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REVIEW ARTICLE

Potential Therapeutic Agents That Target ATP Binding Cassette A1 (ABCA1) Gene Expression

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Abstract
The cholesterol efflux protein ATP binding cassette protein A1 (ABCA) and apolipoprotein A1 (apo A1) are key constituents in the process of reverse-cholesterol transport (RCT), whereby excess cholesterol in the periphery is transported to the liver where it can be converted primarily to bile acids for either use in digestion or excreted. Due to their essential roles in RCT, numerous studies have been conducted in cells, mice, and humans to more thoroughly understand the pathways that regulate their expression and activity with the goal of developing therapeutics that enhance RCT to reduce the risk of cardiovascular disease. Many of the drugs and natural compounds examined target several transcription factors critical for ABCA1 expression in both macrophages and the liver. Likewise, several miRNAs target not only ABCA1 but also the same transcription factors that are critical for its high expression. However, after years of research and many preclinical and clinical trials, only a few leads have proven beneficial in this regard. In this review we discuss the various transcription factors that serve as drug targets for ABCA1 and provide an update on some important leads.

1 Introduction

The ATP binding cassette A1 (ABCA1) efflux protein is a member of the ATP-dependent transport proteins. Upon binding to either lipid-free apolipoprotein (apo A1) or high-density lipoprotein (HDL), ABCA1 transports intracellular or membrane-associated cholesterol in a unidirectional manner out of the cell [1–3]. ABCA1 is expressed in many tissues and has been shown to be essential for the generation of nascent HDL and for cholesterol efflux in macrophage cells. Loss of ABCA1 in mice or in humans (as in Tangier's disease) results in extremely low plasma HDL levels and increases susceptibility to atherosclerosis [4–6]. Therefore, ABCA1 is a key partner in the process of reverse-cholesterol transport (RCT) and numerous preclinical and clinical trials have been carried out to safely enhance its expression and activity. Regulation of the ABCA1 gene is complex. Several intracellular signaling pathways that sense intracellular sterol levels, lipid metabolites, and retinoids regulate ABCA1 promoter activity, as do inflammatory cytokines [7–10]. Furthermore, ABCA1 expression is negatively regulated post-transcriptionally by several micro RNAs and by proteasome-mediated degradation. This review focuses on mechanisms associated with transcriptional regulation of ABCA1 gene expression and describe potential therapeutic agents that target ABC1 gene expression.

2 The ABC Family of Lipid Transporters

The ABC family of proteins is involved in lipid transport to various compartments within and out of cells. Most of these transporters contain two trans-membrane domains each consisting of six hydrophobic helical bundles and two ATP binding domains that hydrolyze ATP, providing the energy required to transport its substrate against a concentration gradient (Fig. 1). Sequence alignments have indicated that this family of proteins can be classified into seven subfamilies. ABCA1 is a cholesterol and phospholipid efflux protein that is mutated in Tangier's disease [4–6], while ATP binding cassette protein G1 (ABCG1) and ATP binding cassette protein B4 (ABCB4, also known as multidrug resistance 3) have been shown

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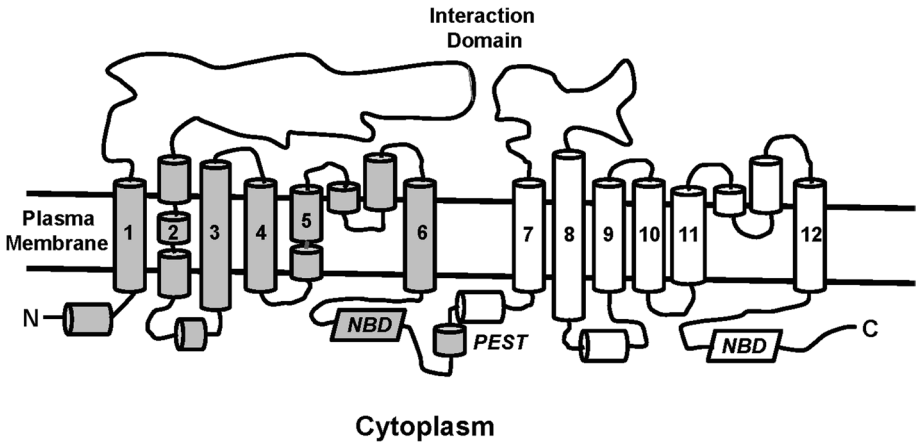

Fig. 1 ABCA1 protein structure and topology. Alpha helices forming transmembrane domains 1-12, extracellular and intracellular helices, nucleotide binding domains (NBDs), and a PEST (Proline, Glutamic acid, Serine, Threonine) domain are indicated. The NBDs bind and hydrolyze ATP driving the transport of cholesterol while ABCA1 protein degradation (half-life) is mediated in part through the PEST domain

to transport cholesterol and phospholipids (ABCG1) and phosphatidylcholine (ABCB4). The human ABCA1 gene, the founding member of the ABCA family [11], encodes a 254 kDa protein and is located on chromosome 9q31. The human ABCA1 gene has 50 exons and spans nearly 150 kbp [12]. The ABCA1 gene encodes two mRNA species: type L, which is expressed in the liver only, and type P, which is expressed in liver and peripheral tissues [7]. Type P ABCA1 mRNA is liver-X-receptor (LXR) -responsive while the type L ABCA1 mRNA is regulated by sterol-responsive element binding protein 2 (SREBP2) [7]. The ABCA1 protein is localized to the cell surface and has been shown to interact with other proteins on its intracellular interface, including the oxysterol receptor liver-X-receptor β (LXRβ [13].

3 The ABCA1 Gene and Atherosclerosis

Numerous studies suggest that ABCA1 is a key component of reverse-cholesterol transport (RCT) [1–3] (Fig. 2) and HDL synthesis in both hepatocytes and intestinal cells [14]. It is noteworthy that the de novo-produced HDL is more likely to have cardioprotective properties than HDL that has accumulated because of reduced clearance [15]. The ABCA1 gene is mutated in Tangier's disease and fibroblasts

