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Review article

ABCA1 and atherosclerosis

S Soumian[a], C Albrecht[b], AH Davies[a] and RGJ Gibbs[a]

Abstract: ATP binding cassette transporter A1 (ABCA1) mediates the cellular efflux of phospholipids and cholesterol to lipid-poor apolipoprotein A1 (apoA1) and plays a significant role in high density lipoprotein (HDL) metabolism. ABCA1's role in the causation of Tangier disease, characterized by absent HDL and premature atherosclerosis, has implicated this transporter and its regulators liver-X-receptorα (LXRα) and peroxisome proliferator activated receptorγ (PPARγ) as new candidates potentially influencing the progression of atherosclerosis. In addition to lipid regulation, these genes are involved in apoptosis and inflammation, processes thought to be central to atherosclerotic plaque progression. A Medline-based review of the literature was carried out. Tangier disease and human heterozygotes with ABCA1 mutations provide good evidence that ABCA1 is a major candidate influencing atherosclerosis. Animal and in vitro experiments suggest that ABCA1 not only mediates cholesterol and phospholipid efflux, but is also involved in the regulation of apoptosis and inflammation. The complex and beneficial interactions between apoA1 and ABCA1 seem to be pivotal for cholesterol efflux. The expression of the ABCA1 is tightly regulated. Furthermore the plaque microenvironment could potentially promote ABCA1 protein degradation thus compromising cholesterol efflux. PPAR-LXR-ABCA1 interactions are integral to cholesterol homeostasis and these nuclear receptors have proven anti-inflammatory and anti-matrix metalloproteinase activity. Therapeutic manipulation of the ABCA1 transporter is feasible using PPAR and LXR agonists. PPAR agonists like glitazones and ABCA1 protein stabilization could potentially modify the clinical progression of atherosclerotic lesions.

Key words: apolipoprotein A1; atherosclerosis; ATP binding cassette transporter 1; HDL cholesterol; Tangier disease

Introduction

Atherosclerosis, a multifactorial disease of great complexity, starts in fetal life, progresses slowly through childhood and adolescence and accelerates in adult life. The characteristic component of the atherosclerotic plaque is the macrophage derived foam cell.[1] This cholesterol laden macrophage is thought to result from the uptake of oxidatively modified low density lipoprotein (LDL).[2] However, intracellular free cholesterol (FC) can be toxic to the cell[3] and therefore an efficient cholesterol efflux mechanism in the macrophage is mandatory to prevent cholesterol accumulation. High density lipoprotein (HDL) and its apolipoproteins, especially apolipoprotein A1 (apoA1), are responsible for the transfer of cholesterol from peripheral cells to the liver for biliary excretion, the process of reverse cholesterol transport.[4] ATP binding cassette transporter A1 (ABCA1), a membrane transporter abundant in macrophages, mediates this cholesterol and phospholipid (PL) efflux to lipid-poor apoA1, the precursor of HDL, and plays a major role in cholesterol homeostasis and reverse cholesterol transport.[5]

The various functions of ABCA1 became apparent after the discovery in 1999 that mutations in the ABCA1 gene caused Tangier disease (TD), an autosomal recessive hereditary disorder characterized by severe HDL deficiency, sterol deposition in macrophages and premature atherosclerosis.[6] TD patients with homozygote mutations in the ABCA1

