results of research on ABCA1 particularly related to AD and neurodegeneration.

3. Genetic variation in ABCA1 and Alzheimer's disease

There is overwhelming data suggesting a link between lipid metabolism, and neurodegeneration. The strongest indication that such a link exists comes from sequence variants of *APOE* and risk for sporadic AD [18–20]. Other cholesterol related genes have been subjected to genetic association studies, but no replicable novel candidates apart from *APOE* have been produced. *ABCA1* is a notable exception which received immediate attention following a report, demonstrating that sequence variation within the gene was associated with altered lipoprotein levels and modified risk for Coronary Artery Disease (CAD) [21].

3.1. Common genetic variants and risk for AD

At least 12 studies, exploring the association of different single nucleotide polymorphisms (SNPs) and risk for AD, have been published since 2003. Their design differs significantly in many ways, thus the comparison of the findings is difficult. Not surprisingly, an integrated hypothesis whether particular SNPs within the *ABCA1* gene have disease modulating effect – and to what extent they are relevant to the risk for AD – is lacking.

In almost all of the reports R219K (rs2230806), I883M (rs4149313), and R1587K (rs2230808) variants are the most extensively investigated since they give rise to amino acid changes, are common in the European population and are closely associated with the risk for CAD. The association of R219K is the most controversial. Five of the studies (case–control series in independent Caucasian populations residing in Europe and USA — [22–25],

Chinese population residing in Hong Kong [26], and family-based series in USA of a population of Caribbean-Hispanic origin [24,27]) using a single marker tests or multiple marker haplotypes found no association. However, Wollmer et al. reported that in patients with late onset, sporadic AD (LOAD), the 219K allele was associated with delayed onset of 1.7 years on average and healthy elderly carriers of the 219K allele had on average 33% lower total cholesterol in cerebrospinal fluid (CSF) than non-carriers [23]. A possible interaction between ABCA1 and APOE in the Hispanic population was observed by Shibata et al. — they found a significant association between AD and the G allele of rs2230806 (R219) in the absence of APOEε4 allele [24].

Katzov et al. reported for the first time that 219K allele is significantly underrepresented in AD patients from population-based Swedish-Twin Registry [28]. The number of the samples has recently been increased by addition of nontwin case–control group comprised of AD and dementia cases. Thus, in their last report, Reynolds et al. presented the results from a detailed survey of genetic variation in the *ABCA1* region in a total of 1567 Swedish dementia cases (1275 of those with AD) and 2203 controls which is the largest cohort so far studied [29]. A thorough analysis of 46 markers showed that two of them — rs2230806 and rs2230805 had the highest statistical significance, confirming the protective effect of the 219K allele. Together with the newly identified marker — rs2230805, this study has presented further evidence of genetic association of *ABCA1* with both AD and dementia for the Swedish population [29]. Importantly, the additional analysis of AD patients included in the study for association of those two markers with AD-related quantitative traits showed a significant effect of the R219K variant on CSF Aβ42 levels, whereby RK heterozygotes had the highest trait levels. A protective effect of K allele carriers for sporadic AD compared to RR genotype was also found in a case–control series consisting of only 168 sporadic AD patients and 123 controls, in unrelated Han Chinese resident in the North of China [30]. There is one additional study which in single marker and haplotype based settings confirms a weak association of rs2230806 (A/G and G/G genotypes) with AD in a sibpair series of AD patients [31]. The association could be demonstrated, in APOEε4 non-carriers only, and the authors pointed to the small number of informative families as one reason for overall unimpressive *p*-value, particularly for the haplotype analysis.

Reports presenting opposite results have also been published. A significant association of 219K allele with AD was found in a group of 372 Spanish patients, compared to 440 controls. The haplotype of coding region *ABCA1* variants 219K, 883I, and 1587R was significantly associated with AD, conferring a risk of 1.78 (*p*=0.007) [32]. Sundar et al. analyzed a large American white cohort of 992 AD cases and 699 controls. It is the only report, where a highly significant (*p*=0.00008) gender×R219K interaction and an increased (*p*=0.00004) risk of 1.75 for developing AD in female carriers of the 219K compared to non-219K carrier females were found. This type of gender specific interaction has not been observed in any of the previous or following studies.

The reason for the controversial results of the studies discussed above is not clear, although different genetic and racial backgrounds are very likely. The frequency of 219K allele, for example, among controls in one study [30] was much higher than in American whites or other Caucasians from previous studies [22,24] — 0.481 versus 0.269. It is not clear, however, if confounding factors imbedded within genotypic and/or phenotypic data, like minor allele frequency is easy to overcome in studies aiming at association of SNPs within *ABCA1*, or hundred of thousands of other SNPs spanning the entire genome, and risk for AD. Spurious associations are difficult to avoid, but one way to ultimately filter those is to establish a biological link between the associated SNPs and AD. In this respect it may be interesting to mention the two very powerful genome wide association studies recently published — [33,34], with a significant number of loci and SNPs at extremely low *p* levels,

and incredibly low number of identified genes with proven functional link to AD, or with a major role in a metabolic network critical for AD pathogenesis. The studies did not specifically comment on *ABCA1* but it is difficult to overlook the fact that in one of those [33], *ABCA1* rs12686004 was associated at $p=5.30E-05$ and OR -1.207 . Overall, the representation of identified genes involved in cholesterol/lipid metabolism in those two studies is impressive, lending further credibility to the results of the studies suggesting a role for *ABCA1*, other cholesterol transporters and *APOE* gene cluster in AD pathogenesis and thus the development of relevant therapeutic approaches.

Rare *ABCA1* genetic variants may also be responsible for an increased risk of AD, which would require the application of a different strategy, based on the data available through the HapMap Project and selection of tag SNPs. A comprehensive study examining tag SNPs spanning across the entire *ABCA1* gene was recently published [26]. The study may be regarded as the first comprehensive profile of the Linkage Disequilibrium (LD) structure of the *ABCA1* gene in case-control cohorts from Chinese populations. Interestingly, the authors did not find any effect of rs2230806 marker, but found three other significant ones — rs2297404, rs2230808, and rs2020927, all located in the same LD block. The most significant and potentially functional SNP was rs2297404 which might regulate alternative *ABCA1* transcripts. Because the significant rs2230808 association with AD, previously identified [22,24,28], was replicated both at a single marker and haplotypic-level associations this study possibly can be regarded as a gene-level replication of previous analyses. It also shows the advantages of using tag SNPs versus coding SNPs as major markers for construction of LD and haplotype blocks. Considering the lack of detailed knowledge about the functional variations in *ABCA1* that influence the risk for LOAD, the gene-based approach for association analysis should be applied in the future and perhaps will provide additional leads for genetic analysis at the functional level.