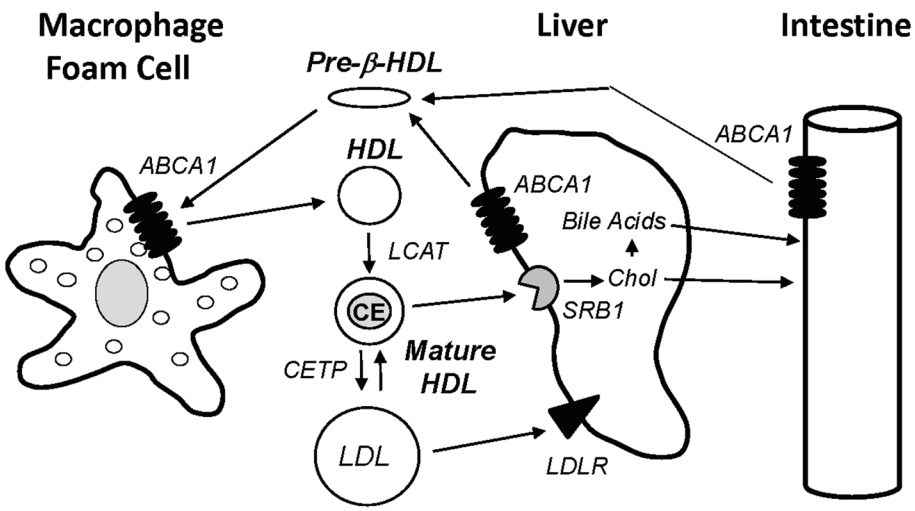

Fig. 2 Reverse-cholesterol transport. Apolipoprotein A-I is synthesized in the liver (primary site) and small intestine and is lipidated by ATP binding cassette A1 (ABCA1) to generate pre-β-high-density lipoprotein (pre-β-HDL). Pre-β-HDL binds ABCA1 and free-cholesterol is transferred, forming HDL. Lecithin-cholesterol acyltransferase (LCAT) esterifies some of the free cholesterol and these cholesterol esters (CE) form the core of the mature HDL particle. Some of the cholesterol is removed from the mature HDL particle and transferred to low-density lipoprotein (LDL) by cholesteryl ester transfer protein (CETP) in exchange for triglyceride. The LDL binds the low-density lipoprotein receptor (LDLR) and the cholesterol is released. The mature HDL particle can also bind scavenger receptor class B type 1 (SRB1), a cholesterol transfer protein that transfers cholesterol (Chol) into the liver. The cholesterol may be converted to bile acids, however both bile acids and cholesterol are transported to the small intestine via the gall bladder

from these patients have reduced cholesterol efflux capacity, extremely low HDL levels, and a higher incidence of cardiovascular disease [4–6]. Genetic studies have also demonstrated that certain ABCA1 gene variants predict the development of ischemic heart disease [16–19]. Furthermore, Frikke-Schmidt [20] demonstrated that several ABCA1 allele variants were predictive of heart disease in subjects enrolled in the Copenhagen City Heart Study. The authors genotyped 9,259 individuals from the general Danish population, examining the presence of six nonsynonymous single nucleotide polymorphisms (SNPs), and found that three of them (V771M, I883M, and E1172D) were the most important predictors of ischemic heart disease.

Obesity and metabolic syndrome are important risk factors for atherosclerosis [21, 22]. ABCA1 and ABCG1 are also expressed in white adipose tissue (WAT) and subcutaneous fat. Adipocytes contain more than 25% of the total cholesterol in the body [23], with 95% in the free form [24]. Obesity is associated with reduced HDL levels [25]. Furthermore, Choromanska et al. [26] demonstrated that plasma membrane-associated ABCA1 levels in WAT decreased significantly in obese individuals without metabolic syndrome whereas total ABCA1 levels were unchanged [26]. Plasma membrane-associated ABCG1 levels were also significantly decreased in obese women with metabolic syndrome, while total ABCG1 levels increased in WAT from obese individuals without metabolic syndrome [26]. These results suggest that obesity-associated adipocytes likely have decreased cholesterol efflux to HDL via ABCA1.

Intracellular cholesterol and triglyceride levels were higher in adipocytes of ABCA1-deficient mice on a high-fat, high-cholesterol diet [27]. As a result, the mice experienced decreased glucose tolerance and insulin sensitivity [27]. Furthermore, Umemoto et al. [28] demonstrated that ABCA1 was essential for the apo A-I and HDL-associated anti-inflammatory effects on adipocytes. Thus, in both mice and humans, ABCA1 is important in modulating adipocyte function.

4 Transcriptional Regulation of the ABCA1 Gene

Early studies indicated that ABCA1 protein levels increase when intracellular sterol and oxysterol levels are elevated. The sterol-responsive region in the ABCA1 gene promoter was mapped to a direct repeat 4 (DR4) element located 63 base pairs 5′ of the transcriptional start site and binds the liver-X- receptor α or β (LXRα, LXRβ)/retinoid- X- receptor α heterodimer [8, 9] (Fig. 3). LXRα is expressed primarily in liver, kidney, macrophage cells, endothelial cells, and intestine while LXRβ is expressed ubiquitously. LXRs bind to oxysterols stimulating LXR/RXR α dimer formation and binding to the DR4 element in the ABCA1 gene promoter. Several oxysterols, including the endogenous 20(S)-hydroxycholesterol, 22(R)-hydroxycholesterol, and 25-hydroxycholesterol, as well as several non-steroidal ligands bind to LXR and activate or repress expression of LXR-dependent genes. Other LXR ligands examined for their capacity to up-regulate ABCA1 gene expression and RCT are listed in Table 1. LXR-623 was the first LXR agonist examined in a clinical trial [59]. In a phase 2 escalating dose trial in normal healthy participants, LXR-623 was rapidly absorbed in a dose-dependent manner with peak concentrations achieved in 2 h [59]. The mean terminal disposition half-life was between 41 and 43 h independent of dose, and LXR-623 induced

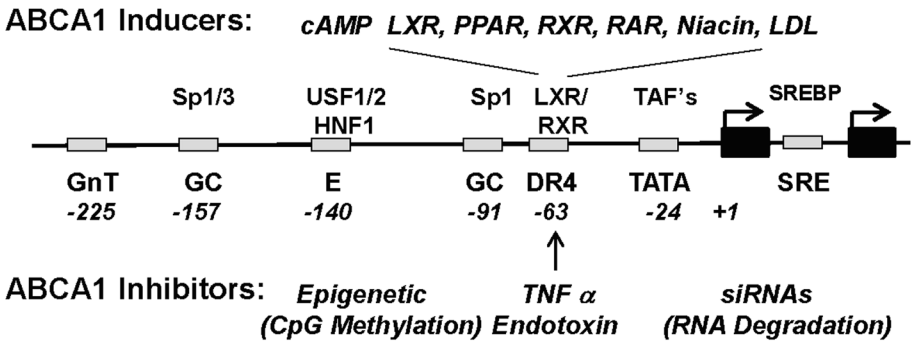

Fig. 3 The ATP binding cassette A1 (ABCA1) gene promoter. The ABCA1 gene promoter is regulated by several tissue-specific, hormonal, and metabolic cues to generate two ABCA1 mRNA species (arrows). Binding sites for hepatocyte nuclear factor 1 (HNF1), liver-X-receptor (LXR), peroxisome proliferator-activated receptor (PPAR), retinoic acid receptor (RAR), retinoid-X-receptor (RXR), sterol-responsive element binding protein (SREBP), specificity protein 1/3 (SP1/3), TATA binding activating factors (TAF's), and upstream stimulatory factor 1/2 (USF1/2) are indicated. Binding sites for these factors include two GC boxes, an E box, a direct-repeat 4 (DR4) element, a TATA box, and an intragenic sterol-responsive element (SRE). Drugs that induce ABCA1 gene expression include agonists for several nuclear receptors (LXR, PPAR, RXR, and RAR) and SREBPs. ABCA1 inhibitors include epigenetic changes (especially cytosine methylation), TNFα, endotoxin, and several siRNAs that promote ABCA1 mRNA degradation

Table 1 The effect of synthetic LXR agonists on ABCA1 expression and cholesterol efflux