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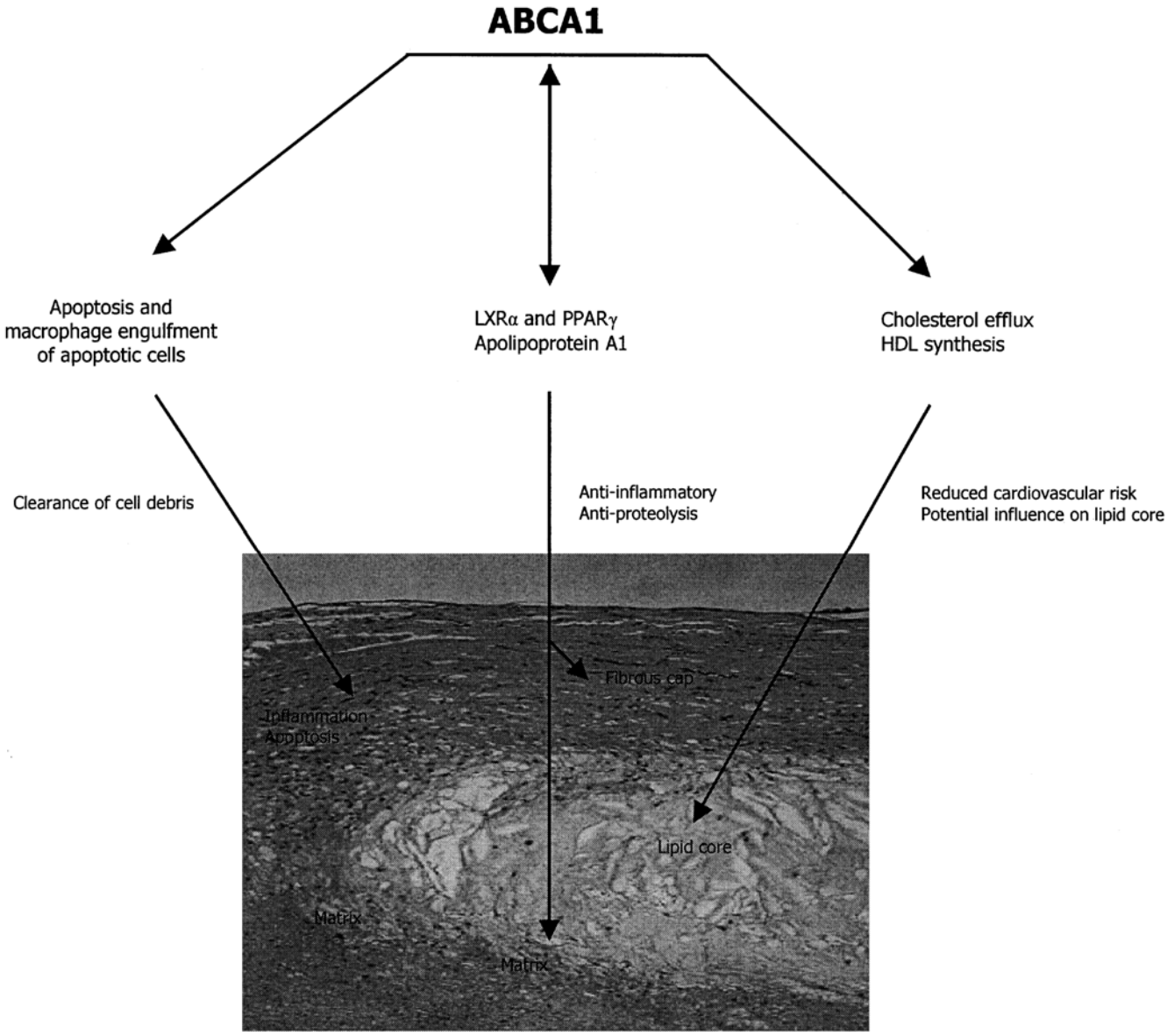

Figure 1 The influence of ABCA1 on the atherosclerotic plaque.

gene have virtually absent HDL and apoA1, decreased low density lipoprotein (LDL) level (40% normal) and hypertriglyceridemia.[7] The association between ABCA1 and HDL is ascertained by the fact that reduction in ABCA1 activity is associated with a significant decrease in plasma HDL levels.[8] Apart from its role in lipid metabolism, ABCA1 has also been implicated in promoting engulfment of apoptotic cells,[9] LDL oxidation[10] and the release of inflammatory mediators.[11,12] ABCA1 also binds to other lipoproteins including apolipoprotein E thus playing a role in its anti-atherogenic effect.[13]

Atherosclerotic plaque composition is the major determinant of plaque disruption and the ensuing complications. The aetio-pathogenesis of an atheromatous plaque is influenced by lipid metabolism, disordered cell turnover and extracellular matrix turnover within its structure. ABCA1 plays a role in all of these events, thus potentially implicating this transporter in the initiation, progression and pathogenesis of atherosclerotic vascular disease (Figure 1). In this review we will focus on the potential role of ABCA1 in atherosclerotic vascular disease.

Structure and distribution

ABCA1 is a member of the superfamily of ABC transporters that utilize ATP as a source of energy to transport various molecules across membranes.[14] The ABCA1 gene consists of 50 exons spanning 149 kb and encodes a protein that contains 2261 amino acids.[15] Immunofluorescence studies suggest that ABCA1 localises in the plasma membrane[16] although

shuttling of ABCA1 between intracellular endocytic components and the plasma membrane has been reported.[17] The structure of ABCA1 is characterized by the presence of two transmembrane domains with six helices each and a nucleotide binding domain containing two conserved peptide motifs (Walker A and B) that are characteristic for the superfamily of ABC transporters. It also has two large extracellular loops joined by a disulfide linkage which are thought to be important for the binding of apoA1.[18]

ABCA1 has been shown to be highly expressed in macrophages.[19,20] Though a near ubiquitous tissue expression has been proposed, Wellington et al[21] have shown a significant discordance between relative mRNA and protein expression patterns of ABCA1 in murine tissues.