3.2. Rare functional variants and AD pathology

Soon after the discovery that point mutations in *ABCA1* cause TD with typical phenotype, premature atherosclerosis and CAD, it became clear that there is a differential contribution of missense mutations to the biochemical, cellular and clinical phenotype. There are two notable examples. N935S mutation was identified in patient with extremely low levels of HDL, but without accelerated development of premature atherosclerosis and with signs of severe dementia and amyloid depositions in the brain at age of 60 [35]. Equally intriguing and unexpected was the response of immortalized fibroblasts, derived from the patient, to the treatment with LXR ligand T0901317 — an increased A β secretion, in opposite to cells expressing non-functional *ABCA1* due to another mutation in a homozygous form [17]. The second example is a compound heterozygous mutation (D1099Y and F2009S) identified in a subject with severe HDL cholesterol deficiency [16]. The patient had no history or clinical manifestation of CAD and no other cardiovascular disease risk factors, except for low HDL cholesterol. There were no clinical signs of TD either. The patient developed and died of complications related to cerebral amyloid angiopathy.

These two examples point to the significance of rare functional SNPs in *ABCA1* which can be associated with AD risk, similar to HDL cholesterol levels [36,37]. A systematic sequencing of the *ABCA1* gene in autopsy confirmed AD cases is a prerequisite for the identification of such rare functional SNPs. Their functional significance will require in addition the generation of animal models by knock-in approach. While the technology for generation of such genetically engineered mice is well developed, in the case of *ABCA1* the requirement for *in vivo* comparative analysis of mouse and human proteins carrying the same mutation may become a significant obstacle.

4. Expression and normal function of ABCA1 in the CNS

Although Luciani et al. used mouse embryonic brain RNA for cloning *ABCA1* and confirmed a relatively high expression in adult mouse brain [2], during the following 10 years neither the gene nor the protein attracted the attention of the neuroscientists, or neuropathologists. A detailed organ, tissue and brain area specific expression profile of rodent and human ABCA1 was published by Schmitz group [38] and later by Lawn et al. [39]. Whitney et al. provided the first *in vitro* and *in vivo* evidence that LXRs regulate lipid homeostasis primarily in glia by transcriptional control of key molecules involved in cholesterol efflux and synthesis, including cholesterol transporters *Abca1*, *Abcg1* and SREBP1 [40]. Widespread expression of *Abca1* in rat brain with the highest level in neuronal layers of the cerebellum, was reported by Fukumoto et al. [41]. Brain area and cell type expression of rat *Abca1*, as well as the response of specific brain cell types to LXR ligand treatment were published in 2003 [42]. The study also demonstrated that functionally the increased expression of *Abca1* in response to LXR ligand treatment of embryonic neurons and astrocytes was followed by elevated ApoA-I- and ApoE-specific cholesterol efflux. The role of *Abca1* in normal brain ApoE metabolism was further characterized by Holtzman's and Wellington's groups [43,44]. In brain ApoE is secreted locally by astrocytes and plays a critical role in CNS cholesterol transport and delivery to neurons. The two studies demonstrated that brain *Abca1* is required for normal secretion and lipidation of ApoE. In the brain of *Abca1^{ko}* mice the impaired ability to efflux cholesterol results in lipid accumulation in astrocytes and microglia, and poorly lipidated, small and very unstable ApoE containing lipoprotein particles. The effect of *Abca1* is ApoE selective as the levels of ApoJ, another lipoprotein secreted by astrocytes, do not change regardless of the absence of functional *Abca1*. Later, the pivotal role of ABCA1 in brain ApoE lipidation and formation of HDL-like particles was demonstrated *in vitro* using human primary neurons — it was shown that ApoE discs potentially accelerated ABCA1 regulated cholesterol efflux in APOE-isoform independent way [45].

5. ABCA1, Alzheimer's disease and neurodegeneration

5.1. APP processing, A β deposition and clearance

A disease related role for ABCA1 in brain was suggested in 2002, when Rebeck's group showed upregulation of mouse *Abca1* following AMPA (alpha-amino-3hydroxyl-5-methyl-4-isoazole-propionate) induced focal lesion [41]. Beginning 3 days after stereotactic AMPA lesioning of the hippocampus ABCA1 mRNA was upregulated gradually and continued to increase through 7 and 11 days post-lesion. Similar results were obtained in rats after controlled traumatic cortical injury — increased *Abca1* levels were detected by immunohistochemistry 6 h after injury and remained elevated as long as 28 days [46]. Changes in *Abca1* protein levels were detected in all hippocampal neurons, and were most robust in the CA3 pyramidal cells, which are particularly sensitive to traumatic injury. Importantly, in this study, a similar time course change in expression levels were observed for both *Abca1* and APP. To the best of our knowledge, these studies did not receive further attention and the question if the upregulation of *Abca1* and facilitated cholesterol efflux are consequences of an increased APP expression and A β secretion in response to brain injury remains to be answered.

Fukumoto et al. [41] also demonstrated that treatment of neuro-blastoma Neuro2a cells with endogenous or synthetic LXR ligands as a way to upregulate *Abca1* levels, caused significant increases in secreted A β 40 and A β 42 which was reduced by RNAi blocking of *ABCA1* expression. Subsequently, studies conducted in other laboratories [42,45,47,48] using different *in vitro* model systems failed to reproduce the above effect of *Abca1* on A β secretion. Collectively those studies concluded that activation of LXR in a variety of cells

expressing hAPP has an inhibitory effect on A β secretion. The ultimate effect was attributed primarily to the transcriptional upregulation of *ABCA1* and possibly the participation of other molecules involved in facilitated cholesterol efflux. The effect has been repeatedly confirmed in different *in vivo* model systems [17,49–51].