Compound	Effects	Species examined	References
Acetyl-podocarpic dimer	↑ ABCA1 mRNA levels in THP-1, Caco-2, and primary hepatocytes; ↑ cholesterol transport to apo A-I in THP-1, Caco-2, monocytes, primary fibroblasts	Human	[29]
N,*N*-Dimethyl-3β-hydroxy cholenamide (DMHCA)	↑ ABCA1 mRNA in THP-1, J774, HepG2, BREC, PM, liver, ileum, aorta; ↑ ABCA1 protein in BREC; increased cholesterol in THP-1 cells	Human, mouse, bovine	[30, 31]
EXEL-04286651/BMS-779788	↑ ABCA1 mRNA in murine blood cells	Mouse	[32]
GW3965	↑ ABCA1 mRNA in THP-1, J774, HepG2, haSMC, BMM, PM, liver, peripheral blood, spleen, proximal small intestine, kidney, duodenum; ↑ ABCA1 protein in liver and proximal small intestine; ↑ cholesterol transport in THP-1 cells and C57BL/6 mice	Human, mouse	[30, 33–35]
LXR-623	↑ ABCA1 mRNA in duodenum, spleen, peripheral blood, PBMCs, and whole blood; ↑ ABCA1 protein in PBMCs	Human, mouse	[36, 37]
Methyl-3β-hydroxy-5α,6α-epoxycholanate	↑ ABCA1 mRNA in THP-1 cells; ↑ ABCA1 protein in aorta	Human, mouse	[38]
(24S)-stigmasta-5,28-diene-3β,24-ol	↑ ABCA1 mRNA in U937 cells	Human	[39]
(24S)-stigmasta-5-ene-3β,24-ol	↑ ABCA1 mRNA in U937 cells	Human	[39]
Stigmasterol derivatives	↑ ABCA1 mRNA in U937 cells	Human	[40]
T0901317	↑ ABCA1 mRNA in THP-1, RAW264.7, J774, U937, HepG2, Caco-1, pBCECs, TR-CSFB3, SAS, haSMC, McARH7777, $CD4^+$ cells, blood derived macrophages, PM, liver, aorta, small intestine, duodenum, peripheral blood, proximal intestine, distal intestine, and brain; ↑ ABCA1 protein in THP-1, RAW264.7, HepG2, HL-1, Caco-1, pBCECs, SAS, haSMC, $CD4^+$ T cells, Jurkat, cerebral endothelial cells, murine immortal macrophages, murine neuro2A, murine BV2, Rat C6, blood derived macrophages, aorta endothelial cells, renal glomerular endothelial cells, PM, liver aorta, and brain; ↑ cholesterol efflux to HDL and apo A-I.	Human, mouse, rat, porcine, rabbit	[30, 33, 34, 36, 38, 40–58]

ABCA1 ATP binding cassette protein A1, *ABCG1* ATP binding cassette protein G1, *AOPEP* aminopeptidase O, *apo A-I* apolipoprotein A-I, *BMM* bone marrow-derived macrophages, *BREC* bovine retinal endothelial cells, *DMHCA* NN-dimethyl-3β-hydroxy cholenamide, *FXR* farnesoid X receptor, *haSMC* human airway smooth muscle cells, *HSMC* human skeletal muscle cells, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *LPS* lipopolysaccharide, *LXR* oxLDL oxidized low-density lipoprotein, *R3HDM1* R3H domain containing 1, *MCM7* mini-chromosome maintenance complex component 7, *MPMs* murine peritoneal macrophages, *PBCECs* porcine brain capillary endothelial cells, *PBMCs* peripheral blood mononuclear cells, *PM* peritoneal macrophages, *RCT* reverse-cholesterol transport, *SAS* human squamous cell carcinoma cells, *SREBP1* sterol responsive element binding protein 1, *SREBP2* sterol responsive element binding protein 2, *VLDL* very low-density lipoprotein

ABCA1 and ABCG1 levels, again in a dose-dependent manner with EC_{50} values of 526 ng/ml and 729 ng/ml, respectively [59]. Unfortunately, central nervous system-related adverse events were reported at the highest doses. Due to the presence of RXR in the activated LXR/RXR heterodimer, many LXR-dependent genes are also regulated by the RXR ligand 9-*cis*-retinoic acid and other retinoids (Table 2). Of the compounds listed in Tables 1 and 2, stigmasterol derivatives are the only agents for which subjects are being enrolled in clinical trials targeting cardiovascular disease (NCT03983603 and NCT02481466). Of note, all clinical trials identified in this review are currently enrolling subjects; we excluded all completed clinical trials. We also focused on trials listed on Clinicaltrials.gov.

Oxysterol binding proteins (OSBPs) have also been shown to alter cholesterol efflux, HDL levels, and ABCA1

Table 2 The effect of retinoids on ABCA1 and cholesterol efflux

Compound	Effects	Species examined	References
Bexarotene	Pan-RXR agonist; ↑ ABCA1 protein in BLECs and cortex; ↑ cholesterol efflux in BLECs	Human, bovine	[60–62]
HX630	RXR agonist; ↑ ABCA1 mRNA expression in THP-1 and RAW264.7; ↑ cholesterol efflux in THP-1	Human, mouse	[63]
LG101305	RXR agonist; ↑ ABCA1 mRNA and cholesterol efflux in RAW264.7 cells	Mouse	[64]
LG268	RXR agonist; ↑ ABCA1 mRNA expression in small intestine and PM; ↑ cholesterol efflux in THP-1	Human, mouse	[65]
Methoprene	RXR agonist; ↑ ABCA1 protein and cholesterol efflux to apo A-I and HDL in astrocytes	Human	[66, 67]
PA024	RXR agonist; ↑ ABCA1 mRNA in THP-1 and RAW264.7; ↑ cholesterol efflux in THP-1	Human, mouse	[63]
Tri-butylin chloride	RXRα agonist; ↑ ABCA1 mRNA and protein in RAW264.7, cortex, and primary mouse astrocytes; ↑ cholesterol efflux in RAW264.7 cells	Mouse	[68, 69]
4-[(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphtalenyl)-1-propenyl] benzoic acid (TTNPB)	Synthetic RAR agonist; ↑ ABCA1 protein in HEK293 and PM; ↓ ABCA1 protein in astrocytes; ↑ ABCA1 mRNA in THP-1 cells; ↑ cholesterol efflux in RAW264.7 cells; ↓ cholesterol efflux in astrocytes	Human, mouse, hamster	[70, 71]

ABCA1 ATP binding cassette protein A1, *apo A-I* apolipoprotein A-I, *BLEC* bovine lens epithelial cells, *HDL* high-density lipoprotein, *PM* peritoneal macrophages, *RAR* retinoic acid receptor, *RXR* retinoid-X-receptor, *RXRα* retinoid-X-receptor α, *TTNPB* 4-[(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphtalenyl)-1-propenyl] benzoic acid

expression. The OSBP and OSBP-related protein (ORPs) families form the largest family of lipid transfer proteins [72]. The OSBPs transfer cholesterol and phosphatidylserine against concentration gradients, transferring phosphoinositide in the opposite direction. These proteins possess lipid-binding and membrane-interacting domains [72]. When late endosomal (LE) lysosomal cholesterol levels are high, ORP1L and ORP1S participate in the transfer of cholesterol from the late endosomal vesicle to the endoplasmic reticulum (ER) where it is esterified [73]. When LE lysosomal cholesterol levels are low, ORP1L transfers cholesterol from the ER to the LE lysosome in a microtubule-guided process and driven by the molecular motor dynein [74]. Interestingly, ORP1S has also been shown to translocate to the nucleus and upregulate apolipoprotein E expression via LXR activation [75]. Whether or not it upregulates ABCA1 gene expression is not known.