Mechanism of cholesterol efflux

Cholesterol efflux occurs through different mechanisms, ABCA1 being one of them. The efflux of FC promoted by ABCA1 is considered to be unidirectional and by active transport to apoA1. It is suggested that the golgi apparatus processes excess intracellular FC into vesicles that are translocated to plasma membrane ABCA1 for exocytosis.[22] Recent literature suggests that ABCA1 mediates concurrent transport of FC and PL to apolipoproteins[23] though the availability of different lipids in the vicinity of ABCA1 may result in modification of the ratio of cholesterol/phospholipid undergoing efflux.[24] It also has been recently shown in transgenic mice that in vivo modification of the PL/apoA1 ratio by various lipases could play a major role in directing FC efflux through either the ABCA1 or the scavenger receptor B1 (SR-B1) pathway.[25]

ApoA1 and ABCA1

It is well established that free apolipoproteins play a role in mediating removal of cellular cholesterol.[26] ApoA1 is the most abundant apolipoprotein in HDL and is known to play a role in cholesterol efflux through ABCA1 dependent[27] and independent mechanisms.[28]

To date no clear consensus exists regarding the process by which apoA1 removes cholesterol and PL from the plasma membrane. There are studies supporting the theory of membrane solubilization wherein apoA1 and ABCA1 simultaneously remove both PL and cholesterol through a single step process.[29] Another proposed mechanism includes a two step process in which ABCA1 lipidates apoA1 with PL first to form phospholipid rich nascent HDL particles which then remove cholesterol from cells by diffusion.[30,31] The flopping of phosphatidylserine (PS) from the inner to the outer leaflet which is promoted by ABCA1 was also thought to play a role in apoA1 mediated lipid efflux[32] although a recent study suggests that the small increase in PS translocation caused by ABCA1 might be insufficient for apoA1 binding and lipid efflux.[33]

There is increasing evidence that apoA1 directly interacts with ABCA1.[27,34] Further proof of this are studies which showed that mutations in the extracellular loops of ABCA1 impaired both cross-linking with apoA1 and lipid efflux.[18] Moreover, truncation mutations of apoA1 lacking helix 10 impaired cholesterol transport through the ABCA1 pathway.[35] For efficient apoA1 mediated transport, a functional ABCA1 protein and specific binding at the plasma membrane[32] is crucial as mutated ABCA1 seen in diseases like TD[6] and familial HDL deficiency,[36] can result in increased catabolism of apoA1 thus affecting HDL production.[37]

Animal studies have revealed that apoA1 itself, independent of HDL cholesterol, has properties that protect against atherosclerosis.[38] ApoA1 has documented roles in inhibiting LDL oxidation,[10,39,40] and also has an anti-inflammatory effect both by inhibiting secretion of interleukin-1β (IL-1β) and tumour necrosis factor-α (TNF-α)[41] and via the removal of reactive oxygen species. It has been suggested that ABCA1 may be linked to these functions via apoA1.[10]

The apoA1 concentration in the extracellular fluid is dependent on synthesis, catabolism, dissociation and its reassociation with the lipoproteins in the plasma compartment represented by the HDL component.[42] This in turn could potentially influence lipid efflux in the plaque environment.

ABCA1 and the atherosclerotic plaque

The atherosclerotic plaque is a dynamic structure composed of lipids, cells and extracellular matrix. Plaques with high levels of collagen and smooth muscle cells providing a thick fibrous cap are characteristic of an advanced stable plaque, while unstable plaques have a thin cap, dense inflammatory infiltrate and a large lipid core.[43] Unstable plaques are prone to rupture with subsequent in situ thrombosis and embolism,[44] leading to significant clinical consequences. The behaviour of these plaques is highly unpredictable and the precise mechanisms causing the transition to instability are incompletely understood. The development and subsequent progression of plaques are determined by changes in its three major constituents, and ABCA1 could potentially influence all of the processes governing plaque architecture, namely:

(1) lipid accumulation and metabolism;
(2) alterations in cell turnover involving apoptosis and inflammation;
(3) altered extracellular matrix turnover.