Perhaps the most compelling evidence for the role of Abca1 in AD pathogenesis comes from complex APP expressing animal models with global deletion of *Abca1* or over-expression of the protein. Three research groups independently showed that in three distinct APP/Abca1^{ko} mouse lines the disruption of Abca1 increased insoluble A β , parenchymal amyloid plaques and CAA with no change in APP processing. CAA related microhemorrhage, however, was found only in APP23/Abca1^{ko} mice. The phenotypes of those animal models differed slightly which was not surprising given the expression of different transgenes, different ratios of secreted A β species with different abilities to aggregate or different tendencies for clearance. Importantly, in three of the four models the elevation in parenchymal and vascular amyloid was accompanied by a dramatic decrease in the levels of soluble ApoE. Considering the well known and repeatedly confirmed lack of fibrillar Thio-S positive plaques in APP mice with global disruption of *ApoE*, this observation was unexpected and somehow difficult to reconcile with the previous findings. Considering the effects of poorly lipidated ApoE on A β aggregation and receptor mediated internalization of ApoE/A β complexes, a severely impaired lipidation status and thus inefficient physiological function of brain apolipoproteins in case of global Abca1 deletion could be a plausible explanation of the phenotype. Thus the level of ApoE in the brain of AD model mice *per se* is not a definitive factor for the amount of the deposited insoluble A β , and if decreased — its lipidation status and rate of degradation would determine the increased amyloid depositions and likely represent the functionality of its major regulator Abca1. On the other side, the increased deposition of fibrillar, Thio-S positive, A β in the brain vasculature in those mice presents a much more complicated picture of the entire phenotype, than just an increased A β aggregation in conditions of missing brain Abca1. The inefficient microglia mediated clearance of A β is certainly an integral component and its role has been elegantly demonstrated by G. Landreth's group [52]. Much more difficult to answer is the question if lipoproteins other than ApoE–ApoA-I in particular, have a role in the development of CAA. Although the expression of APOA-I in brain is considered confined to the vascular endothelial cells, this lipoprotein is certainly present in the brain of APP expressing mice, it exerts an inhibitory effect on A β aggregation and it has been recently shown that its levels in brain depend on conditions of local Abca1 deficiency [53–56]. Regardless of A β clearance mechanisms within the brain which certainly depend to some extent on receptor mediated internalization of A β complexes by microglia and astrocytes, or secretion and extracellular activity of A β degrading enzymes, the impaired clearance of A β through the blood brain barrier remains one of the most important therapeutic targets for AD treatment. In this regard, animal models generated by knock-in technology and expressing ABCA1 mutant forms that have been shown to drive an unusual phenotype in patients with extremely low HDL levels, i.e. no signs of premature atherosclerosis, abundant amyloid depositions in brain parenchyma and/or CAA, as already discussed, [16,17,57] will definitely help in designing better AD therapeutic strategies.

The PDAPP/Abca1 double transgenic mouse generated by D. Holtzman's group further confirmed that the level of functional Abca1 has a significant modulatory effect on A β deposition [58]. The mouse expresses murine Abca1, driven by mouse Prion Promoter (PrP-mAbca1), throughout the brain. The almost complete absence of Thio-S positive amyloid plaques was the most striking phenotypic characteristic of the mouse. The redistribution of significantly less soluble A β load to the hilus of the dentate gyrus in the hippocampus, compared to PDAPP animal, resembled what had already been described for PDAPP/ApoE^{ko} mouse model. Increased lipidation of ApoE containing particles in primary

astrocytes conditioned media and in CSF led to the conclusion that increasing ABCA1 function may have a therapeutic effect on AD.

5.2. Cognitive performance

Using the Morris Water Maze paradigm it has been demonstrated that 2-year-old APP23 mice with one functional copy of *Abca1* (APP23/het), compared with age-matched wild type mice (APP23/wt), have impaired learning during acquisition, and impaired memory retention during the probe trial [59]. The two groups of mice did not differ in the levels of A β and Thio-S positive plaques, but the levels of ApoE in APP23/het mice were decreased. Importantly, dot blot analysis demonstrated that APP23/het mice have a significantly higher level of soluble A11-positive A β oligomers compared with APP23/wt which correlated negatively with cognitive performance. A11 antibody recognizes amino acid sequence-independent oligomers of proteins or peptides but does not recognize monomers or mature fibrils. For example, A11 reacts with soluble A β 40 oligomers and does not react with soluble low-molecular weight A β 40 or A β 40 fibrils. Surprisingly, A11 immunohistochemistry revealed a significant increase of A11-positive oligomer structures (mostly intracellular) in the CA1 region of hippocampi of APP23/het. This characteristic region-specific pattern of A11 staining was age- and *Abca1* gene dose-dependent (was missing in younger APP23 mice lacking *Abca1*). In contrast, the levels of A β *56, as well as other low-molecular-mass A β oligomers, were unchanged among the groups. The reason why A β oligomers are increased in APP23 mice with one functional copy of *Abca1* is not completely understood, however. The decreased total amount of ApoE, which was significantly lower in APP23/het compared with APP23/wt mice could be one potential explanation. The increased amount of soluble A β oligomers in brain parenchyma of Tg-SwDI mice with complete absence of ApoE [60] supports such a conclusion. Several possible explanations for the worse memory performance of APP23/het compared with APP23/wt mice in the MWM have been proposed. It is possible that in aged APP23 mice memory deficits depend on *Abca1* gene dose and are likely to be mediated by the amount and the distribution of high molecular weight soluble A β oligomers deposited in the hippocampus. However, the precise mechanism by which amyloid fibrils or soluble aggregates impair the cognition of APP transgenic mice remains to be elucidated. It could be also linked to brain lipoprotein metabolism and cholesterol transport within the brain and between neurons and glia, which is likely to be inefficient in conditions of low levels of functional *Abca1* and thus insufficient properly lipidated ApoE for the formation of HDL-like particles. Synaptogenesis requires large amounts of cholesterol and therefore depends on its delivery via ApoE containing lipoproteins [61]. In the brain of APP23/het mice, there is less ApoE, which may lead to insufficient amounts of cholesterol being delivered to surrounding axons and therefore less efficient synaptogenesis. One possible consequence of the less efficient synaptogenesis is a behavioral deficit. Experimental paradigm to test such a hypothesis has been proposed a decade ago [62], but has never been applied to *Abca1* deficient mice.

Altogether, the phenotype of APP23/het mice suggests that heterozygous *Abca1* mice could be considered a valuable model. The beneficial effect of *ABCA1*^{wt} homozygosity in humans is underscored by numerous studies demonstrating perturbed cholesterol and lipo-protein homeostasis in individuals heterozygous for *ABCA1* mutant alleles. Therefore, *Abca1* heterozygous mouse models (presumably ones that carry mutant, clinically significant alleles), rather than mice completely lacking *Abca1* should be considered more relevant to study the influence of perturbed brain cholesterol metabolism on molecular pathogenesis and progression of different neurodegenerative disorders.