The OSBPs and ORPs are also involved in dyslipidemia and atherosclerosis. A heterozygous loss-of-function ORP1L allele (C38X) produces a truncated protein and is associated with hypoalphalipoproteinemia [76]. Cultured fibroblasts from these individuals have reduced cholesterol efflux capacity to apo A-1 [76]. These results suggest that a defect in LE lysosomal trafficking can promote dyslipidemia. Activation of ORP7 by 5-arylnicotinamide in kidney podocytes increased ABCA1 protein levels by prolonging its half-life and enhanced cholesterol efflux to HDL [77]. In mouse kidney disease model, 5-arylnicotinamide treatment normalized proteinuria and prevented the decline in renal function [76].

The retinoic acid receptor (RAR), which binds the ligand all-trans-retinoic acid, has also been shown to upregulate ABCA1 gene expression. The specific RAR agonist 4-[(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphtalenyl)-1-propenyl]benzoic acid (TTNPB) (Table 2) increased ABCA1 expression in both mouse and human macrophages [78, 79]. Other retinoids, including 9-*cis*-retinoic acid, also increased ABCA1 gene expression. Manna et al. [55] and Zhou et al. [78] independently demonstrated that 9-*cis*-retinoic acid increased ABCA1 expression in macrophage cells by stimulating the LXRα/RXR heterodimer. The synthetic RXR agonist stimulated ABCA1 expression and cholesterol efflux also through the LXRα/RXR heterodimer while HX630 stimulated ABCA1 gene through the peroxisome proliferator-activated receptor γ (PPARγ/RXR heterodimer in RAW264 cells [64]. Since RXR is an important factor involved in the activity of all class II nuclear hormone receptors including PPARs, thyroid hormone receptor (THR), RAR, vitamin D receptor (VDR), and farnesoid-X-receptor (FXR), use of retinoids targeting this receptor induces a wide spectrum of adverse effects, especially hypertriglyceridemia, limiting their use for reverse cholesterol transport [79].

Located immediately 5′ to the DR4 element is a GC-box containing binding sites for the specificity protein 1 (SP1) family of transcription factors. SP1 has been shown to interact with several nuclear receptors including RXR [80], the

VDR [81], and the estrogen receptor (ER) [82]. Thymiakou et al. [83] demonstrated that induction of ABCA1 promoter activity by LXRα ligands required SP1, and that the SP1 transactivation domain and DNA binding domain were required to interact with the LXRα transactivation/DNA binding domain. Chen et al. [67] demonstrated that low-density lipoprotein (LDL) treatment of mouse macrophage cells induces SP1 binding to a GC box located in the mouse ABCA1 gene promoter (which is conserved in the human gene promoter). Treatment of mouse macrophage cells with LDL increased intracellular phosphatidylinositol-3 (PI-3) kinase and protein kinase t activity, resulting in Sp1 phosphorylation and increased binding to the ABCA1 gene promoter in vivo. Mutation of either the SP1 or LXR element in the ABCA1 gene promoter decreased the capacity of LDL to induce ABCA1 gene expression, while mutation of both elements completely abolished the effect, suggesting that there is cross-talk between the DR4 and SP1 elements.

The DR4 element is also required for induction of ABCA1 promoter activity by niacin. Niacin increases plasma HDL levels significantly and is used therapeutically to manage dyslipidemia [84, 85] but does not reduce the risk of cardiovascular events [86]. Previous studies suggested that niacin increases apo A-I levels by decreasing its catabolic rate [87, 88], while other studies in cell cultures suggest that niacin may increase apo A-I synthesis [89, 90]. Zhang et al. [91] demonstrated that niacin-treatment of HepG2 cells increases ABCA1 expression and increases HDL synthesis by promoting lipidation of nascent apo A-I. Niacin treatment increased LXRα expression and mutation of the LXR binding DR4 element abolished the effect of niacin on ABCA1 promoter activity. It is not clear, however, if niacin mediates these effects through a receptor-mediated mechanism or if LXRα expression and activity is induced by niacin-induced intracellular accumulation of oxidized cholesterol.

The adipocyte-derived bioactive peptide adiponectin has also been shown to regulate hepatic HDL and ABCA1 synthesis [92] and ABCA1 expression in RAW 264.7 macrophage cells [93]. Though the former study did not investigate the molecular mechanisms involved in regulating HDL and ABCA1 synthesis, in the latter study the authors showed adiponectin induced LXRα expression in RAW 264.7 macrophages, which was inhibited by addition of an LXRα-specific small interfering RNA [93]. Likewise, Oku et al. [94] demonstrated that ABCA1 expression and apo A-I synthesis in the liver is dramatically reduced in adiponectin-deficient mice. In most studies, high plasma adiponectin levels are directly correlated with elevated plasma high-density lipoprotein cholesterol (HDLc) levels [95, 96], while hypoadiponectinemia is associated with several risk factor for cardiovascular disease including visceral adiposity, hypertension, impaired glucose tolerance, and low HDLc levels [96]. Adiponectin has been shown to possess anti-inflammatory and anti-atherogenic properties [97, 98], though mechanisms related to their effects remain to be elucidated.

PPAR ligands, commonly used to treat dyslipidemia and diabetes have been shown to impact ABCA1 gene expression (Table 3), though their effects are complex. Mogilenko et al. [103] showed that the peroxisome proliferator activated receptor γ (PPARγ) induces ABCA1 gene transcription; however, it reduced ABCA1 protein levels on the surface of HepG2 liver cells. Cells treated with GW1929, a potent and specific PPARγ agonist, induced LXRβ binding to the ABCA1 gene promoter and increased ABCA1 mRNA levels. GW1929 treatment also led to a disruption in formation of the ABCA1/LXRβ complex, destabilizing the ABCA1 component and leading to its degradation [103]. Interestingly, inhibition of the protein kinases mitogen-activated protein kinase kinase 1/2 (MEK1/2) partially prevented the GW1929-mediated disruption of the ABCA1/LXRβ complex at the cell surface. Since GW1929 is a PPARγ agonist and not a LXR agonist, the authors speculated that GW1929 enhances cytochrome P450-Cyp27 activity increasing the production of 27-hydroxycholesterol, a weak LXR agonist [123].

