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REVIEW

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Nuclear hormone receptors and cholesterol trafficking: the orphans find a new home

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Abstract There are many homeostatic mechanisms that contribute to the regulation of cellular and serum cholesterol levels in humans. Much of our understanding of this regulation arose from studies of the cellular pathways controlling cholesterol synthesis and the uptake and degradation of low-density lipoproteins. The physiology governing cholesterol disposition in whole animals, including the molecular mechanisms responsible for dietary uptake of cholesterol and its subsequent catabolism to bile acids, are only now being uncovered. This review summarizes recent studies that have used modern genetic techniques, as well as cell biological methods, to begin to elucidate the pathways responsible for cholesterol trafficking in vivo. This work has led to the realization that networks of nuclear hormone receptors, including the LXR, FXR, PPAR, and RXR proteins, play critical roles in lipid metabolism by virtue of their transcriptional regulation of the genes that control sterol metabolic pathways. Some of the major downstream targets of these regulatory networks involve members of the ABC transporter family, including ABCA1, ABCG1, ABCG5, ABCG8, MDR3/Mdr2, and SPGP/BSEP. These transporters contribute to the movement of sterols and biliary lipids across cellular membranes via mechanisms that have yet to be elucidated. The potential for manipulating these cholesterol trafficking pathways via drugs targeted to the nuclear hormone receptors has generated great interest in their biology and will undoubtedly lead to new therapeutic approaches to human disorders in the coming years.

Keywords Orphan receptors · ABCA1 · Bile acids · Liver X receptor · Cholesterol absorption

Abbreviations *ABC:* ATP cassette binding protein · *BSEP:* Bile salt export pump · *FXR:* Farnesoid X receptor · *HDL:* High-density lipoprotein · *I-BABP:* Ileal bile acid binding protein · *LDL:* Low-density lipoprotein · *LRH:* Liver receptor homologue · *LXR:* Liver X receptor · *MDR:* Multidrug resistance · *PPAR:* Peroxisome proliferator activated receptor · *RXR*: Retinoid X receptor· *SHP:* Small heterodimeric partner · *SPGP:* Sister of P-glycoprotein

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Introduction

For the past 30 years many of the central insights into the cell biology of cholesterol trafficking have come from studies of the pathways that influence the cellular handling of low-density lipoprotein (LDL) derived cholesterol. Given cholesterol's central role in the generation of normal cellular membranes, steroid hormones, and bile acids, as well as the pathological changes arising in atherosclerotic lesions, these studies have made an enormous contribution to our understanding of human physiology and pathophysiology. The excessive accumulation of cholesterol in tissues, both esterified and unesterified, has consequences that can affect the viability of individual cells as well as whole organisms. Thus, complex regulatory systems have evolved to protect against this unwanted development. Although cells in different tissues, such as macrophages, hepatocytes, adrenal cortical cells, and enterocytes can utilize different strategies to maintain cholesterol homeostasis, they also share common regulatory mechanisms. Our understanding of these regulatory systems at the single cell level has progressed steadily over the years. In particular, the critical roles of the LDL receptor and the sterol sensing transcriptional modulators (which regulate the enzymes involved in cholesterol synthesis) have been elegantly delineated [1, 2].

Control of cholesterol homeostasis at the whole organism level has also been heavily investigated, but the molecular underpinnings of that regulation have been slower to unravel. While it is well appreciated that animals can exert control over their total body cholesterol content through modulation of dietary cholesterol absorption and bile acid excretion, these processes had until recently been much less well characterized at the molecular level. In addition, the importance of cellular pathways that control intracellular cholesterol accumulation via export of sterol from cellular pools and membranes, rather than by the inhibition of cholesterol synthesis or uptake, have been both newly appreciated and clarified. There is increasing evidence that these two different homeostatic mechanisms are under the control of members of the same nuclear hormone receptor family, many of whose members were originally termed orphan receptors because they were cloned well before any functional role could be ascribed to them. The nuclear hormone receptors involved are activated by small lipophilic ligands and, in the activated state, function as transcription factors that can regulate the expression of other genes [3]. One class of genes that they regulate are the ATP binding cassette (ABC) transporters [4], so named because they couple ATP hydrolysis to the transport of substrates across lipid bilayers. ABC transporters have now been shown to have critical roles in hepatic secretion of bile acids, the dietary uptake of cholesterol, and cholesterol efflux from cultured cells. As nuclear hormone receptors are convenient targets for pharmaceutical agents, their linkage to these cholesterol homeostatic processes has created enormous interest in the cell biology of these pathways. Their pharmacological manipulation could constitute novel treatments for lipid disorders and atherosclerosis. The purpose of this review is to provide a succinct summary of our understanding of the role of these nuclear hormone receptor interactions in controlling cholesterol trafficking.

Nuclear hormone receptors and regulation of bile acid metabolism

Nuclear hormone receptors represent a large superfamily of transcriptional factors that regulate various aspects of vertebrate development and adult physiology [5]. As the founding members of this gene family were the receptors for the cholesterol-derived glucocorticoid and estrogen hormones, their involvement in regulating cholesterol transport provides an intriguing biological symmetry. Over the past several years additional work has shown that the receptors for the vitamin A metabolites, all-*trans* and 9- *cis* retinoic acid, as well as other lipophilic hormones such as vitamin D_3 and thyroid hormone, are also members of this expanding family of nuclear hormone receptors [5]. The identification of these receptors explained much of the transcriptional specificity by which the action of various lipophilic hormones is exerted.

Structurally, the nuclear hormone receptors are characterized by a central DNA binding domain that allows them to bind response elements within the promoters of target genes. These proteins can bind as monomeric proteins or as homo or heterodimers (Fig. 1). When the receptor's carboxy terminal domain binds its cognate lipophilic hormone, thereby altering the conformational state of the receptor, the receptor along with recruited cofactors can either stimulate or repress transcription. Using homology screening techniques based on the conservation of functional domains within the receptor family, additional members of the family were identified and cloned that had no known ligands. These were the so-called orphan receptors. Two members originally termed orphans, the liver X receptor (LXR) and the farnesoid X receptor (FXR), have now been decisively shown to be the receptors for hydroxycholesterols and bile acids, respectively [6, 7, 8, 9, 10, 11, 12]. Both LXR and FXR function as obligate heterodimers with the retinoid X receptor (RXR) as a common partner (Fig. 1).

The identification of nuclear hormone receptors that bind hydroxycholesterols and bile acids is of physiological importance, because the conversion of cholesterol to bile acids is the major route by which up to 50% of whole-body cholesterol is excreted. In this process cholesterol is converted principally to the cholic and chenodeoxycholic bile acids by two pathways, both of which involve oxidation of hydrogen at the 7th position of cholesterol's ring structure (Fig. 2). In the neutral pathway cholesterol is directly oxidized in a reaction catalyzed by the enzyme cholesterol 7α-hydroxylase, encoded by the