ABCA1 and lipid metabolism

A large lipid core in the atheromatous plaque is one of the major indicators of potential instability. Inefficient macrophage function to clear lipids and cell debris could lead to an increase in the volume of lipid within the central core of the plaque. In the Tromso study[45,46] it was reported that lipid rich echolucent carotid plaques are associated with low levels of HDL cholesterol and increased risk of ischemic cerebrovascular events independent of the degree of stenosis and cardiovascular risk factors. Furthermore low HDL levels were shown to be associated with increased carotid intima-media thickness independent of other risk factors.[47]

Cholesterol from peripheral cells is returned to the liver by ABCA1 dependent and independent mechanisms. ApoA1 that is secreted or regenerated from HDL by the liver is lipidated by ABCA1 in peripheral cells to form pre-β HDL (nascent HDL) which then collects cholesterol from various cells. Although a basal level of phospholipidation of apoA1 may occur through an ABCA1 independent pathway,[48] the major part of it is done by ABCA1. It is also thought that the cholesterol processed from LDL receptor uptake in the liver is transferred to HDL by hepatic ABCA1 to be secreted into bile. In addition ABCA1 might also be involved in the removal of FC through apoA1 independent mechanisms via the formation of large membrane FC rich vesicles.[49]

Animal studies have provided further proof of ABCA1 function. Classical examples are ABCA1 knock out[42] and transgenic mice[50–53] as well as the Wisconsin Hypoalpha Mutant Chicken (WHAM)[54,55] which is the naturally occurring animal model of TD. In the context of human studies on ABCA1, a 2–3-fold increase in cardiovascular disease in TD patients and obligate ABCA1 heterozygotes as compared to age and sex matched controls from the Framingham study[56] was found. A recent study revealed that heterozygotes with ABCA1 mutations had lower amounts of cholesterol efflux, lower HDL concentrations and greater carotid intima-media thickness than the control group.[57] This study also indicated that the upper limit of normal intima-media thickness (0.80 mm) is reached in ABCA1 heterozygotes at the age of 55 as compared to 80 years in the control group.

In this context, a potentially variable role of ABCA1 in hepatocytes and macrophages towards its contribution to HDL formation has been suggested. Studies in mice have highlighted the importance of both hepatic and macrophage ABCA1. Mice specifically overexpressing ABCA1[58] in hepatocytes and macrophages showed significant increases in HDL levels. However, selective inactivation studies of ABCA1 in macrophages showed clear evidence of increased atherosclerosis in hyperlipidemic mice[58] but had very minimal impact on HDL formation.[59] Similarly mice selectively deficient in leukocyte ABCA1 developed large advanced atherosclerotic lesions without any change in plasma HDL levels.[60] This implies that hepatic ABCA1 may be responsible for the main contribution of ABCA1 to plasma HDL. Recent studies by Sahoo et al[61] seem to support this finding. Taken together, these findings suggest that hepatic ABCA1 exerts a generalized anti-atherogenic effect via its contribution to HDL formation while macrophage ABCA1 provides a peripheral anti-atherogenic effect on the vasculature.

However, interesting questions did arise by studying TD and ABCA1 deficient mice. First, the accumulation of cholesteryl esters in these conditions is localized primarily to macrophages and certain tissues.[7] The reason for this observation is still under investigation, but it has been suggested that lipids accumulate predominantly in tissues with high cell turnover and a large population of macrophages. Secondly, TD patients have only a 4-fold increase in atherosclerotic disease compared to the general population, despite the fact that more severe atherosclerosis would be expected as a consequence of the complete absence of HDL.

It has been proposed[7] that the source of cholesterol may differ between different macrophage subtypes with arterial macrophages primarily obtaining cholesterol from lipoproteins while other peripheral macrophages accumulate cholesterol from phagocytosed cell membranes. Thus despite ABCA1 deficiency and low HDL levels in TD patients, the expected aggressive atherosclerosis fails to develop in the background of a less atherogenic lipid profile (less than 40% LDL) which provides a potentially diminished cholesterol pool for arterial macrophages. Hence it may be speculated that in the presence of normal or increased levels of LDL, ABCA1 deficiency could potentially enhance atherosclerosis.