6. Therapeutic implications

The discovery that mouse and human *ABCA1* are under the transcriptional control of LXR made both of them very attractive and realistic therapeutic targets in atherosclerosis [10]. Since 2003, the therapeutic effect of activated LXR and/or increased levels of functional ABCA1 on A β deposition, its clearance and behavior in AD mouse models has been demonstrated numerous times, and in many of those reports the upregulation of *Abca1* gene and protein was regarded as promising therapeutic strategies [17,50–52,58].

The therapeutic effect of activated LXR, however, is considered much broader than just an upregulation of *ABCA1* and is possibly an integrated result of the LXR mediated control over distinct, yet interrelated pathways of AD pathogenesis: A β deposition, inflammatory reactions and clearance of A β soluble aggregates [50,52,63]. A major obstacle to developing successful therapies based on LXR mediated upregulation of *ABCA1*, however, has been its “side effects” — upregulation of *SREBP1*, fatty acid synthase and increased levels of plasma triglycerides. LXR β receptor-specific agonists or selective modulators could provide the desired atheroprotection, modulation of AD pathology, control of inflammatory reactions and other benefits without the undesirable concomitant liver triglycerides accumulation. An interesting approach in addition to drug development strategies for synthesis of LXR receptor type-specific agonists, whose application would minimize the “side effects”, could be a systematic evaluation of known pharmacological agents with relatively low LXR agonist-like activity, compared to the powerful synthetic ones. The beneficial effect of a low but sustainable *Abca1* upregulation on AD phenotype in model mice supports such a strategy [50]. In this regard the identification of the proton pump inhibitors Lansoprazole and Pantoprazole as LXR agonists in a drug screening program is promising and warrants further *in vivo* preclinical testing [64].

ABCA1 expression levels can also be increased by LXR-independent mechanisms. One study has shown that Verapamil and other common calcium channel blockers increased the apolipoprotein mediated release of cellular cholesterol by induction of ABCA1 expression via a LXR-independent mechanism [65]. A post-translational regulatory mechanism for controlling ABCA1 expression with possible therapeutic implications was proposed by A. Tall group. It is based on a PEST sequence — proline (P), glutamate (E), serine (S) and threonine (T), which was identified in the intracellular loop of ABCA1, downstream of the first ATP-binding segment [66,67]. PEST sequence enhances the degradation of proteins by calpain and thereby is likely to control cell surface expression of ABCA1 and thus regulated cholesterol efflux [68,69]. Calpain mediated degradation pathway is distinct from ubiquitin proteasomal pathway, which has also been demonstrated for ABCA1 [70]. The inhibition of these two pathways would ultimately result in stabilization of ABCA1. Although the application of small molecules that modulate the local interaction of ABCA1 and calpain is appealing, the possibility and the result of such an intervention have never been explored in the brain or in the context of AD. It is interesting to mention that ApoA-I and ApoE inhibit calpain and proteasomal mediated degradation of ABCA1 and ABCA1–ApoA-I interaction leads to an increased expression of ABCA1 at the cell surface. However, even if the infusion of ApoA-I for increased stabilization of ABCA1 and generation of mature HDL is a prospective therapeutic approach against arteriosclerosis, the penetration of blood brain barrier (BBB) for ApoA-I is an obstacle and prevents development of similar AD therapeutic strategies. While the expression of *Abca1* in BBB models has been demonstrated [71–73], there is no data so far that *Abca1* (or any other ATP-binding transporter) is directly involved in A β clearance at the level of BBB. Targeted upregulation of ABCA1 in any of the cellular components of the BBB in the context of LXR mediated transcriptional control of ABCA1 should be considered a valuable tool. In this regard, a better understanding of ABCA1–ApoA-I relationship in brain will help significantly.

Acknowledgments

The work presented here was supported by grants from NIA AG031956 (IL), NIA AG027973 (RK) and Alzheimer's Drug Discovery Foundation (IL).

References

1. Dean M, Hamon Y, Chimini G. The human ATP-binding cassette (ABC) transporter superfamily. *J Lipid Res.* 2001; 42(7):1007–1017. [PubMed: 11441126]
2. Luciani MF, Denizot F, Savary S, Mattei MG, Chimini G. Cloning of two novel ABC transporters mapping on human chromosome 9. *Genomics.* 1994; 21(1):150–159. 10.1006/geno.1994.1237. [PubMed: 8088782]
3. Luciani MF, Chimini G. The ATP binding cassette transporter ABC1, is required for the engulfment of corpses generated by apoptotic cell death. *EMBO J.* 1996; 15(2):226–235. [PubMed: 8617198]
4. Hamon Y, Broccardo C, Chambenoit O, Luciani MF, Toti F, Chaslin S, Freyssinet JM, Devaux PF, McNeish J, Marguet D, Chimini G. ABC1 promotes engulfment of apoptotic cells and transbilayer redistribution of phosphatidylserine. *Nat Cell Biol.* 2000; 2(7):399–406. 10.1038/35017029. [PubMed: 10878804]
5. Santamarina-Fojo S, Peterson K, Knapper C, Qiu Y, Freeman L, Cheng JF, Osorio J, Remaley A, Yang XP, Haudenschild C, Prades C, Chimini G, Blackmon E, Francois T, Duverger N, Rubin EM, Rosier M, Denèfle P, Fredrickson DS, Brewer HB Jr. Complete genomic sequence of the human ABCA1 gene: analysis of the human and mouse ATP-binding cassette A promoter. *Proc Natl Acad Sci U S A.* 2000; 97(14):7987–7992. [PubMed: 10884428]
6. Oram JF, Lawn RM. ABCA1: the gatekeeper for eliminating excess tissue cholesterol. *J Lipid Res.* 2001; 42(8):1173–1179. [PubMed: 11483617]
7. Bodzioch M, Orsó E, Klucken J, Langmann T, Böttcher A, Diederich W, Drobnik W, Barlage S, Büchler C, Porsch-Ozçürüm M, Kaminski WE, Hahmann HW, Oette K, Rothe G, Aslanidis C, Lackner KJ, Schmitz G. The gene encoding ATP-binding cassette transporter 1 is mutated in Tangier disease. *Nat Genet.* 1999; 22(4):347–351. 10.1038/11914. [PubMed: 10431237]
8. Brooks-Wilson A, Marcil M, Clee SM, Zhang LH, Roomp K, van Dam M, Yu L, Brewer C, Collins JA, Molhuizen HO, Loubser O, Ouelette BF, Fichter K, Ashbourne-Excoffon KJ, Sensen CW, Scherer S, Mott S, Denis M, Martindale D, Frohlich J, Morgan K, Koop B, Pimstone S, Kastelein JJ, Genest J Jr, Hayden MR. Mutations in ABC1 in Tangier disease and familial high-density lipoprotein deficiency. *Nat Genet.* 1999; 22(4):336–345. 10.1038/11905. [PubMed: 10431236]
9. Rust S, Rosier M, Funke H, Real J, Amoura Z, Piette JC, Deleuze JF, Brewer HB, Duverger N, Denèfle P, Assmann G. Tangier disease is caused by mutations in the gene encoding ATP-binding cassette transporter 1. *Nat Genet.* 1999; 22(4):352–355. 10.1038/11921. [PubMed: 10431238]
10. Repa JJ, Turley SD, Lobaccaro JA, Medina J, Li L, Lustig K, Shan B, Heyman RA, Dietschy JM, Mangelsdorf DJ. Regulation of absorption and ABC1-mediated efflux of cholesterol by RXR heterodimers. *Science.* 2000; 289(5484):1524–1529. [PubMed: 10968783]
11. Denis M, Haidar B, Marcil M, Bouvier M, Krimbou L, Genest J. Characterization of oligomeric human atp binding cassette transporter a1. Potential implications for determining the structure of nascent high density lipoprotein particles. *J Biol Chem.* 2004; 279(40):41529–41536. 10.1074/jbc.M406881200. [PubMed: 15280376]
12. Trompier D, Alibert M, Davanture S, Hamon Y, Pierres M, Chimini G. Transition from dimers to higher oligomeric forms occurs during the atpase cycle of the ABCA1 transporter. *J Biol Chem.* 2006; 281(29):20283–20290. 10.1074/jbc.M601072200. [PubMed: 16709568]
13. Vedhachalam C, Ghering AB, Davidson WS, Lund-Katz S, Rothblat GH, Phillips MC. ABCA1-induced cell surface binding sites for ApoA-I. *Arterioscler Thromb Vasc Biol.* 2007; 27(7):1603–1609. 10.1161/ATVBAHA.107.145789. [PubMed: 17478755]
14. Vedhachalam C, Duong PT, Nickel M, Nguyen D, Dhanasekaran P, Saito H, Rothblat GH, Lund-Katz S, Phillips MC. 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.* 2007; 282(34):25123–25130. 10.1074/jbc.M704590200. [PubMed: 17604270]