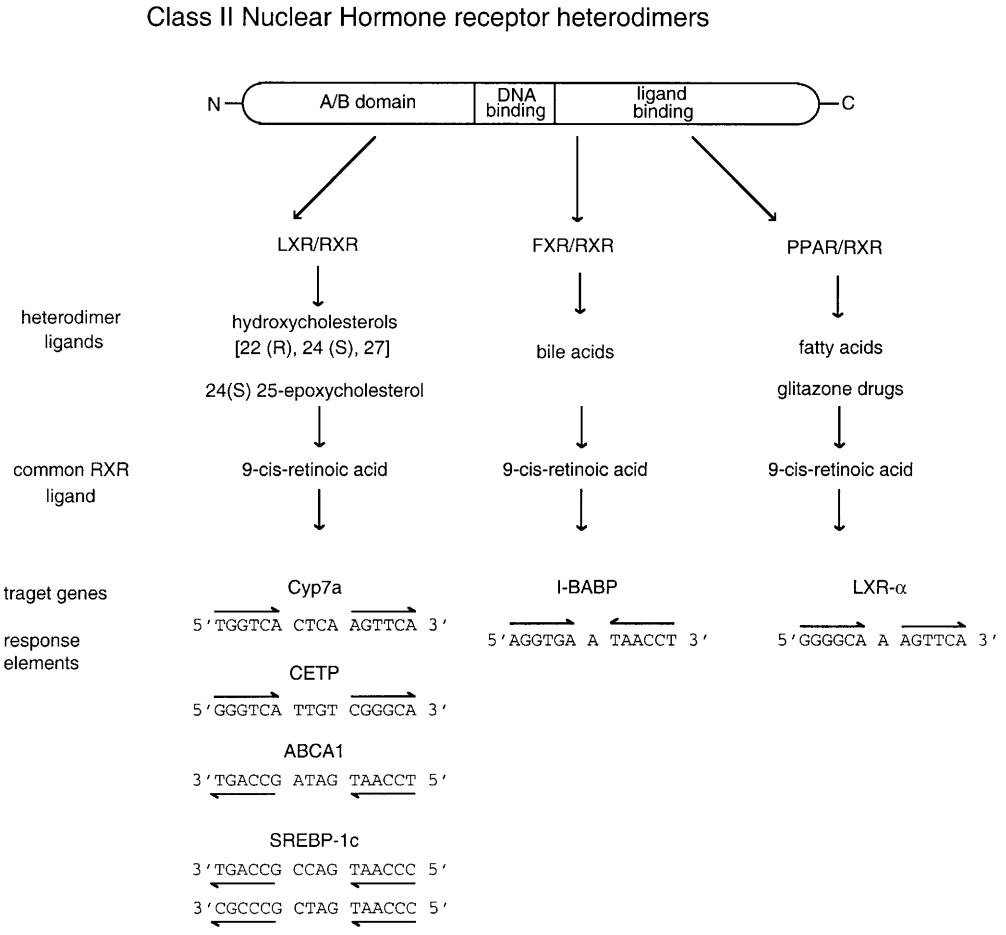


Fig. 1 Nuclear hormone receptors involved in cholesterol homeostasis. *Top* Diagram of key structural features defining the nuclear hormone family. These include the amino-terminal A/B domain that has transcriptional activation elements, the central DNA binding domain, and the carboxy-terminal ligand binding domain. *Middle* Nuclear hormone receptors involved in lipid metabolism: the liver X receptor (*LXR*), the farnesoid X receptor (*FXR*), and the peroxisome proliferator-activated receptor (*PPAR*) heterodimerize with the retinoid X receptor (*RXR*) as a common partner. The respective heterodimers are activated by their cognate ligands, hydroxycholesterols, bile acids, or fatty acids, respectively. *Bottom* Activated heterodimers bind response elements in the promoter regions of target genes. *ABCA1* ATP cassette binding protein A1; *CETP* cholesteryl ester transfer protein; *SREBP-1c* sterol response element binding protein 1c; *I-BABP* ileal bile acid binding protein

Cyp7a gene. Analysis of Cyp7a null mice revealed profound defects in bile acid metabolism leading to a high mortality rate soon after birth [13]. Furthermore, an alternative to the neutral pathway (the acidic pathway) was uncovered in the Cyp7a null mice which is initiated by oxidation of the 27th position in the side chain of cholesterol by the activity of Cyp27 [14]. The generated 27-hydroxycholesterol is then a substrate for 7α-hydroxylase action encoded by a separate gene, called Cyp7b [14] eventually leading to the production of chenodeoxycholic acid. (For more in depth reviews on oxysterol and bile acid metabolism see [15, 16, 17].)

The intimate catabolic relationship between cholesterol and bile acids is further controlled through both feedforward and negative feedback relations that help maintain homeostasis in the face of variable dietary loads of cholesterol. During dietary cholesterol excess, murine species increase the catabolism of cholesterol to bile acids in part by up-regulating the expression of Cyp7a. This increased expression was found to be a transcriptional event driven by the orphan nuclear hormone receptor LXR-α [6, 7]. The induction was found to be direct in that the Cyp7a promoter contained an LXR response element and was transactivated by LXR/RXR heterodimers in promoter assays (Fig. 1B). These observations fit with work showing that LXR receptors are bound and activated by oxysterols arising from oxidation of the cholesterol side arm [22(R)-hydroxycholesterol, 24(S)-hydroxycholesterol, 24(S),25-epoxycholesterol] [6, 7, 8]. More recently 27-hydroxycholesterol generated by the activity of Cyp27 has also been suggested to be a ligand for LXR [18]**.** This is of interest since Cyp27 activity is involved in both the neutral and alternative pathways of bile acid production (Fig. 2) and may also be involved in generating LXR signaling activity in nonhepatic tissues. Thus it appears that the oxysterols can act as small molecule sensors of whole-body cholesterol levels and thus alter gene transcription through LXR/RXR dependent pathways.

Mice null for LXR-α dramatically demonstrated the physiological importance of this hypothesis [19]. Although outwardly normal and fertile when fed a low fat, standard chow diet, the LXR null mice accumulated profound levels of liver cholesterol when fed a diet rich in cholesterol. This accumulation eventually leads to hepatic toxicity (Table 1). Significantly, any level of cholesterol in the diet beyond that supplied by endogenous synthesis caused cholesterol accumulation in the liver of these mice, indicating that LXR-α is a critical sensor for dietary cholesterol loads [19]. As would be predicted, the molecular phenotype of the LXR-α null animals involved an inability to increase bile acid production