ABCA1 and alterations in cell turnover

Apoptosis

Apoptosis is known to play a major role in regulating cell turnover in the plaque. Apoptosis (Greek: leaf-fall), often used synonymously with programmed cell death, is a physiologically highly selective method to eliminate old or injured cells before the leakage of intracellular contents can induce an immune response. The initial phase of apoptosis has to be followed by an efficient phagocytic phase to render the process immunologically silent. Therefore recognition of an apoptotic cell by the phagocyte is crucial. After stimulation, PS, an anionic phospholipid which resides in the inner leaflet, is translocated to the outer leaflet, a process which is sufficient to guarantee recognition by the phagocyte.[62] ABCA1 was found to be involved in PS translocation and in promoting engulfment of apoptotic cells.[9] This study revealed that phagocytosis

is impaired in ABCA1 deficient macrophages and that forced expression of ABCA1 can confer engulfment ability to non-phagocytic cells. ABCA1 null animals were found to manifest reduced externalization of PS and similar findings were obtained in other studies.[33] The externalization of PS is paramount in the atherosclerotic plaque due to its known tendency to promote procoagulant potential[63,64] and the coagulation cascade. ABCA1 was also shown to interact with the Fas associated death domain (FADD) protein,[65] a process which may play a role in regulating apoptosis.

Inflammation

Cellular cholesterol levels determine the levels of intracellular oxygenated sterols which in turn regulates LDL oxidation, activation of IL-1[66] and promotion of apoptotic pathways.[67] ABCA1 which is proven to selectively remove cytotoxic FC from the cell[68] could potentially control intracellular oxysterol levels. Macrophages and activated T lymphocytes in the plaque[69] release proinflammatory cytokines, mainly interferon-gamma (IFN-γ) from T lymphocytes), TNF and IL-1 (both from macrophages). These cytokines have been reported to decrease the mRNA and protein levels of ABCA1.[16,70–73] Moreover, lipopolysaccharide found in infectious agents like *Chlamydia* was also reported to downregulate ABCA1 expression.[70,74] It has been demonstrated that IFN-γ can cause a 3-fold downregulation of ABCA1 and simultaneously an increase in acyl- CoA: cholesterol acyltransferase (ACAT) activity[71,73] thus promoting atherosclerosis. IL-1β, responsible for the activation of MMPs and other interleukins have also been reported to inhibit ABCA1 function thus promoting lipid accumulation.[72] It has been recently reported that myeloperoxidase present in atheromas[75] promotes atherogenesis by impairing ABCA1 function.[76] There is evidence that ABCA1 is involved in the secretion of IL-1β and macrophage inhibitory factor (MIF) from macrophages and monocytes respectively.[11,12,77] However, the role of ABCA1 in the transport of these proinflammatory cytokines needs further evaluation.

Hence it could be speculated that a vicious cycle might ensue where the initial cytokine induction could cause ABCA1 deficiency, which in turn results in inadequate clearance of apoptotic and necrotic cells that further aggravates inflammatory mediators leading to plaque instability. All of the previously mentioned findings suggest that therapeutic upregulation of ABCA1 expression could be a promising approach in the context of treatment of atherosclerosis.

ABCA1 and extracellular matrix turnover

The integrity of the extracellular matrix (ECM) which influences the strength of the fibrous cap in the plaque[78] is determined by the balance between matrix metalloproteinases (MMP) and tissue inhibitors of MMPs.[79] There is general agreement that increased levels of intra-plaque MMPs could lead to plaque rupture[80] and clinically significant plaque instability has been shown to be associated with increased levels of MMP-9.[81] The MMPs which are secreted by inflammatory cells promote VSMC migration and ECM degradation.[82] The proinflammatory cytokine IL-1β is reported to upregulate MMP-9 production.[83,84] The interaction of ABCA1 with apoA1 may reduce MMP-9 production as apoA1 is documented to suppress cytokine IL-1β production.[41] Furthermore the nuclear receptors liver-X-receptor (LXR) and peroxisome proliferator-activated receptor (PPAR), which are the key regulators of ABCA1 function, have documented anti-inflammatory and anti-MMP activity.[85–89]

Regulation of ABCA1

The pivotal role played by ABCA1 in cholesterol homeostasis mandates a tight regulatory pathway. In addition to increased lipid efflux, a consequence of ABCA1 overexpression could also be the potential alteration of membrane structure with subsequent detrimental effects.[16] Evidence for the tight regulation of ABCA1 is the short half life of the ABCA1 protein[90,91] and its rapid turnover in macrophage cell lines.[92] It is regulated at transcriptional and post-transcriptional levels (Figure 2).

Transcriptional regulation

Sterols

The large intracellular sterol concentration in foam cells plays a major role in ABCA1 regulation. Acetylated LDL upregulates ABCA1 mRNA and protein which can be reversed by incubation of these macrophages in HDL.[19] It was also reported that ABCA1 mRNA and protein were upregulated in a time and dose dependent fashion by native LDL.[93]

Nuclear receptors

Nuclear receptors are ligand activated transcription factors that regulate the expression of their target genes. The tissue specific expression and ligand availability tightly controls its activity.[94] LXR and PPAR, belonging to a subgroup called adopted orphan nuclear receptor group, are the major players in ABCA1 regulation and will therefore be discussed below.