There are many randomized clinical trials examining the effects of pioglitazone (PPARγ agonist) on various components that mediate RCT. Yoshi et al. [124] performed a randomized multicenter open-label comparative study in 522 patients with diabetes. Each patient was randomly assigned to receive pioglitazone (n = 254) or not (n = 268) and observed for a medium of 672 days [124]. The primary outcome was the time to first occurrence of a composite all-cause death, nonfatal cerebral infarction, and nonfatal myocardial infarction. Pioglitazone treatment reduced HbA1c levels, diastolic blood pressure, LDL-cholesterol levels, and importantly increased HDL-cholesterol levels. However, there was no difference in the cumulative incidence of the primary outcomes (nine in the pioglitazone group and ten in the non-pioglitazone group) [124]. In the Diabetes Atherosclerosis Intervention Study, the effect of fenofibrate (PPARα agonist) on HDL and cardiovascular disease was examined [125]. Those who were assigned to 200 mg of fenofibrate had higher HDL α-2 and α-3 levels. Fenofibrate treatment had no effect on total LDLc and small dense LDLc but decreased triglyceride and remnant-like particle cholesterol [125]. Also, a randomized, placebo-controlled, cross-over study (three 8-week treatment periods with 40 mg daily simvastatin, 400 mg daily bezafibrate (pan-PPAR agonist), alone and in combination) was carried out in 14 men with type 2 diabetes and cholesterol efflux was measured in THP-1 macrophage cells and pre- β -HDL was measured using crossed immunoelectrophoresis [126]. Pre- β -HDL levels were increased in all three treatment groups, as was cholesterol efflux capacity [126].

Table 3 The effect of PPAR agonists on ABCA1 expression and cholesterol efflux

Compound	Effects	Species examined	References
Ciglitazone	PPARγ agonist; ↑ ABCA1 mRNA and cholesterol efflux in THP-1 cells	Human	[99]
E3317	PPARγ agonist; ↑ ABCA1 and cholesterol efflux in RAW264.7 cells	Mouse	[100]
GQ-11	PPARγ/α agonist; ↑ increased ABCA1 in liver	Mouse	[101]
GW1929	PPARγ agonist; ↑ ABCA1 mRNA and protein in HepG2 cells	Human	[47]
GW7845	PPARγ agonist; ↑ ABCA1 mRNA and cholesterol efflux in THP-1 cells	Human	[70]
Pioglitazone	PPARγ agonist; ↑ ABCA1 protein in THP-1, HepG2, pBCECs, gBECs, WI38 fibroblasts; ↑ ABCA1 mRNA in THP-1, pBCECs, WI38 fibroblasts, monocyte-derived macrophages, diabetic patients, rat cortical neurons; ↓ ABCA1 mRNA and protein in PM; ↑ cholesterol efflux to apo A1 and HDL in THP-1; ↑ cholesterol efflux in gBECs, WI38 fibroblasts, PM (HDL only, not apo A-I), diabetic patients; decreased cholesterol efflux in pBCECs,	Human, mouse, rat, porcine	[40, 62, 101–110]
Rosiglitazone	PPARγ agonist; ↑ ABCA1 protein in THP-1 cells, HepG2 cells, and PM; ↑ ABCA1 mRNA in THP-1, RAW264.7, hepatocytes; ↑ cholesterol efflux in THP-1 cells, RAW264.7, macrophages, PM, hepatocytes	Human, mouse	[69, 70, 111–114]
Troglitazone	PPARγ agonist; ↑ ABCA1 protein in pBCECs, gBECs; ↑ ABCA1 mRNA in THP-1 cells; ↓ ABCA1 mRNA in pBCECs; ↓ ABCA1 mRNA and protein in PM; ↑ cholesterol efflux to HDL in pBCECs, and PM, reduced cholesterol efflux to apo A-I in pBCECs and PM	Human, mouse, porcine	[40, 62, 107, 110]
Bezafibrate	Pan-PPAR agonist; ↑ ABCA1 protein in THP-1, HepG2, WI38 fibroblasts; primary hepatocytes; ↑ ABCA1 mRNA in THP-1, HepG2, WI38 fibroblasts, HMC, and primary hepatocytes; ↑ cholesterol efflux in THP-1, HepG2, WI38 fibroblasts, lipid loaded HMC, and primary hepatocytes	Human	[40, 108, 115]
Clofibrate	PPARα agonist; ↑ ABCA1 mRNA in HepG2 and liver	Human	[116]
Fenofibrate	PPARα agonist; ↑ ABCA1 protein in THP-1, RAW264.7, HepG2, pBCECs, Balb/3T3, WI38 fibroblasts, primary hepatocytes, and PM; ↑ ABCA1 mRNA in THP-1, RAW264.7, HepG2, Balb/3T3, WI38 fibroblasts, primary hepatocytes, liver, diabetic patients, and aorta; ↑ cholesterol efflux in THP-1, RAW264.7, HepG2, WI38 fibroblasts, and primary hepatocytes	Human, mouse	[36, 62, 108, 117–119]
Gemfibrozil	PPARα agonist; ↑ ABCA1 mRNA and protein in THP-1, HepG2, WI38 fibroblasts, and primary hepatocytes; ↑ cholesterol efflux in THP-1, HepG2, WI38 fibroblasts, and primary hepatocytes	Human	[109, 118]
GW7647	PPARα agonist; ↑ ABCA1 protein in RAW264.7, BMM; ↑ ABCA1 mRNA in THP-1, RAW264.7, and BMM; ↑ cholesterol efflux to apo A1 in RAW264.7 and BMM	Human, mouse	[113]
LY518674	PPARα agonist; ↑ ABCA1 mRNA and protein in THP-1, HepG2, WI38 fibroblast, primary hepatocytes; ↑ cholesterol efflux in THP-1, HepG2, WI38 fibroblasts, and primary hepatocytes	Human	[109, 118]
WY14643	PPARα agonist; ↑ ABCA1 mRNA and protein in THP-1, RAW264.7, gBECs, and Balb/3T3; ↑ ABCA1 mRNA in liver; ↑ cholesterol efflux in THP-1, RAW264.7, and liver	Human, mouse	[37, 49, 113, 118]
WY14563	PPARα agonist; ↑ cholesterol efflux in THP-1 cells	Human	[62]
Carbaprostacyclin	PPARδ agonist; ↑ cholesterol transport in THP-1 cells	Human	[62]
GW0742	PPARδ agonist; ↑ cholesterol transport in BMM	Human	[114, 120]
GW501515	PPARδ agonist; ↑ ABCA1 protein in THP-1, WI38 fibroblasts; ↑ ABCA1 mRNA in THP-1, WI38 fibroblasts, 1BR3N fibroblasts, intestinal FHS74 HSKM; ↑ cholesterol efflux in THP-1, WI38 fibroblasts, 1BR3N fibroblasts, and intestinal HSKM	Human	[42, 109, 121, 122]

ABCA1 ATP binding cassette protein A1, *apo A-I* apolipoprotein A1, *BMMs* bone marrow-derived macrophages, *gBECs* gall bladder epithelial cells, *HDL* high-density lipoprotein, *HMC* human mast cells, *HSKM* human skeletal muscle cell, *pBCECs* porcine brain capillary endothelial cells, *PM* peritoneal macrophages, *PPAR* peroxisome proliferator activated receptor, *PPARα* peroxisome proliferator-activated receptor α, *PPARγ* peroxisome proliferator-activated receptor γ, *PPARγ/α* peroxisome proliferator-activated receptor γ/α

Of all the compounds listed in Table 3, there are only two pioglitazone trials targeting cardiovascular disease (NCT04123067 and NCT04419337) and one atherosclerosis trial (NCT04392557). There are four fenofibrate trials targeting cardiovascular disease (NCT04907084, NCT04661358, NCT01320345, and NCT04748965) and one clinical trial looking at atherosclerosis (NCT00965315)