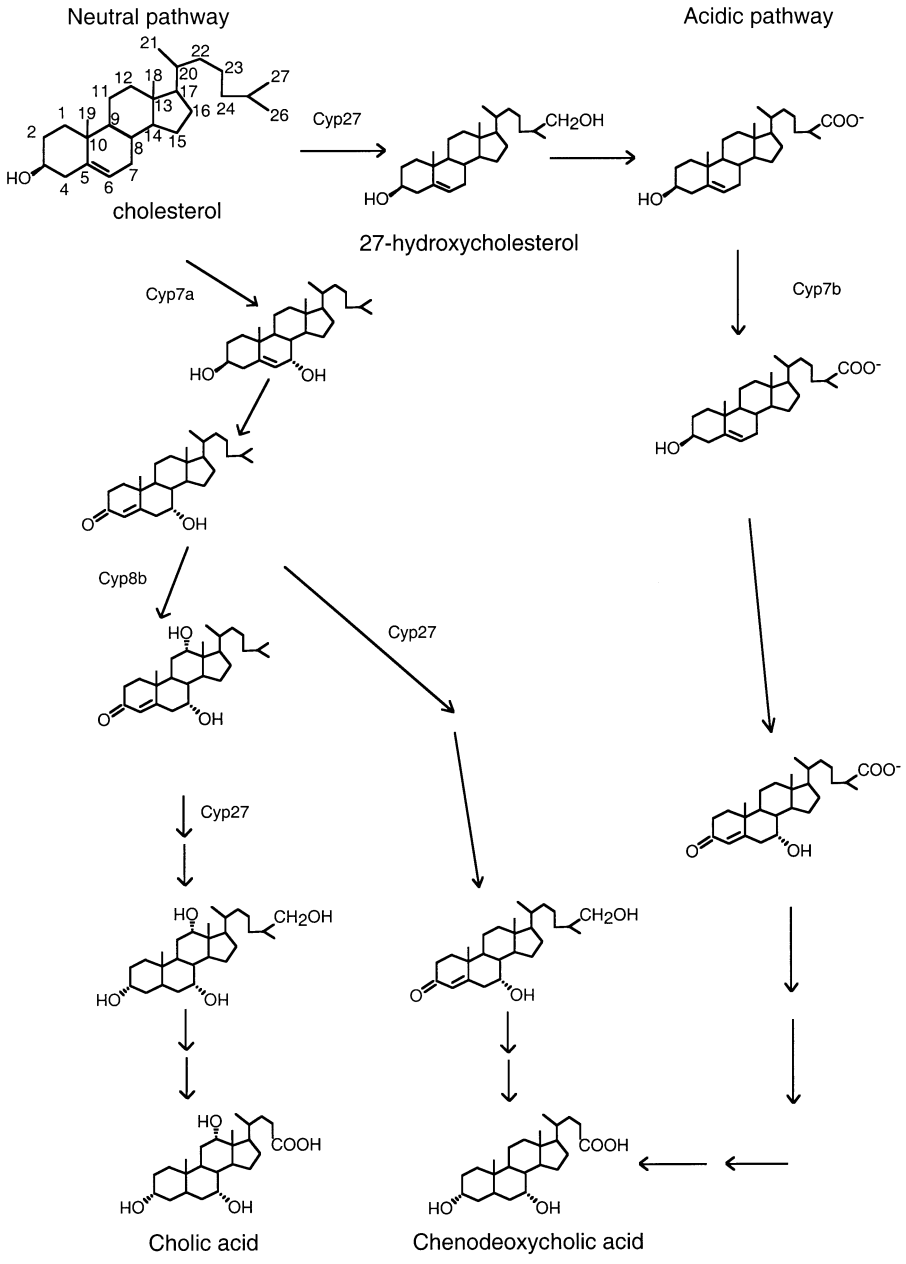


Fig. 2 Catabolism of cholesterol to bile acids. Cholesterol (*upper left corner*) is converted to the primary bile acids cholic acid and chenodeoxycholic acid by both neutral and acidic pathways. Shown are key enzymatic transformations carried out by the cytochrome P-450 enzymes encoded by the Cyp7A, Cyp7B, and Cyp8b loci that are differentially regulated by LXR and FXR activity. Hydroxylation of the 27th position of cholesterol or other intermediates occurs in both the neutral and acid pathways and is of importance since 27-oxysterols may be endogenous ligands for LXR. (Adapted from [16, 17])

through the up-regulation of Cyp7a. Thus a variety of both molecular and physiological lines of evidence have established that LXR-α and Cyp7a are part of a feedforward network for the conversion of cholesterol to bile acids.

In an elegant symmetry to the feedforward induction of bile acid synthesis, a negative regulatory loop has also been uncovered for the repression of the Cyp7a locus and the production of bile acids. Again, nuclear hormone receptors and small molecule sensors play a prominent role in this regulatory network. Here it is the bile acids themselves that interact with FXR, another nuclear hormone receptor that heterodimerizes with RXR [20]. Although initial studies found that FXR can be activated by high concentrations of farnesol, an isoprene metabolite of mevalonate [21], more recent studies have shown that physiological levels of bile acids bind activate FXR [9, 10, 12]. Activated FXR was found to mediate the bile acid repression of the Cyp7a promoter [9].

Furthermore, FXR appears to be responsible for the induction of ileal bile acid binding protein (I-BABP) in enterocytes since an FXR response element with an inverted orientation of the binding half sites is present in the promoter of the I-BABP gene (Fig. 1) [11]. Thus it was suggested that FXR acts as a sensor of elevated bile acid levels and represses bile acid synthesis in a negative feedback loop while at the same time increasing bile acid enteric/portal recirculation. Targeted disruption of FXR in mice confirmed a critical role for the receptor in bile acid homeostasis [22]. On a standard diet the mice

Table 1 Key nuclear hormone receptors and ABC transporters regulating cholesterol homeostasis and their phenotypes in mice and humans when mutated (*PFIC* progressive familial intrahepatic cholestasis)

Mutated loci	Gene family	Phenotype	Reference
Mouse knock-out models			
LXR-α	Nuclear hormone receptor	Liver accumulation of cholesterol and proatherogenic lipoprotein profile, lack of Cyp7a induction	19
FXR	Nuclear hormone receptor	Increased serum bile acids and proatherogenic lipoprotein profile, lack of SPGP/BSEP and I-BABP expression, loss of negative feedback regulation of bile acid synthesis	22
Mdr2	ABC transporter	Hepatotoxicity, lack of phosphatidylcholine and cholesterol in bile	27
ABCA1	ABC transporter	Extremely low serum HDL and apolipoprotein A-I levels, splenomegaly	66, 67, 68, 69
SPGP/BSEP	ABC transporter	Nonprogressive but persistent intrahepatic cholestasis, increased cholesterol and phospholipid in bile	31
Human familial diseases			
MDR3 (homologue of Mdr2)	ABC transporter	PFIC with defective bile salt secretion and high serum γ-glutamyltransferase	70
SPGP/BSEP	ABC transporter	PFIC with defective bile salt secretion, normal serum cholesterol and γ-glutamyltransferase	30
ABCA1	ABC transporter	Tangier disease: low serum HDL and apolipoprotein A-I levels, splenomegaly, peripheral neuropathy	36, 37, 38, 39, 40
ABCG5, ABCG8	ABC transporter	Sitosterolemia: high serum sitosterol and cholesterol, tuberous xanthomas, accelerated atherosclerosis, premature coronary artery disease	53, 54

were again outwardly normal and fertile. In contrast, on a diet supplemented with 1% cholic acid, the FXR null mice exhibited a profound wasting phenotype that included hypothermia and loss of adipose tissue. Bile acid homeostasis was disrupted in these mice, with the defect localizing at the level of hepatic uptake of bile acids from the blood and possibly hepatic canalicular secretion. At the molecular level, loss of FXR ablated the down-regulation of the Cyp7a and Cyp8b genes in response to dietary cholic acid, likely through effects on the expression of LXR-α and another orphan nuclear receptor, small heterodimeric partner (SHP) 1. In this interaction the regulation of bile acid homeostasis has additional complexities in that SHP-1 does not contain a conventional nuclear hormone DNA binding domain, but it is capable of heterodimerizing with other nuclear hormone receptors, leading to repressive transcriptional effects [23]. Thus in the FXR null mouse loss of SHP expression results in loss of its repressive activity on liver receptor homologue (LRH) 1, another orphan nuclear receptor that is a known positive regulator of Cyp7a expression [24]. In summary, a variety of evidence has shown that FXR represents the major bile acid sensor and that the transcriptional network controlled by FXR appears to antagonize LXR activity (Fig. 3B).

ABC transporters of the MDR/TAP subfamily and bile acid trafficking

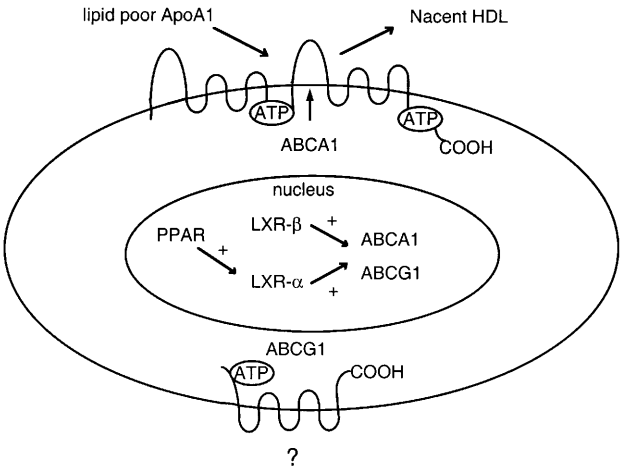
Homeostatic regulation of the cholesterol-bile acid network extends beyond transcriptional control of synthesis and catabolism. Evidence gathered since the early 1990s increasingly points to members of the ABC transporter superfamily as important players in whole-body cholesterol homeostasis [25]. It is the ability of ABC transporters to couple ATP hydrolysis to the movement of cholesterol and bile acids out of cells that has been conclusively tied to the maintenance of cholesterol plasma levels and bile secretion.