15. Yvan-Charvet L, Wang N, Tall AR. Role of HDL, ABCA1, and ABCG1 transporters in cholesterol efflux and immune responses. *Arterioscler Thromb Vasc Biol.* 2010; 30(2):139–143. 10.1161/ATVBAHA.108.179283. [PubMed: 19797709]
16. Ho Hong S, Rhyne J, Zeller K, Miller M. Novel ABCA1 compound variant associated with HDL cholesterol deficiency. *Biochim Biophys Acta.* 2002; 1587(1):60–64. [PubMed: 12009425]
17. Koldamova RP, Lefterov IM, Staufenbiel M, Wolfe D, Huang S, Glorioso JC, Walter M, Roth MG, Lazo JS. The liver X receptor ligand T0901317 decreases amyloid beta production in vitro and in a mouse model of Alzheimer's disease. *J Biol Chem.* 2005; 280(6):4079–4088. 10.1074/jbc.M411420200. [PubMed: 15557325]
18. Saunders AM, Strittmatter WJ, Schmechel D, George-Hyslop PH, Pericak-Vance MA, Joo SH, Rosi BL, Gusella JF, Crapper-MacLachlan DR, Alberts MJ. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. *Neurology.* 1993; 43(8):1467–1472. [PubMed: 8350998]
19. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, Roses AD, Haines JL, Pericak-Vance MA. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science.* 1993; 261(5123):921–923. [PubMed: 8346443]
20. Poirier J, Davignon J, Bouthillier D, Kogan S, Bertrand P, Gauthier S. Apolipoprotein E polymorphism and Alzheimer's disease. *Lancet.* 1993; 342(8873):697–699. [PubMed: 8103819]
21. Clee SM, Zwinderman AH, Engert JC, Zwarts KY, Molhuizen HO, Roomp K, Jukema JW, van Wijland M, van Dam M, Hudson TJ, Brooks-Wilson A, Genest J Jr, Kastelein JJ, Hayden MR. Common genetic variation in ABCA1 is associated with altered lipoprotein levels and a modified risk for coronary artery disease. *Circulation.* 2001; 103(9):1198–1205. [PubMed: 11238261]
22. Li Y, Tacey K, Doil L, van Luchene R, Garcia V, Rowland C, Schrodi S, Leong D, Lau K, Catanese J, Sninsky J, Nowotny P, Holmans P, Hardy J, Powell J, Lovestone S, Thal L, Owen M, Williams J, Goate A, Grupe A. Association of ABCA1 with late-onset Alzheimer's disease is not observed in a case-control study. *Neurosci Lett.* 2004; 366(3):268–271. 10.1016/j.neulet.2004.05.047. [PubMed: 15288432]
23. Wollmer MA, Streffer JR, Lütjohann D, Tsolaki M, Iakovidou V, Hegi T, Pasch T, Jung HH, Bergmann K, Nitsch RM, Hock C, Papassotiropoulos A. ABCA1 modulates CSF cholesterol levels and influences the age at onset of Alzheimer's disease. *Neurobiol Aging.* 2003; 24(3):421–426. [PubMed: 12600718]
24. Shibata N, Kawarai T, Lee JH, Lee HS, Shibata E, Sato C, Liang Y, Duara R, Mayeux RP, St George-Hyslop PH, Rogaeva E. Association studies of cholesterol metabolism genes (CH25H, ABCA1 and CH24H) in Alzheimer's disease. *Neurosci Lett.* 2006; 391(3):142–146. 10.1016/j.neulet.2005.08.048. [PubMed: 16157450]
25. Wahrle SE, Shah AR, Fagan AM, Smemo S, Kauwe JSK, Grupe A, Hinrichs A, Mayo K, Jiang H, Thal LJ, Goate AM, Holtzman DM. Apolipoprotein E levels in cerebrospinal fluid and the effects of ABCA1 polymorphisms. *Mol Neurodegener.* 2007; 2:7. 10.1186/1750-1326-2-7. [PubMed: 17430597]
26. Chu LW, Li Y, Li Z, Tang AYB, Cheung BMY, Leung RYH, Yik PY, Jin DY, Song YQ. A novel intronic polymorphism of ABCA1 gene reveals risk for sporadic Alzheimer's disease in Chinese. *Am J Med Genet B Neuropsychiatr Genet.* 2007; 144B(8):1007–1013. 10.1002/ajmg.b.30525. [PubMed: 17510949]
27. Bertram L, Hiltunen M, Parkinson M, Ingelsson M, Lange C, Ramasamy K, Mullin K, Menon R, Sampson AJ, Hsiao MY, Elliott KJ, Velicelebi G, Moscarillo T, Hyman BT, Wagner SL, Becker KD, Blacker D, Tanzi RE. Family-based association between Alzheimer's disease and variants in UBQLN1. *N Engl J Med.* 2005; 352(9):884–894. 10.1056/NEJMoa042765. [PubMed: 15745979]
28. Katzov H, Chalmers K, Palmgren J, Andreasen N, Johansson B, Cairns NJ, Gatz M, Wilcock GK, Love S, Pedersen NL, Brookes AJ, Blennow K, Kehoe PG, Prince JA. Genetic variants of ABCA1 modify Alzheimer disease risk and quantitative traits related to beta-amyloid metabolism. *Hum Mutat.* 2004; 23(4):358–367. 10.1002/humu.20012. [PubMed: 15024730]
29. Reynolds CA, Hong MG, Eriksson UK, Blennow K, Bennet AM, Johansson B, Malmberg B, Berg S, Wiklund F, Gatz M, Pedersen NL, Prince JA. A survey of ABCA1 sequence variation confirms