3-Hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors have also been shown to increase ABCA1 mRNA levels in liver cells in vitro [127, 128]. Maejima et al. [50] showed that pitavastatin, atorvastatin, and simvastatin, but not pravastatin, induced ABCA1 expression in rat McARH7777 hepatoma cells. Surprisingly, treatment with pitavastatin repressed P-type ABCA1 mRNA but increased the amount of ABCA1 L-type mRNA. Pitavastatin treatment also increased PPARα receptor (as well as its target genes), inhibiting LXR activity and enhanced ABCA1 protein stability [50]. In another study, ABCA1 mRNA levels in pravastatin-treated murine RAW264.7 cells decreased when cells were cultured in lipoprotein-deficient conditions [129]. Interestingly, this inhibition was blunted when cells were treated with mevalonic acid and cholesterol, or treated with LXR agonist 22(R)-hydroxycholesterol. Pravastatin had no effect on ABCA1 mRNA and protein levels in HepG2 cells. In mice administered pravastatin (0.1% in drinking water) for 2 weeks, hepatic and leukocyte LXRα levels increased but there was no change in ABCA1 gene expression. It is not clear why pravastatin does not decrease ABCA1 in HepG2 cells as observed in macrophage cells. HMG-CoA reductase inhibitors activate PPARα [130] and PPARγ [131], elevating LXRα levels and ABCA1 expression [66, 110]. Another factor may be related to the level of endogenous LXR agonists in HepG2 cells relative to macrophage cells. High endogenous LXR agonist levels may compensate for the mevalonic acid-related inhibition of LXRα activity in hepatocytes where oxysterol levels are much higher than in macrophage cells.

Many clinical trials have examined the effects of various statins on HDLc and apo A-I. Lee et al. [132] examined the effects of atorvastatin (20 mg; $n = 11$), or atorvastatin plus ezetimibe (10 mg; $n = 10$) combination in randomized patients for 8 weeks. Cholesterol efflux capacity increased to similar extents in both treatment groups, as did apo A-I, apo A-II, and HDL levels.

Insulin has been shown to induce apo A-I gene expression through a GC-rich insulin-responsive core element (IRCE) in the apo A-I gene promoter following phosphorylation and binding of SP1 to the element [133, 134]. Insulin treatment decreases ABCA1 levels by increasing ABCA1 tyrosine phosphorylation (1206) promoting its degradation and efflux capacity [135]. In the latter study, insulin-mediated decreases in ABCA1 were associated with lower HDLc and HDL phospholipid levels but had no effect on ABCA1 mRNA expression. Furthermore, inhibition of calpain and proteasome activity with calpeptin/*N*-[*N*-(*N*-acetyl-L-leucyl)-L-leucyl]-L-norleucine (ALLN) and MG-132, respectively, reversed most of the decrease in ABCA1 protein levels in insulin-treated cells [135]. Similar results were observed in vivo in male Crl:CD rats fed a high-fructose diet to promote insulin resistance/hyperinsulinemia [135].

Epigenetics, in particular DNA methylation, has also been shown to play an important role in regulating ABCA1 gene expression. Cytosine methylation in the context of a CpG dinucleotide is generally associated with gene repression and is believed to influence DNA structure and/or binding of methylation-specific trans-acting factors that repress gene transcription [136, 137]. Tobi et al. [138] demonstrated that the ABCA1 gene promoter is more methylated in adults prenatally exposed to starvation decades prior, and also demonstrated that there is considerable inter-individual variation in ABCA1 gene promoter methylation status [139]. However, they did not determine if the methylation status was associated with altered lipid levels or elevated risk for coronary artery disease. To address these issues, Guay et al. [140] determined whether or not ABCA1 promoter methylation was associated with changes in HDL particle size and concentration as well as coronary artery disease in patients with familial hypercholesterolemia (FH) and carrying the W66G mutation in the LDL receptor and not under lipid-lowering treatment. Changes in the epigenome may account for the variability in the presentation of FH in each patient [141] as well as the observation that maternal transmission of FH has an influence on lipid metabolism in the offspring [142]. ABCA1 promoter methylation was negatively correlated with plasma HDLc and HDL2-phospholipid levels, and correlated with the prior risk of coronary artery disease [140] in the 97 FH patients. Furthermore, many of the methylated CpGs identified in the study mapped to a CpG island in the proximal promoter of the ABCA1 gene containing consensus binding sites for the transcription factors SP1, signal transducer and activator of transcription (STAT), activator protein -1 (AP-1), activator protein-2 (AP-2), activator protein-4 (AP-4), ETS1, and sex-determining region Y (SRY) [140]. A critical caveat of these studies is that they were all performed with leukocytes, not with hepatocytes, macrophages, or intestinal cells; there may be important tissue-specific differences in ABCA1 promoter methylation status. However, if epigenetic control of ABCA1 gene expression is conserved between leukocytes, hepatocytes, and macrophage cells, it is likely that the observations made in leukocytes are also applicable to the other cell types. All of the key transcription factors are expressed in leukocytes, hepatocytes, and macrophage cells. Regardless, leukocyte proliferation

and differentiation is suppressed by HDL (through its anti-inflammatory effects) in response to ABCA1/apo A1 binding, potentially suppressing atherosclerosis [19].

5 Regulation of ABCA1 Gene Expression by Natural Compounds

The search for natural therapeutics that target and increase ABCA1 expression and RCT has yielded several important leads. A thorough review was recently published on this topic [143]. Natural compounds upregulate ABCA1 expression in three ways; (1) by preventing ABCA1 degradation, (2) by increasing ABCA1 mRNA stability, and (3) by increasing ABCA1 gene transcription (the most commonly employed mechanism) (Table 4).

Two compounds, 6-dihydroparadol (from the ginger species Zingiber *officinale*) [144] and paeonol (from Paeonia *suffruticosa*) [154, 155] increased ABCA1 protein levels by inhibiting proteasomal ABCA1 degradation and calpain-mediated ABCA1 degradation in THP-1 and RAW264.7 macrophages and apoE$^{-/-}$ knockout mice. Three compounds, betulinic acid (a terpenoid from the bark of Tetracera *potatoria*) [147], diosgenin (a steroid from Dioscorea *nippionica*) [152], and protocatechuic acid (a polyphenol from the medicinal herb danshen) [156] increased ABCA1 gene expression by downregulating miR-33a and b, miR-10b, and miR-19b expression, respectively. These microRNAs down regulate ABCA1 gene expression by targeting its mRNA for degradation (see below). These effects were observed in THP-1 and murine peritoneal macrophage (MPM) cells in vitro and apoE$^{-/-}$ mice in vivo.