This causal link was first uncovered by investigations into the normal physiological role of the multidrug resistance (MDR) class of ABC transporters. The term MDR arises from the ability of this subfamily of transporters when overexpressed in cells to impart a broad spectrum resistance to anticancer agents [26]. However, mice with homozygous null mutations in the mdr2 locus were found to have a profound defect in secretion of phosphatidylcholine and cholesterol into bile [27]. In this mouse model the loss of Mdr2 expression only leads to mild liver disease. In contrast, in humans mutations in the Mdr2 homologue (MDR3) are characterized by a more severe form of liver disease, progressive intrahepatic cholestasis, which may be due to the increased hydrophobic character of human bile acids (Table 1). Mechanistically, cell free assays have indicated Mdr2 couples ATP hydrolysis to the flipping of phosphatidylcholine in the lipid bilayer [28]. It is thought that this activity, when localized to canalicular membranes of hepatocytes, effluxes phosphatidylcholine which, along with cholesterol and bile acids, form micelles within the canalicular space (Fig. 3B).

Along with lipid efflux into bile additional ABC transporters are directly involved in bile acid transport

A

Macrophage efflux of cholesterol and phospholipid from peripheral tissues



B

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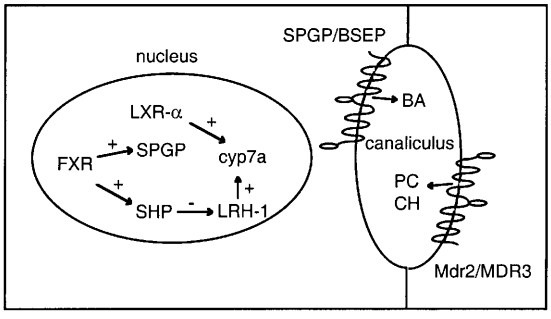
Hepatocyte efflux of bile acids, phospholipid and cholesterol into the canalicular space



C

Proposed pathway of enterocyte efflux of cholesterol and plant sterols into the intestinal space. Also depicted is bile acid uptake for recircularization

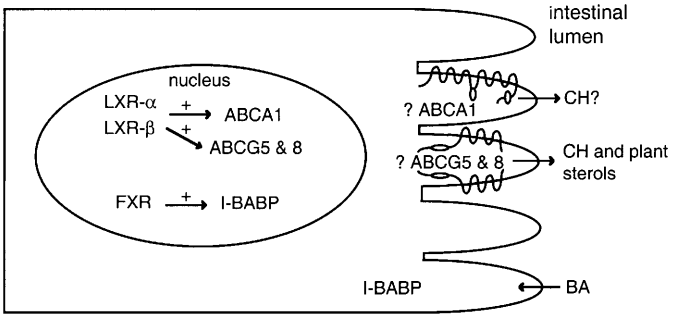


Fig. 3A–C Regulation of cholesterol and bile acid homeostasis in macrophages, hepatocytes, and enterocytes. **A** Macrophage efflux of cholesterol and phospholipid from peripheral tissues. In macrophages LXR-α and LXRβ act to up-regulate expression of ABCA1 and ABCG1 with PPAR activity (α, β, γ) playing an indirect role by stimulating LXR-α expression. ABCA1, a multispanning transmembrane protein, couples the hydrolysis of ATP to the acquisition of lipid by apolipoprotein A-I, forming nascent HDL. The exact activity of ABCG1 is unknown. **B** Hepatocyte efflux of bile cells, phospholipid, and cholesterol into the canicular space. In the hepatocyte LXR activity increases Cyp7A expression to increase bile acid production. FXR counters this effect by driving the expression of SHP-1 a nuclear hormone that antagonizes the positive regulation of Cyp7A by LRH-1. FXR also positively regulates SPGP/BSEP. This, in concert with Mdr2/MDR3, results in the efflux of bile acids and phosphotidylcholine into the canalicular space. The activity of both ATP transporters also influences the secretion of cholesterol into bile. **C** Proposed pathway of enterocyte efflux of cholesterol and plant sterols into the intestinal space; also depicted is bile acid uptake for recirculation. In the enterocyte LXR-α and LXR-β activity increases the expression of ABCA1 and likely also ABCG5 and ABCG8, while FXR activity positively regulates I-BABP, a cytosolic factor involved in the hepatic/portal recircularization of bile acids. It is hypothesized that ABCG5 and ABCG8, and perhaps ABCA1 as well, are involved in the efflux of cholesterol and other sterols into the intestinal lumen. This has yet to be experimentally verified

across the canilicular membrane. Sister of P-glycoprotein (SPGP, also known as bile salt export pump, BSEP) is another member of the MDR/Tap subfamily of ABC transporters [4]. Gerloff et al. [29] suggested that SPGP is the major canalicular BSEP of mammalian cells since its overexpression in *Xenopus* oocytes induced efflux of taurocholate, the preferred bile acid effluxed by isolated rat livers. In addition, SPGP is expressed almost exclusively on the canalicular microvilli, giving additional support for this hypothesis [29]. The recent mapping of the locus for progressive familial intrahepatic cholestasis, a condition characterized by early infancy liver disease and reduced bile flow, to the SPGP locus confirms the critical role of this transporter in bile acid efflux [30]. In mice the loss of SPGP expression produced a less severe phenotype than in humans, suggesting that mice have a more robust alternative pathway for the secretion of multiply hydroxylated bile acids [31]. Interestingly, however, the SPGP null mice show greatly increased levels of cholesterol and phospholipid in the bile, a finding that again points to the complex relationship between bile acid secretion and cholesterol homeostasis. In support of this tight linkage, in the FXR null mouse SPGP mRNA levels were reduced both at baseline and when mice were fed a diet rich in cholic acid [22]. The loss of SPGP expression in the FXR null mice accords well with the hypothesis that both FXR and SPGP are part of a feedforward regulatory loop for the hepatic-portal trafficking of bile acids. Thus FXR activity in the liver works during a scarcity of dietary cholesterol to down-regulate the conversion of cholesterol to bile acids, while up-regulating the expression of SPGP to increase bile acid but not cholesterol secretion into the bile. In addition to up-regulating expression of SPGP in the liver, FXR acts to increase expression of I-BABP in the small intestine, allowing increased ileal uptake and portal recirculation of bile acids [22]. The net effect of this action is thought to maximize the extraction of lipids from ingested food.

ABCA full transporters and ABCG half transporters control plasma HDL levels and cholesterol efflux

As with bile acids, control of cholesterol trafficking in individual cells, as well as gut tissues, has now been shown to be affected by the activity of ABC transporters. In peripheral tissues high-density lipoproteins (HDL) are believed to facilitate the removal of cholesterol from cells and then transport the sterol back to the liver where it can be reused or catabolized and secreted into the bile. It is in the performance of this task that HDL levels are thought to represent a measure of the flux of cholesterol through this reverse transport pathway, and they have long been known to have a strong inverse relationship to the risk of cardiovascular disease [32]. In the rare genetic disorder called Tangier disease [33] patients have little or no circulating HDL, build up cholesterol esters in peripheral tissues, and lack the capacity to efflux cholesterol to lipid poor HDL or its major apoprotein, apolipoprotein A-I [34, 35].

As with the bile acid transporters, mapping studies have again identified members of the ATP transported superfamily as key gatekeepers for the movement of cholesterol out of cells. In the case of Tangier disease several groups have recently reported that mutations in ABCA1 are causally linked to the disease [36, 37, 38, 39, 40]. In heterozygotes HDL levels and cholesterol efflux activity are at intermediate levels relative to wild-type and homozygous null conditions [41]. These findings indicated that HDL levels and cholesterol efflux activity are tightly linked, and that both are critically dependent upon ABCA1 function.