- association with dementia. *Hum Mutat.* 2009; 30(9):1348–1354. 10.1002/humu.21076. [PubMed: 19606474]
30. Wang F, Jia J. Polymorphisms of cholesterol metabolism genes CYP46 and ABCA1 and the risk of sporadic Alzheimer's disease in Chinese. *Brain Res.* 2007; 1147(1):34–38. cited by (since 1996) 9. (URL <http://www.scopus.com/inward/record.url?eid=2-s2.0-34147158749&partnerID=40>). [PubMed: 17335784]
 31. Wavrant-De Vrièze F, Compton D, Womick M, Arepalli S, Adighibe O, Li L, Pérez-Tur J, Hardy J. ABCA1 polymorphisms and Alzheimer's disease. *Neurosci Lett.* 2007; 416(2):180–183. 10.1016/j.neulet.2007.02.010. [PubMed: 17324514]
 32. Rodríguez-Rodríguez E, Mateo I, Llorca J, Sánchez-Quintana C, Infante J, García-Gorostiaga I, Sánchez-Juan P, Berciano J, Combarros O. Association of genetic variants of ABCA1 with Alzheimer's disease risk. *Am J Med Genet B Neuropsychiatr Genet.* 2007; 144B(7):964–968. 10.1002/ajmg.b.30552. [PubMed: 17510946]
 33. Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, Pahwa JS, Moskvina V, Dowzell K, Williams A, Jones N, Thomas C, Stretton A, Morgan AR, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Morgan K, Brown KS, Passmore PA, Craig D, McGuinness B, Todd S, Holmes C, Mann D, Smith AD, Love S, Kehoe PG, Hardy J, Mead S, Fox N, Rossor M, Collinge J, Maier W, Jessen F, Schürmann B, van den Bussche H, Heuser I, Kornhuber J, Wiltfang J, Dichgans M, Frölich L, Hampel H, Hüll M, Rujescu D, Goate AM, Kauwe JSK, Cruchaga C, Nowotny P, Morris JC, Mayo K, Sleegers K, Bettens K, Engelborghs S, De Deyn PP, Van Broeckhoven C, Livingston G, Bass NJ, Gurling H, McQuillin A, Gwilliam R, Deloukas P, Al-Chalabi A, Shaw CE, Tsolaki M, Singleton AB, Guerreiro R, Muhleisen TW, Nothen MM, Moebus S, Jöckel K-H, Klopp N, Wichmann H-E, Carrasquillo MM, Pankratz VS, Younkin SG, Holmans PA, O'Donovan M, Owen MJ, Williams J. Genome-wide association study identifies variants at *CLU* and *PICALM* associated with Alzheimer's disease. *Nat Genet.* 2009; 41(10):1088–1093. 10.1038/ng.440. [PubMed: 19734902]
 34. Lambert J-C, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, Combarros O, Zelenika D, Bullido MJ, Tavernier B, Letenneur L, Bettens K, Berr C, Pasquier F, Fiévet N, Barberger-Gateau P, Engelborghs S, De Deyn P, Mateo I, Franck A, Helisalmi S, Porcellini E, Hanon O, de Pancorbo MM, Lendon C, Dufouil C, Jaillard C, Leveillard T, Alvarez V, Bosco P, Mancuso M, Panza F, Nacmias B, Bossù P, Piccardi P, Annoni G, Seripa D, Galimberti D, Hannequin D, Licastro F, Soininen H, Ritchie K, Blanché H, Dartigues J-F, Tzourio C, Gut I, Van Broeckhoven C, Alperovitch A, Lathrop M, Amouyel P. European Alzheimer's Disease Initiative Investigators. Genome-wide association study identifies variants at *CLU* and *CR1* associated with Alzheimer's disease. *Nat Genet.* 2009; 41(10):1094–1099. 10.1038/ng.439. [PubMed: 19734903]
 35. Walter M, Kerber S, Fechttrup C, Seedorf U, Breithardt G, Assmann G. Characterization of atherosclerosis in a patient with familial high-density lipoprotein deficiency. *Atherosclerosis.* 1994; 110(2):203–208. [PubMed: 7848370]
 36. Cohen JC, Kiss RS, Pertsemlidis A, Marcel YL, McPherson R, Hobbs HH. Multiple rare alleles contribute to low plasma levels of HDL cholesterol. *Science.* 2004; 305(5685):869–872. 10.1126/science.1099870. [PubMed: 15297675]
 37. Iatan I, Alrasadi K, Ruel I, Alwaili K, Genest J. Effect of ABCA1 mutations on risk for myocardial infarction. *Curr Atheroscler Rep.* 2008; 10(5):413–426. [PubMed: 18706283]
 38. Langmann T, Klucken J, Reil M, Liebisch G, Luciani MF, Chimini G, Kaminski WE, Schmitz G. Molecular cloning of the human ATP-binding cassette transporter 1 (hABC1): evidence for sterol-dependent regulation in macrophages. *Biochem Biophys Res Commun.* 1999; 257(1):29–33. 10.1006/bbrc.1999.0406. [PubMed: 10092505]
 39. Lawn RM, Wade DP, Couse TL, Wilcox JN. Localization of human ATP-binding cassette transporter 1 (ABC1) in normal and atherosclerotic tissues. *Arterioscler Thromb Vasc Biol.* 2001; 21(3):378–385. [PubMed: 11231917]
 40. Whitney KD, Watson MA, Collins JL, Benson WG, Stone TM, Numerick MJ, Tippin TK, Wilson JG, Winegar DA, Kliewer SA. Regulation of cholesterol homeostasis by the liver X receptors in the central nervous system. *Mol Endocrinol.* 2002; 16(6):1378–1385. [PubMed: 12040022]
 41. Fukumoto H, Deng A, Irizarry MC, Fitzgerald ML, Rebeck GW. Induction of the cholesterol transporter ABCA1 in central nervous system cells by liver X receptor agonists increases secreted