By far the largest number of natural compounds enhance ABCA1 gene expression by targeting signaling pathways and transcription factors that enhance ABCA1 gene transcription. Kuwanon G (a flavonoid from root bark of Morus *alba*) induced ABCA1 gene expression by directly stimulating LXRα and LXRβ activity [153]. Puerarin (a flavonoid

Table 4 Natural compounds and ABCA1

Compound	Model	Mechanism of action	Species examined	References
6-Dihydroparadol (from ginger Zingiber *officinale*)	THP-1, RAW264.7	↑ ABCA1	Human, mouse	[144]
Alpinetin (ginger flavonoid Alpinia *katsumadai*)	THP-1, HMDMs	↑ ABCA1, ↑ PPARγ, ↑ LXRα	Human	[145]
All-trans retinoic acid (vitamin A rich vegetables)	MPMs, HMDMs, THP-1, RAW264.7	↑ ABCA1, ↑ LXRα	Human, mouse	[57, 81, 146]
Betulinic acid (terpenoid from Tetracera *potatoria* bark)	THP-1, apo E$^{-/-}$	↑ ABCA1, ↓ NF-κB, ↓ p-NF-κB, ↓ IκBα, ↓ miRNA-33a/b	Human, mouse	[147]
β-Carotene (vitamin A rich vegetables)	THP-1	↑ ABCA1, ↑ LXRα, ↑ p-AMPK	Human	[148]
Curcumin (from Curuma *longa*)	J774A.1, RAW264.7, THP-1, apoE$^{-/-}$	↑ ABCA1, ↑ LXRα, ↑ PPARγ, ↑ HDL, ↑ p-AMPK	Mouse	[149–151]
Diosgenin (steroid from Dioscorea *nippionica*)	THP-1, MPMs, apoE$^{-/-}$	↑ ABCA1, ↓ miRNA-19b	Human, mouse	[152]
Kuwanon G (flavonoid from Morus *alba* root bark)	RAW264.7	↑ ABCA1, ↑ LXRα, ↓ p-NF-κB	Mouse	[153]
Paeonol (from Paeonia *suffruticosa*)	RAW264.7, apoE$^{-/-}$	↑ ABCA1, ↑ LXRα, ↑ RXRα, all ↑, ↓ TC, ↓ TG	Mouse	[154, 155]
Protocatechuic acid (polyphenol from the medicinal herb danshen)	THP-1, MPMs, apoE$^{-/-}$	↑ ABCA1, ↓ miRNA-10b, ↑ RCT	Human, mouse	[156]
Puerarin (flavonoid from Pueraria *lobate* root)	THP-1	↑ ABCA1, ↑ PPARγ, ↑ p-AMPK, ↑ LXRα, ↓ miRNA7	Human	[157]
Quercetin (flavonoid from numerous fruits and vegetables)	RAW264.7, THP-1, apoE$^{-/-}$ on HFD	↑ ABCA1, ↑ LXRα, ↑ PPARγ, ↑ SP1; ↑ TAK1, ↑ MMK3/6, ↑ p-P38	Mouse	[158, 159]
Tanshinone IIA (terpenoid from Salvia *miltiorrhiza* rhizome)	THP-1, MPMs, HMDMs, apoE$^{-/-}$, SD rats on HFD	↑ ABCA1, ↑ p-ERK, ↑ p-NRF2, ↑ HO-1	Human, mouse	[160, 161]

ABCA1 ATP binding cassette protein A1, *p-AMPK* phospho-AMP kinase, *p-ERK* phospho-extracellular-signal regulated kinase, *HDL* high-density lipoprotein, *HFD* high fat diet, *HMDMs* human monocyte-derived macrophages, *HO-1* heme oxygenase-1, *IκBα* nuclear factor of κ light polypeptide gene enhancer in B-cells inhibitor α, *LXRα* liver-X-receptor α, *MMK3/6* mitogen-activated protein kinase kinase 3/6, *MPMs* murine peripheral macrophages, *NF-κB* nuclear factor κB, *p-NF-κB* phospho-nuclear factor κB, *NRF2* nuclear factor erythroid 2-related factor 2, *p-P38* phospho-P38 mitogen-activated protein kinase, *PPARγ* peroxisome proliferator activated receptor γ, *RCT* reverse cholesterol transport, *RXRα* retinoid-X-receptor α, *SD* Sprague-Dawley, *SP1* specificity protein 1, *TAK1* tachykinin precursor 1, *TC* total cholesterol, *TG* triglycerides

from Pueraria *lobate* root) enhanced ABCA1 gene expression by stimulating PPARγ and LXRα via AMPK [157], while alpinetin (a ginger flavonoid from Alpinia *katsumadai*) induced PPARγ and LXRα activity directly [145]. Quercetin (a flavonoid from numerous fruits and vegetables) enhanced ABCA1 gene expression by stimulating LXRα and SP1 via tachykinin precursor 1 (TAK1), mitogen-activated protein kinase kinase 3/6 (MKK3/6), and p38 mitogen-activated protein (MAP) kinase [158, 159]. In a randomized, double-blinded, placebo-controlled, crossover study ($n = 93$) where the subjects received 150 mg/day quercetin for 6 weeks followed by a 5-week washout period, quercetin treatment had beneficial effect on diastolic blood pressure but HDLc levels decreased [162]. Total plasma cholesterol and triglyceride levels did not change with quercetin treatment [162]. Currently, there are three clinical trials examining the effect of quercetin on cardiovascular disease (NCT03943459 and NCT04907253) and atherosclerosis (NCT02998918). Likewise, curcumin (a non-flavonoid from Curuma *longa*) induced ABCA1 gene expression by stimulating LXRα and PPARγ activity via AMP-activated protein kinase (AMPK) [149–151]. A recent double-blinded, placebo-controlled, clinical trial in men ($n = 22$) examined the effect of enhanced bioavailable curcumin versus placebo on obesity-related cardiovascular risk factors after 12 weeks of treatment [163]. Curcumin treatment increased HDLc and reduced homocysteine levels; however, there were no differences in plasma insulin, glucose, leptin, or adiponectin levels between the two groups [163]. There are currently two clinical trials examining the effect of curcumin on cardiovascular disease (NCT02998918 and NCT04458116). Betulinic acid (a terpenoid from Tetracera *potatoria* bark) also elevated ABCA1 gene expression by stimulating SREBP activity [147]. Tanshindiol IIA (a terpenoid from the Salvia *miltiorrhiza* rhizome) induced ABCA1 gene expression via heme oxygenase (HO-1), requiring both ERK and nuclear factor erythroid 2-related factor 2 (Nrf2) [160, 161]. There is one clinical trial currently under way (NCT02524964) examining the effect of Tashinone IIA on cardiovascular disease. Finally, all-*trans*-retinoic acid [57, 81, 146] and β -carotene (both from vitamin A-rich vegetables) [148] increased ABCA1 gene expression by stimulating RAR and RXR activity, respectively. In total, these effects were observed in vitro (THP-1, RAW264.7, MPMs, human monocyte-derived macrophages (HMDM), and J77A.1 cells) and in vivo (apo $E^{-/-}$ mice and Sprague Dawley rats on a high-fat diet). Unfortunately, none of these observations have led to the development of therapeutics to enhance RCT in humans. Indeed, a recent meta-analysis comparing the results of clinical trials examining the effects of β -carotene supplementation on cardiovascular disease risk failed to show any benefit [164]. In fact, there was a slight increase in risk associated with β -carotene use [164].

6 Inhibition of ABCA1 Gene Expression by Endotoxin and Pro-Inflammatory Cytokines

Several studies indicate that atherosclerosis is associated with chronic sub-clinical endotoxemia. In contrast to high-dose lipopolysaccharide (LPS) (> 10 ng/ml), which is associated with septic shock and cytokine storms, chronic subclinical endotoxemia (< 100 pg/ml) induces only a mild but persistent increase in inflammatory mediators, potentially enhancing atherosclerosis. Indeed, currently available cardioprotective drugs have anti-inflammatory properties and reduce proinflammatory cytokine secretion from human coronary artery endothelial cells [165]. Maitra and Li [166] demonstrated that subclinical amounts of endotoxin suppressed ABCA1 expression, as well as expression of ABCG1 and SR-B1 in macrophages.