As in the case of Mdr2 and SPGP, ABCA1 is a full transporter with one open reading frame encoding a tandem array of two six transmembrane cassettes and two nucleotide binding domains (Fig. 3A). However, ABCA1 contains two additional hydrophobic segments that provide defining characteristics for inclusion into the unique A class of ABC transporters. One of the hydrophobic segments resides at the very amino-terminus of the open reading frame and has signal-anchor activity that drives the extracellular disposition of a large loop in the first 6-transmembrane cassette [42]. In addition to the signal anchor sequence, ABCA1 is essentially bisected by an additional hydrophobic sequence. These amino acids have been modeled as forming a hairpin loop at the lipid bilayer [43, 44]. However, recent topological studies on ABCR (ABCA4), a close homologue of ABCA1, suggests that the central hydrophobic domain also traverses the lipid bilayer leading to the extracellular disposition of a second loop of approximately 280 amino acids (Fig. 3A) [45]. The possibility that ABCA1 has two very large extracellular loops is of interest because a significant number of missense mutations associated with the Tangier phenotype fall within these loops, both of which were previously modeled as being intracellular domains [36, 37, 38, 40, 46]. These loops could provide an important structure for the ABCA1 interactions with extracellular cholesterol acceptors. Mechanistically, when ABCA1 is transfected into cells, its expression promotes cellular binding to the major apolipoprotein of HDL, apolipoprotein A-I, which can be directly cross-linked to ABCA1 [47, 48]. As yet it is still unclear how this close association between apolipoprotein A-I and ABCA1 relates to the transfer of lipid to the apoprotein [49]. However, recent evidence suggests that, as with the MDR transporters, ABCA1 is flipping phospholipid within the bilayer and does not directly interact with cholesterol [50]. These important questions regarding the relationship of apolipoprotein A-I binding to ABCA1 and the mechanism of cholesterol efflux are in need of additional clarification.

Other ABC transporters may also be involved in actively extruding cholesterol from cells. Members of the ABCG class appear to be possible candidates for this role by two lines of evidence. First, as with ABCA1, ABCG1 in macrophages is induced by sterol loading and

treatment with hydroxycholesterols [51, 52]. Direct evidence for the participation of novel G class transporters in the extrusion of cholesterol has emerged from mapping studies of the disease sitosterolemia [53, 54]. Sitosterolemia is an autosomal recessive lipid dystrophy characterized by elevated plasma sterol levels. The elevated plasma sterol levels appear to arise from a defect in intestinal handling of dietary sterols, as patients with the disorder have strikingly elevated plasma levels of the diet-derived plant sterol, sitosterol. Mutations in two ABCG class transporters ABCG5 and ABCG8 were identified in individuals affected with sitosterolemia [53]. Since sitosterol is found at only trace amounts in the plasma of normal individuals, it was proposed that these ABCG class transporters act to extrude sterols back into the intestine or bile from the apical surfaces of enterocytes and hepatocytes (Fig. 3B, C). The finding of mutations in either ABCG5 or ABCG8 (but, to date, not both) in patients with sitosterolemia also suggests that these half transporters act as heterodimers. Such a hypothesis is intriguing in light of the close genomic proximity between the G5 and G8 loci. The ABCG5 and ABCG8 open reading frames are in a head-to-head disposition, suggesting that these genes are coordinately regulated by common genetic control sequences, and that they arose from the inverted duplication of an ancestral ABC transporter [53].

Nuclear hormone stimulation of reverse cholesterol transport

Although a mechanistic understanding of the role ABCA1 plays in the transfer of lipid to apolipoprotein A-I is as yet incomplete, evidence reported within the past year clearly indicates that ABCA1 expression and cholesterol efflux is tightly regulated at the transcriptional level. Prior to the association of ABCA1 with the Tangier phenotype it was known that sterol loading of normal fibroblasts, or cAMP treatment of mouse macrophage lines, potently stimulates cellular efflux of cholesterol [55]. Subsequent studies have demonstrated that sterol loading and cAMP treatment also induce ABCA1 mRNA levels [56, 57]. Interestingly, removal of cAMP results in a rapid loss of the induced ABCA1 protein indicating that, at least in the macrophage lines, ABCA1 protein is rapidly turned over [48]. Whether protein stability represents an in vivo point of regulatory control for ABCA1 activity has yet to be addressed. However, it is now increasingly clear that cholesterol efflux and ABCA1 activity are transcriptionally controlled by nuclear hormone signaling pathways.

Several lines of evidence have demonstrated that ABCA1 transcription is directly induced by LXR/RXR heterodimers. Costet et al. [58] reported that 22(R)-hydroxycholesterol and 9-*cis*-retinoic acid, LXR and RXR ligands respectively, induced expression of ABCA1. Using a luciferase reporter assay they showed the induction was direct and depended upon an LXR response motif in the human promoter proximal to a newly identified upstream exon in the ABCA1 locus (Fig. 1). A nearly contemporaneous report by Repa et al. [59] confirmed the physiological importance of LXR/RXR transcriptional control of whole-body cholesterol homeostasis and ABCA1 expression. Mice treated with the RXR agonist LG268 showed a dramatic decrease in the absorption of dietary cholesterol. This response was correlated with a large decrease in liver cholesterol and a more modest increase in the level of circulating HDL. A significant portion of the rexinoid inhibition of dietary cholesterol absorption could be attributed to the alteration in the bile acid pool size and composition. Rexinoid induction of ABCA1 was put forward as a mechanism to explain the dietary inhibition not accounted for by the altered bile acid pool. Interestingly, in addition to LXR/RXR induction of ABCA1 in isolated peritoneal macrophages, ABCA1 mRNA was strongly induced by RXR and LXR specific agonists in the small intestine [59]. This finding led to the proposal that, in addition to the accepted role of ABCA1 in mediating cholesterol efflux from peripheral tissues for catabolism in the liver, ABCA1 also acts in the apical membranes of enterocytes to efflux cholesterol back into the intestinal lumen, thereby directly inhibiting dietary absorption of cholesterol (Fig. 3B). However, evidence for direct ABCA1 mediated sterol transport into the gut was not provided, and two recent reports have challenged this view of the role of ABCA1 in gut sterol metabolism. Drobnik et al. [60], using a dual stable isotope method to measure intestinal cholesterol absorption, actually found that ABCA1 deficient mice had reductions in cholesterol absorption with enhanced fecal loss of neutral sterols. Groen and colleagues [61] found that ABCA1 deficiency had no effect on hepatic cholesterol and phospholipid content in mice fed low or high cholesterol diets, and that fecal excretion of neutral and acidic sterols were similar in the groups with and without functioning ABCA1 protein. Thus the role of ABCA1 in the gut remains uncertain, and the impact of the LXR activators on cholesterol absorption may eventually be ascribed to the regulation of other lipid transporters. It is also important to remember that mice and humans differ in important ways in their sterol metabolism, and that findings in the ABCA1 deficient mice may or may not mimic the results that one would find in patients with Tangier disease.

The capacity of LXR signaling to up-regulate ABCA1 expression and apo A-I mediated efflux of cholesterol was confirmed by Venkateswaren et al. [62] This group also showed that the stimulation of efflux was ABCA1 dependent, as the effect of LXR/RXR ligands was lost in Tangier fibroblasts with known mutations in ABCA1. Interestingly, two features of ABCA1 regulation by LXR/RXR signaling are distinctive, relative to the LXR/RXR regulation of Cyp7a and bile acid metabolism. First, LXR/RXR regulation of ABCA1 is most prominent in nonhepatic tissues (intestine and macrophages) whereas the high basal expression of ABCA1 mRNA in the liver is not modulated by LXR/RXR acti-

vation [59]. Second, as opposed to the regulation of Cyp7a, which is dependent only upon the LXR-α isoform, regulation of ABCA1 in macrophages appears to involve both the α and (the more ubiquitously expressed) β isoforms of LXR [59].