LXRs act as cholesterol sensors that respond to elevated sterol concentrations and activate a cadre of genes that govern transport, catabolism and elimination of cholesterol.[95] LXRα expressed in the macrophage is important in terms of plaque physiology as it seems to be capable of activating and suppressing the ABCA1 gene based on ligand availability.[96] The ligands that activate these receptors in the macrophage are mainly oxysterols like 27-hydroxycholesterol.[97]

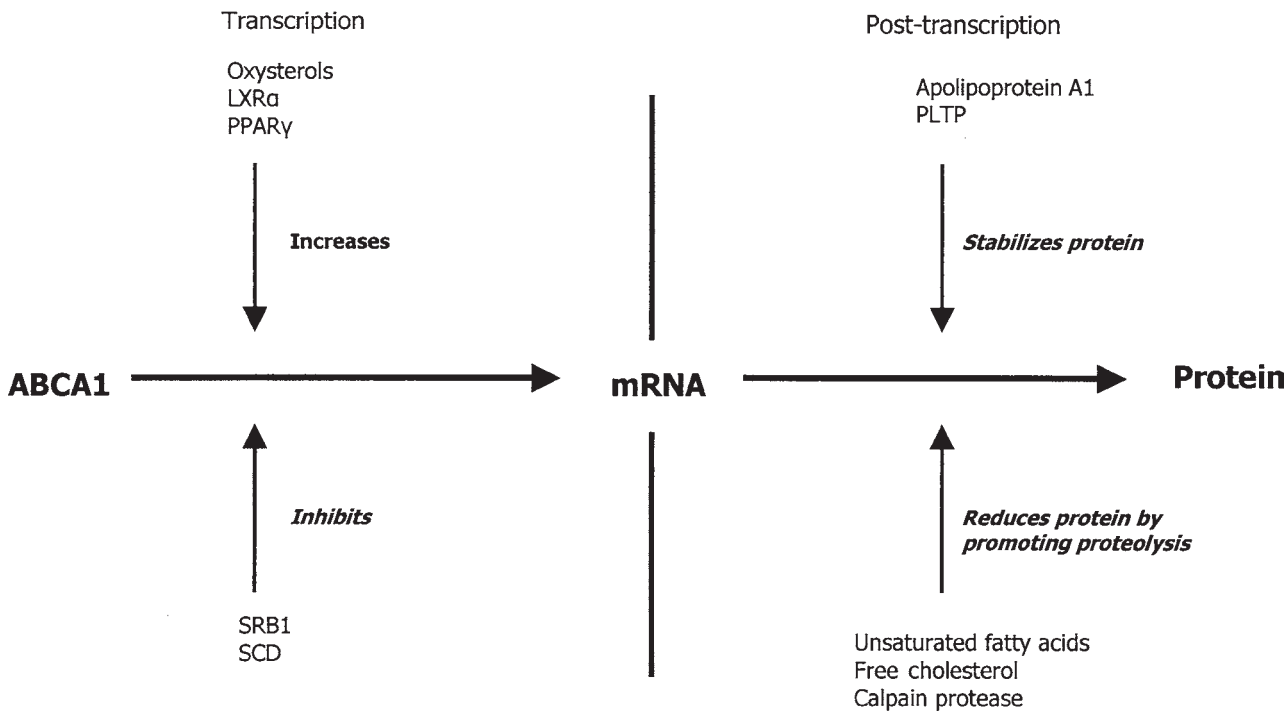

Figure 2 Regulation of ABCA1 at transcriptional and post-transcriptional levels.

LXRα influences ABCA1 expression transcriptionally and post-transcriptionally (Figure 3). Studies have reported that the oxysterol induction of ABCA1 is partly through the LXR pathway.[98,99] Recent studies have highlighted the anti-atherogenic activity of LXR.[100,101] In human macrophages exclusively, it has been observed that the LXRα gene itself is a target for the LXR signaling pathway, an effective autoregulatory mechanism to amplify the ABCA1 lipid efflux pathway.[102,103]

PPARs have been implicated in the regulation of both inflammation and lipid homeostasis in the macrophage and polyunsaturated fatty acids serve as their ligands.[94] PPARγ enhances cholesterol efflux by inducing the transcription of LXRα and thus ABCA1.[104,105] The observation that PPAR agonists and LXR ligands are ineffective in macrophages of TD patients[99,105] indicates that functional ABCA1 is required for this pathway of cholesterol efflux. With regard to the role of these nuclear receptors in the context of plaque pathophysiology, LXRα and PPARγ have been documented to have anti-inflammatory[86–88] and anti-MMP activity.[85,89] The PPARγ–LXRα –ABCA1 cascade does represent a powerful means of cholesterol efflux from the macrophage and therefore could play a significant role in influencing the progression of atherosclerotic plaques.