- A β levels. *J Biol Chem*. 2002; 277(50):48508–48513. 10.1074/jbc.M209085200. [PubMed: 12384498]
42. Koldamova RP, Lefterov IM, Ikonovic MD, Skoko J, Lefterov PI, Isanski BA, DeKosky ST, Lazo JS. 22r-hydroxycholesterol and 9-cis-retinoic acid induce ATP-binding cassette transporter A1 expression and cholesterol efflux in brain cells and decrease amyloid beta secretion. *J Biol Chem*. 2003; 278(15):13244–13256. 10.1074/jbc.M300044200. [PubMed: 12547833]
 43. Wahrle SE, Jiang H, Parsadanian M, Legleiter J, Han X, Fryer JD, Kowalewski T, Holtzman DM. ABCA1 is required for normal central nervous system ApoE levels and for lipidation of astrocyte-secreted apoE. *J Biol Chem*. 2004; 279(39):40987–40993. 10.1074/jbc.M407963200. [PubMed: 15269217]
 44. Hirsch-Reinshagen V, Zhou S, Burgess BL, Bernier L, McIsaac SA, Chan JY, Tansley GH, Cohn JS, Hayden MR, Wellington CL. Deficiency of ABCA1 impairs apolipoprotein E metabolism in brain. *J Biol Chem*. 2004; 279(39):41197–41207. 10.1074/jbc.M407962200. [PubMed: 15269218]
 45. Kim WS, Rahmanto AS, Kamili A, Rye KA, Guillemin GJ, Gelissen IC, Jessup W, Hill AF, Garner B. Role of ABCG1 and ABCA1 in regulation of neuronal cholesterol efflux to apolipoprotein E discs and suppression of amyloid-beta peptide generation. *J Biol Chem*. 2007; 282(5):2851–2861. 10.1074/jbc.M607831200. [PubMed: 17121837]
 46. Ikonovic M, Abrahamson E, Koldamova R, Lefterov I, Isanski B, Lazo J, DeKosky S. Changes in brain cholesterol transporter ABCA1 following controlled cortical injury in rats. *J Neurotrauma*. 2003; 20(10):P359.
 47. Brown J III, Theisler C, Silberman S, Magnuson D, Gottardi-Littell N, Lee JM, Yager D, Crowley J, Sambamurti K, Rahman MM, Reiss AB, Eckman CB, Woloizin B. Differential expression of cholesterol hydroxylases in Alzheimer's disease. *J Biol Chem*. 2004; 279(33):34674–34681. 10.1074/jbc.M402324200. [PubMed: 15148325]
 48. Sun Y, Yao J, Kim TW, Tall AR. Expression of liver X receptor target genes decreases cellular amyloid beta peptide secretion. *J Biol Chem*. 2003; 278(30):27688–27694. 10.1074/jbc.M300760200. [PubMed: 12754201]
 49. Burns MP, Vardanian L, Pajoohesh-Ganji A, Wang L, Cooper M, Harris DC, Duff K, Rebeck GW. The effects of ABCA1 on cholesterol efflux and A β levels in vitro and in vivo. *J Neurochem*. 2006; 98(3):792–800. 10.1111/j.1471-4159.2006.03925.x. [PubMed: 16771834]
 50. Lefterov I, Bookout A, Wang Z, Staufenbiel M, Mangelsdorf D, Koldamova R. Expression profiling in APP23 mouse brain: inhibition of A β amyloidosis and inflammation in response to LXR agonist treatment. *Mol Neurodegener*. 2007; 2:20. 10.1186/1750-1326-2-20. [PubMed: 17953774]
 51. Riddell DR, Zhou H, Comery TA, Kouranova E, Lo CF, Warwick HK, Ring RH, Kirksey Y, Aschmies S, Xu J, Kubek K, Hirst WD, Gonzales C, Chen Y, Murphy E, Leonard S, Vasylyev D, Oganessian A, Martone RL, Pangalos MN, Reinhart PH, Jacobsen JS. The LXR agonist TO901317 selectively lowers hippocampal A β 42 and improves memory in the Tg2576 mouse model of Alzheimer's disease. *Mol Cell Neurosci*. 2007; 34(4):621–628. 10.1016/j.mcn.2007.01.011. [PubMed: 17336088]
 52. Jiang Q, Lee CYD, Mandrekar S, Wilkinson B, Cramer P, Zelcer N, Mann K, Lamb B, Willson TM, Collins JL, Richardson JC, Smith JD, Comery TA, Riddell D, Holtzman DM, Tontonoz P, Landreth GE. ApoE promotes the proteolytic degradation of A β . *Neuron*. 2008; 58(5):681–693. 10.1016/j.neuron.2008.04.010. [PubMed: 18549781]
 53. Karasinska JM, Rinninger F, Lütjohann D, Ruddle P, Franciosi S, Kruit JK, Singaraja RR, Hirsch-Reinshagen V, Fan J, Brunham LR, Bissada N, Ramakrishnan R, Wellington CL, Parks JS, Hayden MR. Specific loss of brain ABCA1 increases brain cholesterol uptake and influences neuronal structure and function. *J Neurosci*. 2009; 29(11):3579–3589. 10.1523/JNEUROSCI.4741-08.2009. [PubMed: 19295162]
 54. Koldamova RP, Lefterov IM, Lefterova MI, Lazo JS. Apolipoprotein A-I directly interacts with amyloid precursor protein and inhibits A-beta aggregation and toxicity. *Biochemistry*. 2001; 40(12):3553–3560. [PubMed: 11297421]
 55. Balazs Z, Panzenboeck U, Hammer A, Sovic A, Quehenberger O, Malle E, Sattler W. Uptake and transport of high-density lipoprotein (HDL) and HDL-associated alpha-tocopherol by an in vitro