As with LXR control of bile acid metabolism, regulation of ABCA1 and cholesterol efflux appears to have additional complexities. Here the peroxisome proliferator activated receptor (PPAR) class of nuclear hormone receptors may also participate in a feedforward mechanism, up-regulating ABCA1 and reverse cholesterol transport. PPARs derive their name from early work which showed that one form of these transcription factors (now called PPARα) is a target for compounds that induce proliferation of peroxisomes in the liver. PPARα, PPARγ, and PPARδ (also referred to as PPARβ, NUC1, or FAAR) comprise the group. As with other nuclear hormone receptors, PPARs have a canonical domain structure that includes an incompletely characterized N-terminal region that is thought to participate in *trans*-activation functions, followed by a DNA binding domain, and a carboxy terminus that is responsible for ligand binding and receptor dimerization (Fig. 1). PPARs bind to DNA sequences known as PPAR response elements and interact with other coactivator molecules to regulate gene transcription. PPARγ has been the most thoroughly studied of the isoforms and has been shown to play a critical role in adipocyte differentiation. It has also been implicated in other pathways that are potentially relevant to the biology of cancer, diabetes, and atherosclerosis (see below and [63] for more details).

PPAR signaling first came to prominence in relation to cholesterol trafficking when activators of PPARγ were found to induce expression of the class B scavenger receptor CD36 [64]. This work raised concerns over the clinical use of the thiazolidinedione drug class (PPARγ activators) in the treatment of diabetes, as a PPARγ induced expression of CD36 would be predicted to increase cholesterol accumulation in arterial wall macrophages. However, more recent work indicates that this concern is probably unwarranted, as PPARγ activators have now been shown to have multiple lipid regulating activities that influence not only the uptake but also the efflux of cholesterol from macrophages [65, 66]. These studies indicate that activation of PPARγ divergently regulates the two major scavenger receptors for modified (e.g., oxidized) LDL uptake, CD36 and scavenger receptor A, resulting in no appreciable increase in cholesterol uptake [65]. Moreover, PPARγ activation also resulted in the up-regulation of ABCA1 expression, thereby stimulating cholesterol efflux. PPARα, the target of the fibrate drugs often used to treat patients with hyperlipidemia, was shown to share this inductive action [67].

Contemporaneously Chawla et al. [68] reported similar results and added mechanistic details as to how PPAR activation modulates efflux. It was found that the LXR-α promoter contains a PPAR response element with specificity for the γ isoform (Fig. 1). In PPARγ null macrophages it was found that LXR-α expression was reduced along with that of ABCA1 and ABCG1, and that these macrophages had a diminished capacity to efflux cholesterol. In an elegant experiment, this group transplanted PPAR-γ null bone marrow into atherosclerosis-prone apolipoprotein E null mice and found that this increased atherosclerotic lesion development, suggesting a net protective action of PPARγ signaling through the stimulation of reverse cholesterol transport. A third report also confirms that PPAR activation modulates reverse cholesterol transport, but found that a PPAR-δ specific agonist was most efficient in increasing cholesterol efflux and improving the lipoprotein profiles in obese, hyperglycemic rhesus monkeys [69]. The combined results indicate that PPAR mediated transcriptional activity has a positive impact on circulating lipid profiles and cholesterol metabolism such that the risk for development of atherosclerotic disease is reduced. Further details about the impact of PPAR-γ activation on macrophage activation and atherosclerosis can be found in a recent review of that topic by Moore et al. [70].

Conclusions

Over the past few years the field of lipid metabolism has witnessed the discovery of new cell biological pathways that contribute to the control of cellular and organismal cholesterol homeostasis. In this review we summarize the work that links these pathways to the nuclear hormone receptors and the ABC transporters that are targets of nuclear hormone regulation. At this juncture our understanding of the transcriptional mechanisms that regulate the expression of the transporters that move lipids across plasma membranes is much further advanced than our knowledge of the transporter's actions themselves. For example, it is unclear whether ABCA1 and members of the ABCG class share common mechanistic features, and whether they represent two checkpoints in a common pathway for extruding cellular cholesterol. How the activity of either transporter results in cholesterol translocation remains an intriguing mystery. From a clinical viewpoint, the regulation of cholesterol transport by nuclear hormone receptors has generated great interest because pharmacological manipulation of this regulation could lead to new therapeutic modalities for important human diseases. At present, however, the available activators of perhaps the most intriguing class of nuclear hormone receptors for lipid regulation, the LXRs, also appear to stimulate unwanted lipid side effects, such as hypertriglyceridemia, perhaps through their activation of sterol binding proteins. Whether it will be possible to design therapeutic agents that selectively modulate the lipid pathways of interest through these receptors is a question that is likely to occupy the pharmaceutical industry for some time to come. While the lipid research community has been delighted to offer a home for these orphan receptors, the burgeoning scientific literature concerning their activity suggests that they have now been welcomed at many a laboratory door.