Post-transcriptional regulation

Studies in mice have revealed a significant discordance between ABCA1 protein and mRNA levels, suggesting that post-transcriptional regulation plays a major role[21] in ABCA1 protein expression. Unsaturated fatty acids have been found to promote ABCA1 protein degradation directly[92,106] and indirectly.[107,108] This may be significant in disorders like type 2 diabetes and insulin resistance, conditions with increased levels of fatty acids where accelerated atherosclerosis is observed. Cytotoxic levels of intracellular FC[109] were also found to promote ABCA1 protein degradation through the proteolysis pathway. ABCA1 phosphorylation, which is reported to be influenced by apoA1[110] and protein kinase C,[111] may also have a major effect on protein stability. The PEST sequence identified in ABCA1 by Wang et al[112] appears significant in protein degradation as deletion of this motif resulted in a 4–5-fold increase in ABCA1 protein, increased ABCA1 mediated efflux and enhanced apoA1 binding.

In vitro experiments with peritoneal macrophages, transfected cells and mouse primary hepatocytes have shown that apoA1 binding increased ABCA1 protein without affecting mRNA levels.[112] Interestingly this apoA1 mediated stabilization of ABCA1 protein is achieved by inhibition of PEST sequence mediated degradation by proteases.[90,112] There is also evidence that PLTP interacts with ABCA1 for its function in cholesterol efflux and also stabilizes ABCA1 protein.[113]

We have reported that, in human carotid atherosclerotic plaques, ABCA1 protein is significantly reduced despite increased mRNA.[114] The observed upregulation in this study of both LXRα and ABCA1

mRNA in atherosclerotic tissues could be attributed to the oxysterol-rich environment inside the plaque potentially amplified by low ABCA1 protein levels. It is possible that the degradation of ABCA1 protein in the plaque microenvironment might be the key factor influencing cholesterol homeostasis at the macrophage level. The resulting localized deficiency in ABCA1 function could lead to decreased lipid efflux, accumulation of oxysterols and acceleration of the atherosclerotic process.

Therapeutic modulation

The nuclear receptors PPARγ and LXRα are promising targets for pharmacological manipulation of the ABCA1 pathway. In vitro studies have shown that PPAR agonists such as the glitazones used in type 2 diabetes induce cholesterol efflux from macrophages through the activation of ABCA1.[105,115] It is interesting to note that PPAR agonists can effectively override the cytokine IL-1β induced suppression of ABCA1 and promote cholesterol efflux.[72] This effect in itself may be valuable in terms of plaque pathophysiology. ACAT inhibitors which increase intracellular FC levels have also been reported to upregulate ABCA1 both at the mRNA and protein level[116] but are unlikely to be considered for general use.

Studies on rats showed that clofibrate, widely used as a hypolipidemic agent, increases ABCA1 mRNA through activation of LXRα.[117] Recently verapamil was shown to enhance both ABCA1 mRNA and protein expression through LXR independent mechanisms.[118] Ando et al[119] demonstrated that in vivo pravastatin increased LXRα mRNA levels. Statins increase HDL levels in addition to the significant reductions in total cholesterol and triglycerides.[120,121] In fact it is suggested that the increase in HDL cholesterol produced by statins could partly also be through the upregulation of ABCA1 and apoA1.[122,123] PPAR and LXR agonism may be beneficial in terms of its generalized effect on HDL and inflammation but its effect on the localized atheromatous plaque has not been studied in detail.

The benefits of transcriptional upregulation may be potentially annulled by the in vivo plaque microenvironment that promotes ABCA1 protein degradation.[114] In addition to ABCA1 transcriptional upregulation, ABCA1 protein stabilization may be crucial to promote function of cholesterol efflux.