- blood–brain barrier model. *J Neurochem.* 2004; 89(4):939–950. 10.1111/j.1471-4159.2004.02373.x. [PubMed: 15140193]
56. Panzenboeck U, Balazs Z, Sovic A, Hrzenjak A, Levak-Frank S, Wintersperger A, Malle E, Sattler W. ABCA1 and scavenger receptor class B, type I, are modulators of reverse sterol transport at an in vitro blood–brain barrier constituted of porcine brain capillary endothelial cells. *J Biol Chem.* 2002; 277(45):42781–42789. 10.1074/jbc.M207601200. [PubMed: 12202492]
 57. Hong SH, Riley W, Rhyne J, Friel G, Miller M. Lack of association between increased carotid intima-media thickening and decreased HDL-cholesterol in a family with a novel ABCA1 variant, g2265t. *Clin Chem.* 2002; 48(11):2066–2070. [PubMed: 12407001]
 58. Wahrle SE, Jiang H, Parsadanian M, Kim J, Li A, Knoten A, Jain S, Hirsch-Reinshagen V, Wellington CL, Bales KR, Paul SM, Holtzman DM. Overexpression of ABCA1 reduces amyloid deposition in the PDAPP mouse model of Alzheimer disease. *J Clin Invest.* 2008; 118(2):671–682. 10.1172/JCI33622. [PubMed: 18202749]
 59. Lefterov I, Fitz NF, Cronican A, Lefterov P, Staufenbiel M, Koldamova R. Memory deficits in APP23/Abca1+/- mice correlate with the level of A β oligomers. *ASN Neuro.* 1(2) 10.1042/AN20090015.
 60. Miao J, Vitek MP, Xu F, Previti ML, Davis J, Van Nostrand WE. Reducing cerebral microvascular amyloid-beta protein deposition diminishes regional neuroinflammation in vasculotropic mutant amyloid precursor protein transgenic mice. *J Neurosci.* 2005; 25(27):6271–6277. 10.1523/JNEUROSCI.1306-05.2005. [PubMed: 16000616]
 61. Pfrieder FW, Barres BA. Synaptic efficacy enhanced by glial cells in vitro. *Science.* 1997; 277(5332):1684–1687. [PubMed: 9287225]
 62. Mauch DH, Nägler K, Schumacher S, Göritz C, Müller EC, Otto A, Pfrieder FW. CNS synaptogenesis promoted by glia-derived cholesterol. *Science.* 2001; 294(5545):1354–1357. 10.1126/science.294.5545.1354. [PubMed: 11701931]
 63. Zelcer N, Khanlou N, Clare R, Jiang Q, Reed-Geaghan EG, Landreth GE, Vinters HV, Tontonoz P. Attenuation of neuroinflammation and Alzheimer's disease pathology by liver x receptors. *Proc Natl Acad Sci U S A.* 2007; 104(25):10601–10606. 10.1073/pnas.0701096104. [PubMed: 17563384]
 64. Cronican AA, Fitz NF, Pham T, Fogg A, Kifer B, Koldamova R, Lefterov I. Proton pump inhibitor Lansoprazole is a nuclear liver X receptor agonist. *Biochem Pharmacol.* 2010; 79(9):1310–1316. 10.1016/j.bcp.2009.12.018. [PubMed: 20060385]
 65. Suzuki S, Nishimaki-Mogami T, Tamehiro N, Inoue K, Arakawa R, Abe-Dohmae S, Tanaka AR, Ueda K, Yokoyama S. Verapamil increases the apolipo-protein-mediated release of cellular cholesterol by induction of ABCA1 expression via Liver X receptor-independent mechanism. *Arterioscler Thromb Vasc Biol.* 2004; 24(3):519–525. 10.1161/01.ATV.0000117178.94087.ba. [PubMed: 14726413]
 66. Wang N, Tall AR. Regulation and mechanisms of ATP-binding cassette transporter A1-mediated cellular cholesterol efflux. *Arterioscler Thromb Vasc Biol.* 2003; 23(7):1178–1184. 10.1161/01.ATV.0000075912.83860.26. [PubMed: 12738681]
 67. Wang N, Chen W, Linsel-Nitschke P, Martinez LO, Agerholm-Larsen B, Silver DL, Tall AR. A PEST sequence in ABCA1 regulates degradation by calpain protease and stabilization of ABCA1 by apoA-I. *J Clin Invest.* 2003; 111(1):99–107. 10.1172/JCI16808. [PubMed: 12511593]
 68. Chen W, Wang N, Tall AR. A PEST deletion mutant of ABCA1 shows impaired internalization and defective cholesterol efflux from late endosomes. *J Biol Chem.* 2005; 280(32):29277–29281. 10.1074/jbc.M505566200. [PubMed: 15951431]
 69. Martinez LO, Agerholm-Larsen B, Wang N, Chen W, Tall AR. Phosphorylation of a pest sequence in ABCA1 promotes calpain degradation and is reversed by ApoA-I. *J Biol Chem.* 2003; 278(39):37368–37374. 10.1074/jbc.M307161200. [PubMed: 12869555]
 70. Feng B, Tabas I. ABCA1-mediated cholesterol efflux is defective in free cholesterol-loaded macrophages. Mechanism involves enhanced ABCA1 degradation in a process requiring full NPC1 activity. *J Biol Chem.* 2002; 277(45):43271–43280. 10.1074/jbc.M207532200. [PubMed: 12215451]

71. Park SK, Prolla TA. Lessons learned from gene expression profile studies of aging and caloric restriction. *Ageing Res Rev.* 2005; 4(1):55–65. cited by (since 1996): 32. [PubMed: 15619470]
72. Panzenboeck U, Kratzer I, Sovic A, Wintersperger A, Bernhart E, Hammer A, Malle E, Sattler W. Regulatory effects of synthetic liver X receptor- and peroxisome-proliferator activated receptor agonists on sterol transport pathways in polarized cerebrovascular endothelial cells. *Int J Biochem Cell Biol.* 2006; 38(8):1314–1329. 10.1016/j.biocel.2006.01.013. [PubMed: 16530456]
73. Gosselet F, Candela P, Sevin E, Berezowski V, Cecchelli R, Fenart L. Transcriptional profiles of receptors and transporters involved in brain cholesterol homeostasis at the blood–brain barrier: use of an in vitro model. *Brain Res.* 2009; 1249:34–42. 10.1016/j.brainres.2008.10.036. [PubMed: 18996096]