References

1. Brown MS, Goldstein JL (1986) A receptor-mediated pathway for cholesterol homeostasis. Science 232:34
2. Brown MS, Goldstein JL (1997) The SREBP pathway: regulation of cholesterol metabolism by proteolysis of a membrane-bound transcription factor. Cell 89:331
3. Mangelsdorf DJ, Thummel C, Beato M, Herrlich P, Schutz G, Umesono K, Blumberg B, Kastner P, Mark M, Chambon P, et al (1995) The nuclear receptor superfamily: the second decade. Cell 83:835
4. Klein I, Sarkadi B, Varadi A (1999) An inventory of the human ABC proteins. Biochim Biophys Acta 1461:237
5. Mangelsdorf DJ, Evans RM (1995) The RXR heterodimers and orphan receptors. Cell 83:841
6. Janowski BA, Willy PJ, Devi TR, Falck JR, Mangelsdorf DJ (1996) An oxysterol signalling pathway mediated by the nuclear receptor LXR alpha. Nature 383:728
7. Lehmann JM, Kliewer SA, Moore LB, Smith-Oliver TA, Oliver BB, Su JL, Sundseth SS, Winegar DA, Blanchard DE, Spencer TA, Willson TM (1997) Activation of the nuclear receptor LXR by oxysterols defines a new hormone response pathway. J Biol Chem 272:3137
8. Janowski BA, Grogan MJ, Jones SA, Wisely GB, Kliewer SA, Corey EJ, Mangelsdorf DJ (1999) Structural requirements of ligands for the oxysterol liver X receptors LXRalpha and LXRbeta. Proc Natl Acad Sci USA 96:266
9. Makishima M, Okamoto AY, Repa JJ, Tu H, Learned RM, Luk A, Hull MV, Lustig KD, Mangelsdorf MJ, Shan B (1999) Identification of a nuclear receptor for bile acids. Science 284: 1362
10. Parks DJ, Blanchard SG, Bledsoe RK, Chandra G, Consler TG, Kliewer SA, Stimmel, Willson TM, Zavacki AM, Moore DD, Lehmann JM (1999) Bile acids: natural ligands for an orphan nuclear receptor. Science 284:1365
11. Grober J, Zaghini I, Fujii H, Jones SA, Kliewer SA, Willson TM, Ono T, Besnard P (1999) Identification of a bile acid-responsive element in the human ileal bile acid-binding protein gene. Involvement of the farnesoid X receptor/9-cis-retinoic acid receptor heterodimer. J Biol Chem 274:29749
12. Wang H, Chen J, Hollister K, Sowers LC, Forman BM (1999) Endogenous bile acids are ligands for the nuclear receptor FXR/BAR. Mol Cell 3:543
13. Ishibashi S, Schwarz M, Frykman PK, Herz J, Russell DW (1996) Disruption of cholesterol 7alpha-hydroxylase gene in mice. I. Postnatal lethality reversed by bile acid and vitamin supplementation. J Biol Chem 271:18017
14. Schwarz M, Lund EG, Setchell KD, Kayden HJ, Zerwekh JE, Bjorkhem I, Herz J, Russell DW (1996) Disruption of cholesterol 7alpha-hydroxylase gene in mice. II. Bile acid deficiency is overcome by induction of oxysterol 7alpha-hydroxylase. J Biol Chem 271:18024
15. Schroepfer GJ Jr (2000) Oxysterols: modulators of cholesterol metabolism and other processes. Physiol Rev 80:361
16. Russell DW, Setchell KD (1992) Bile acid biosynthesis. Biochemistry 31:4737
17. Repa JJ, Mangelsdorf DJ (2000) The role of orphan nuclear receptors in the regulation of cholesterol homeostasis. Annu Rev Cell Dev Biol 16:459
18. Fu X, Menke JG, Chen Y, Zhou G, MacNaul KL, Wright SD, Sparrow CP, Lund EG (2001) 27-Hydroxycholesterol is an endogenous ligand for LXR in cholesterol-loaded cells. J Biol Chem 14:14
19. Peet DJ, Turley SD, Ma W, Janowski BY, Lobaccaro JM, Hammer RE, Mangelsdorf DJ (1998) Cholesterol and bile acid metabolism are impaired in mice lacking the nuclear oxysterol receptor LXR alpha. Cell 93:693
20. Russell DW (1999) Nuclear orphan receptors control cholesterol catabolism. Cell 97:539
21. Forman BM, Goode E, Chen J, Oro AE, Bradley DJ, Perlmann T, Noonan DJ, Burka LT, McMorris T, Lamph WW, et al (1995) Identification of a nuclear receptor that is activated by farnesol metabolites. Cell 81:687
22. Sinal CJ, Tohkin M, Miyata M, Ward JM, Lambert G, Gonzalez FJ (2000) Targeted disruption of the nuclear receptor FXR/BAR impairs bile acid and lipid homeostasis. Cell 102: 731
23. Seol W, Choi HS, Moore DD (1996) An orphan nuclear hormone receptor that lacks a DNA binding domain and heterodimerizes with other receptors. Science 272:1336
24. Goodwin B, Jones SA, Price RR, Watson MA, McKee DD, Moore LB, Galardi C, Wilson JG, Lewis MC, Roth ME, Maloney PR, Willson TM, Kliewer SA (2000) A regulatory cascade of the nuclear receptors FXR, SHP-1, and LRH-1 represses bile acid biosynthesis. Mol Cell 6:517
25. Borst P, Zelcer N, van Helvoort A (2000) ABC transporters in lipid transport. Biochim Biophys Acta 1486:128
26. Gottesman MM, Pastan I (1993) Biochemistry of multidrug resistance mediated by the multidrug transporter. Annu Rev Biochem 62:385
27. Smit JJ, Schinkel AH, Oude Elferink RP, Groen AK, Wagenaar E, van Deemter L, Mol CA, Ottenhoff R, van der Lugt NM, van Roon MA, et al (1993) Homozygous disruption of the murine mdr2 P-glycoprotein gene leads to a complete absence of phospholipid from bile and to liver disease. Cell 75:451
28. Ruetz S, Gros P (1994) Phosphatidylcholine translocase: a physiological role for the mdr2 gene. Cell 77:1071
29. Gerloff T, Stieger B, Hagenbuch B, Madon J, Landmann L, Roth J, Hofmann AF, Meier PJ (1998) The sister of P-glycoprotein represents the canalicular bile salt export pump of mammalian liver. J Biol Chem 273:10046
30. Strautnieks SS, Bull LN, Knisely AS, Kocoshis SA, Dahl N, Arnell H, Sokal E, Dahan K, Childs S, Ling V, Tanner MS, Kagalwalla AF, Nemeth A, Pawlowska J, Baker A, Mieli-Vergani G, Freimer NB, Gardiner RM, Thompson RJ (1998) A gene encoding a liver-specific ABC transporter is mutated in progressive familial intrahepatic cholestasis. Nat Genet 20:233
31. Wang R, Salem M, Yousef IM, Tuchweber B, Lam P, Childs SJ, Helgason CD, Ackerley C, Phillips MJ, Ling V (2001) Targeted inactivation of sister of P-glycoprotein gene (spgp) in mice results in nonprogressive but persistent intrahepatic cholestasis. Proc Natl Acad Sci U S A98:2011
32. Despres JP, Lemieux I, Dagenais GR, Cantin B, Lamarche B (2000) HDL-cholesterol as a marker of coronary heart disease risk: the Quebec cardiovascular study. Atherosclerosis 153: 263
33. Hoffman HN, Fredrickson DS (1965) Tangier disease (familial high density lipoprotein deficiency). Clinical and genetic features in two adults. Am J Med 39:582
34. Francis GA, Knopp RH, Oram JF (1995) Defective removal of cellular cholesterol and phospholipids by apolipoprotein A-I in Tangier disease. J Clin Invest 96:78
35. Rogler G, Trumbach B, Klima B, Lackner KJ, Schmitz G (1995) HDL-mediated efflux of intracellular cholesterol is impaired in fibroblasts from Tangier disease patients. Arterioscler Thromb Vasc Biol 15:683
36. 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, Hayden MR (1999) Mutations in ABC1 in Tangier disease and familial high-density lipoprotein deficiency. Nat Genet 22:336
37. Bodzioch M, Orso E, Klucken J, Langmann T, Bottcher A, Diederich W, Drobnik W, Barlage S, Buchler C, Porsch-Ozcurumez M, Kaminski WE, Hahmann HW, Oette K, Rothe G, Aslanidis C, Lackner KJ, Schmitz G (1999) The gene encoding ATP-binding cassette transporter 1 is mutated in Tangier disease. Nat Genet 22:347
38. Rust S, Rosier M, Funke H, Real J, Amoura Z, Piette JC, Deleuze F, Brewer HB, Duverger N, Denefle P, Assmann G