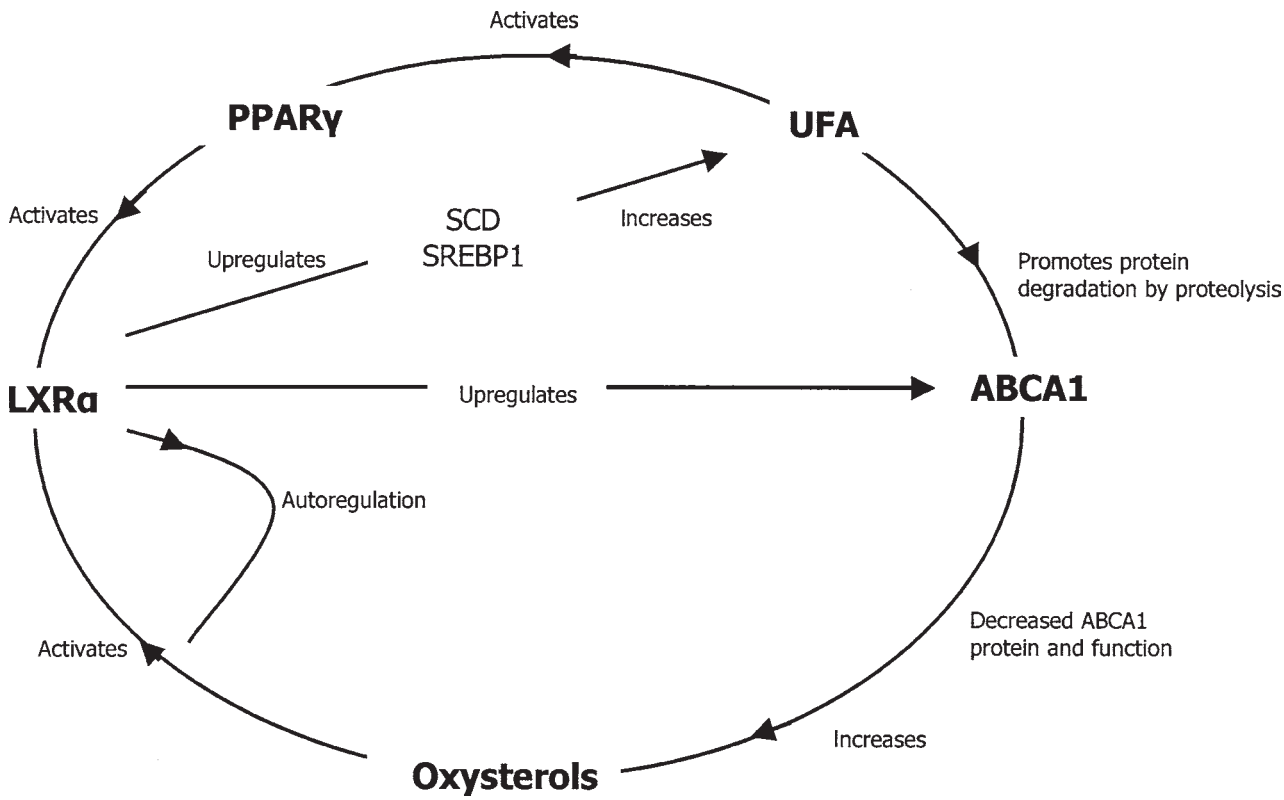

Figure 3 Influence of nuclear receptors LXRα and PPARγ on ABCA1 expression. LXRα has been shown to activate the sterol regulatory element binding protein-1 (SREBP-1)[124] and stearoyl-CoA desaturases-1 and 2 (SCD)[108] which results in increased unsaturated fatty acid synthesis. These unsaturated fatty acids serve as ligands for PPAR activation[94] but have been implicated in causing ABCA1 protein degradation.[92,106] Therefore the enhanced ABCA1 transcription induced by LXR ligands may be counteracted by increased ABCA1 protein degradation.

Synthetic peptides based on the structure of apoA1 have been found to be effective in stabilizing ABCA1 protein.[125,126] Calpain protease inhibitors and specific LXR agonists[127] are further venues for exploration in the quest to promote cholesterol efflux therapeutically. Therefore it would be interesting to assess the effect of combined transcriptional upregulation with protein stabilization of ABCA1 in the context of treatment of atherosclerosis.

Conclusion

The critical role of ABCA1 at the macrophage and hepatic level regarding lipid efflux and HDL formation could have a major influence on the biogenesis and progression of atheromatous plaques. Further studies need to be focused on apoA1 and ABCA1 interactions that seem to regulate each other and have a potent role in protection against atherosclerosis. The PPAR–LXR–ABCA1 cascade has a substantial role in cholesterol homeostasis and inflammation and therefore has a promising potential for therapeutic manipulation. The efficacy of combined therapy with ABCA1 transcriptional upregulation and protein stabilization needs to be evaluated. Further work needs to be undertaken to unravel other functions of this transporter and its pathways so that therapeutic strategies could be devised to prevent atherosclerotic disease and its complications.

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