(1999) Tangier disease is caused by mutations in the gene encoding ATP-binding cassette transporter 1. Nat Genet 22:352
39. Lawn RM, Wade DP, Garvin MR, Wang X, Schwartz K, Porter JG, Seilhamer JJ, Vaughan AM, Oram JF (1999) The Tangier disease gene product ABC1 controls the cellular apolipoprotein-mediated lipid removal pathway. J Clin Invest 104: R25
40. Brousseau ME, Schaefer EJ, Dupuis J, Eustace B, Van Eerdewegh P, Goldkamp AL, Thurston LM, FitzGerald MG, Yasek-McKenna D, O'Neill G, Eberhart GP, Weiffenbach B, Ordovas JM, Freeman MW, Brown RH Jr, Gu JZ (2000) Novel mutations in the gene encoding ATP-binding cassette 1 in four Tangier disease kindreds. J Lipid Res 41:433
41. Brousseau ME, Eberhart GP, Dupuis J, Asztalos BF, Goldkamp AL, Schaefer EJ, Freeman MW (2000) Cellular cholesterol efflux in heterozygotes for tangier disease is markedly reduced and correlates with high density lipoprotein cholesterol concentration and particle size. J Lipid Res 41:1125
42. Fitzgerald ML, Mendez AJ, Moore KJ, Andersson LP, Panjeton HA, Freeman MW (2001) ATP-binding cassette transporter A1 contains an NH2-terminal signal anchor sequence that translocates the protein's first hydrophilic domain to the exoplasmic space. J Biol Chem 276:15137
43. Luciani MF, Denizot F, Savary S, Mattei MG, Chimini G (1994) Cloning of two novel ABC transporters mapping on human chromosome 9. Genomics 21:150
44. Becq F, Hamon Y, Bajetto A, Gola M, Verrier B, Chimini G (1997) ABC1, an ATP binding cassette transporter required for phagocytosis of apoptotic cells, generates a regulated anion flux after expression in Xenopus laevis oocytes. J Biol Chem 272:2695
45. Bungert S, Molday LL, Molday RS (2001) Membrane topology of the atp binding cassette transporter abcr and its relationship to abc1 and related abca transporters. identification of n-linked glycosylation sites. J Biol Chem 276:23539
46. Lapicka-Bodzioch K, Bodzioch M, Krull M, Kielar D, Probst M, Kiec B, Andrikovics H, Bottcher A, Hubacek J, Aslanidis C, Suttorp N, Schmitz G (2001) Homogeneous assay based on 52 primer sets to scan for mutations of the ABCA1 gene and its application in genetic analysis of a new patient with familial high-density lipoprotein deficiency syndrome. Biochim Biophys Acta 1537:42
47. Wang N, Silver DL, Costet P, Tall AR (2000) Specific binding of ApoA-I, enhanced cholesterol efflux, and altered plasma membrane morphology in cells expressing ABC1. J Biol Chem 275:33053
48. Oram JF, Lawn RM, Garvin MR, Wade DP (2000) ABCA1 is the cAMP-inducible apolipoprotein receptor that mediates cholesterol secretion from macrophages. J Biol Chem 275: 34508
49. Chambenoit O, Hamon Y, Marguet D, Rigneault H, Rosseneu M, Chimini G (2001) Specific docking of apolipoprotein A-I at the cell surface requires a functional ABCA1 transporter. J Biol Chem 276:9955
50. Wang N, Silver DL, Thiele C, Tall AR (2001) Atp-binding cassette transporter a1 (abca1) functions as a cholesterol efflux regulatory protein. J Biol Chem 276:23742
51. Klucken J, Buchler C, Orso E, Kaminski WE, Porsch-Ozcurumez M, Liebisch G, Kapinsky M, Diederich W, Drobnik W, Dean M, Allikmets R, Schmitz G (2000) ABCG1 (ABC8), the human homolog of the Drosophila white gene, is a regulator of macrophage cholesterol and phospholipid transport. Proc Natl Acad Sci U S A 97:817
52. Venkateswaran A, Repa JJ, Lobaccaro JM, Bronson A, Mangelsdorf DJ, Edwards PA (2000) Human white/murine ABC8 mRNA levels are highly induced in lipid-loaded macrophages. A transcriptional role for specific oxysterols. J Biol Chem 275:14700
53. Berge KE, Tian H, Graf GA, Yu L, Grishin NV, Schultz J, Kwiterovich P, Shan B, Barnes R, Hobbs HH (2000) Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters. Science 290:1771
54. Lee MH, Lu K, Hazard S, Yu H, Shulenin S, Hidaka H, Kojima H, Allikmets R, Sakuma N, Pegoraro R, Srivastava AK, Salen G, Dean M, Patel SB (2001) Identification of a gene, ABCG5, important in the regulation of dietary cholesterol absorption. Nat Genet 27:79
55. Smith JD, Miyata M, Ginsberg M, Grigaux C, Shmookler E, Plump AS (1996) Cyclic AMP induces apolipoprotein E binding activity and promotes cholesterol efflux from a macrophage cell line to apolipoprotein acceptors. J Biol Chem 271: 30647
56. Langmann T, Klucken J, Reil M, Liebisch G, Luciani MF, Chimini G, Kaminski WE, Schmitz G (1999) Molecular cloning of the human ATP-binding cassette transporter 1 (hABC1): evidence for sterol-dependent regulation in macrophages. Biochem Biophys Res Commun 257:29
57. Bortnick AE, Rothblat GH, Stoudt G, Hoppe KL, Royer LJ, McNeish J, Francone OL (2000) The correlation of ATP-binding cassette 1 mRNA levels with cholesterol efflux from various cell lines. J Biol Chem 275:28634
58. Costet P, Luo Y, Wang N, Tall AR (2000) Sterol-dependent transactivation of the ABC1 promoter by the liver X receptor/retinoid X receptor. J Biol Chem 275:28240
59. Repa JJ, Turley SD, Lobaccaro JA, Medina J, Li L, Lustig K, Shan B, Heyman RA, Dietschy JM, Mangelsdorf DL (2000) Regulation of absorption and ABC1-mediated efflux of cholesterol by RXR heterodimers. Science 289:1524
60. Drobnik W, Lindenthal B, Lieser B, Ritter M, Christiansen Weber T, Liebisch G, Giesa U, Igel M, Borsukova H, Buchler C, Fung-Leung WP, Von Bergmann K, Schmitz G (2001) ATP-binding cassette transporter A1 (ABCA1) affects total body sterol metabolism. Gastroenterology 120:1203
61. Groen AK, Bloks VW, Bandsma RH, Ottenhoff R, Chimini G, Kuipers (2001) Hepatobiliary cholesterol transport is not impaired in Abca1-null mice lacking HDL. J Clin Invest 108:843
62. Venkateswaran A, Laffitte BA, Joseph SB, Mak PA, Wilpitz DC, Edwards PA, Tontonoz P (2000) Control of cellular cholesterol efflux by the nuclear oxysterol receptor LXR alpha. Proc Natl Acad Sci U S A 97:12097
63. Rosen ED, Spiegelman BM (2001) Ppargamma: a nuclear regulator of metabolism, differentiation, and cell growth. J Biol Chem 276:37731
64. Tontonoz P, Nagy L, Alvarez JGA, Thomazy VA, Evans R (1998) PPARg promotes monocyte/macrophage differentiation and uptake of oxidized LDL. Cell 93:241
65. Moore KJ, Rosen ED, Fitzgerald ML, Randow F, Andersson LP, Altshuler D, Milstone DS, Mortensen RM, Spiegelman BM, Freeman MW (2001) The role of PPAR-gamma in macrophage differentiation and cholesterol uptake. Nat Med 7:41
66. Chawla A, Barak Y, Nagy L, Liao D, Tontonoz P, Evans RM (2001) PPAR-gamma dependent and independent effects on macrophage-gene expression in lipid metabolism and inflammation. Nat Med 7:48
67. Chinetti G, Lestavel S, Bocher V, Remaley AT, Neve B, Torra IP, Teissier E, Minnich A, Jaye M, Duverger N, Brewer HB, Fruchart JC, Clavey V, Staels B (2001) PPAR-alpha and PPAR-gamma activators induce cholesterol removal from human macrophage foam cells through stimulation of the ABCA1 pathway. Nat Med 7:53
68. Chawla A, Boisvert WA, Lee CH, Laffitte BA, Barak Y, Joseph SB, Liao D, Nagy L, Edwards PA, Curtiss LK, Evans RM, Tontonoz P (2001) A PPAR gamma-LXR-ABCA1 pathway in macrophages is involved in cholesterol efflux and atherogenesis. Mol Cell 7:161
69. Oliver WR Jr, Shenk JL, Snaith MR, Russell CS, Plunket KD, Bodkin NL, Lewis MC, Winegar DA, Sznaidman ML, Lambert MH, Xu HE, Sternbach DD, Kliewer SA, Hansen BC, Willson TM (2001) A selective peroxisome proliferator-activated receptor delta agonist promotes reverse cholesterol transport. Proc Natl Acad Sci U S A 98:5306
70. Moore KJ, Fitzgerald ML, Freeman MW: (2001) Peroxisome proliferator-activated receptors in macrophage biology: friend or foe? Curr Opin Lipidol 12:519