Patients with Crohn's disease have persistently low HDL levels as well as accelerated atherosclerosis [167]. In addition, patients with sepsis can have transient dyslipidemia mimicking the plasma lipid profile of Tangier disease [168]. Field et al. [10] hypothesized that the potent pro-inflammatory cytokine TNFα, which has been shown to play a major role in Crohn's disease [169] may promote atherogenic dyslipidemia in part by repressing ABCA1 gene expression leading to lower HDL levels. Treatment of Caco-2 intestinal cells with TNFα down-regulated basolateral cholesterol efflux to apo A-I and also diminished ABCA1 promoter activity. TNFα treatment had no effect on expression of LXRα or LXRβ, or on the expression of other genes involved in cholesterol transport including ABCG1, ABCG8, or SR-B1, but did enhance the rate of ABCA1 degradation. Furthermore, inhibition of nuclear factor-κB activity, a pathway known to be activated by TNFα, partially prevented these effects [10].

Extracellular-signal regulated kinase 1/2 (ERK1/2) activity is important in regulating cellular growth and differentiation, especially in cardiac development and hypertrophy [170]. ERK1/2 is a Ser/Thr protein kinase that functions through the RAS-RAF-mitogen-activated protein kinase (MEK)-ERK1/2 signaling cascade and is activated by several growth factors [171] as well as TNFα [172]. Zhou et al. [173] demonstrated that inhibiting ERK1/2 activity by treatment with the ERK1/2 inhibitors PD98059 and U0126 inhibited cholesterol efflux in macrophage cells. In contrast, inhibition of protein kinase C (PKC), protein kinase A (PKA), p38 MAP kinase, and c-*jun*-N-terminal kinase (JNK) had no effect on cholesterol efflux to apo A-I or HDL [173]. Furthermore, addition of both PD98059 and U0126 induced ABCA1 protein and mRNA expression, as did treatment with siRNA specific for ERK1/2 [173]. ABCA1 protein levels were enhanced

by ERK1/2 inhibitor treatment by elevating its mRNA and prolonging the proteins half-life, however treatment with the ERK1/2 inhibitors had no effect on LXRα and LXRβ expression. Furthermore, treatment with the ERK1/2 inhibitors and the LXR agonist T0901317 had synergistic effects on ABCA1 expression [173]. Thus, elevated ABCA1 levels (protein or mRNA) are not necessarily associated with increased cholesterol efflux.

7 Regulation of ABCA1 Expression by MicroRNAs

MicroRNAs (miRNA) are important modulators of ABCA1 expression and HDL metabolism. MicroRNAs are small (~ 22 nucleotides), non-coding RNA molecules that regulate gene expression by base pairing with a partially complementary RNA sequence on the target RNA (usually within the 3′ untranslated region), either inhibiting its translation or initiating its degradation via the RNA-induced silencing complex (RISC) [174]. miRNAs are encoded in both intergenic and intronic regions of the genome [175] and in most cases miRNAs suppress gene expression. However, there are instances where miRNAs act on a target gene in a positive manner enhancing its expression. Since the inhibitory effect of a single miRNA is small (10–30%), two or more miRNAs function primarily to control the output of gene networks, partially inhibiting the expression of numerous genes within each pathway, culminating in robust pathway inhibition [176]. miRNAs not only function in the cell in which they are produced but several have been shown to be transported by lipoproteins in the plasma [177] and by small extracellular vesicles (sEVs) [178]. Several excellent reviews on the role of miRNAs in HDL metabolism and atherosclerosis have been published [179–182].

Several miRNAs have been implicated in regulating ABCA1 mRNA and protein levels (Table 5). As discussed above, LXRα is a key regulator of ABCA1 gene transcription. Adding more complexity, microRNA-206 was shown to regulate LXRα activity differently in hepatocytes and macrophage cells [193]. In hepatocytes, miR-206 suppressed LXRα expression and activity, and down-regulated LXRα target genes without altering LXRβ expression and activity. In macrophage cells however, miR-206 enhanced LXRα activity and expression, enhanced the expression of LXRα genes and increased cholesterol efflux. In macrophage cells, treatment with LXRα agonists suppressed miR-206 expression while treatment with TNF α or LPS enhanced miR-206 expression. The ABCG1 expression and possibly cholesterol efflux was increased with miR-206. It is not entirely clear why miR-206 has opposite effects in hepatocytes and macrophage cells. The miR-206 is localized to both the cytoplasm and nucleus [196] and in the cytoplasm, miR-206 interacts with the 3′-untranslated region of the LXRα mRNA {193] which may enhance its translation [197]. In silico studies indicate that there may be miR-206 interacting sites in the ABCA1 (907 bp 5′ of the transcriptional start site) and the ABCG1 gene promoter (4809 bp 5′ of the transcriptional start site) [193]. After promoter binding, mrR-206 enhances transcription of these target genes as well as others through an unknown mechanism. Much work remains to examine these possibilities. These observations taken together suggest that miR206 regulates ABCA1 gene expression in a tissue-specific fashion.

The miRNA-328-5P also effects ABCA1 gene expression, however by a different mechanism (194). The miRNA-328-5P inhibits histone deacetylase 3 levels by targeting the 3′-untranslated region of its mRNA, leading to higher ABCA1 levels. Consequently, in THP-1 macrophage foam cells, a miRNA-328-5P mimic increased cholesterol efflux, decreased total and free cholesterol, cholesteryl ester, and reduced lipid droplet formation. Though it is likely that mi328-5P-mediated histone deacetylase 3 expression alters the expression of many genes, there were no changes in scavenger receptor-A, thrombospondin receptor (CD36), and ABCG1 expression [194].

8 Conclusions

Numerous preclinical studies in animals and human trials have revealed that ABCA1 is an important therapeutic target for treating cardiovascular disease by specifically enhancing RCT. Several limitations to this strategy remain due to the protein's short half-life on the cell surface. Considering the fact that the ABCA1 mRNA is targeted by several inhibitory siRNAs is also of concern. Likewise, long-term protease inhibitor use to inhibit ABCA1 degradation will likely have significant side effects. While several lines of drugs targeting LXR, PPAR, RXR, and RAR in animal studies and clinical trials in humans have been tested, none have proven safe and effective at enhancing ABCA1 expression and/or activity. Likewise, numerous natural compounds have not proven useful in this regard, and siRNA-based therapeutics seem unlikely due to the fact that ABCA1 is targeted by multiple inhibitory miRNAs. Therefore, a drug combination that specifically and significantly increases ABCA1 gene transcription and extends the half-life of the ABCA1 protein may be more effective for enhancing RCT. A variety of technologies may be employed to address these goals, including small-molecule inducers and inhibitors, siRNA- or antisense oligonucleotide-based therapeutics, or genetically engineered adeno-associated virus-gene or lentivirus-based gene therapies. However, since ABCA1 is expressed in most tissues in the body, local regulation of ABCA1 gene expression should be the goal. Since hepatocytes and macrophage

Table 5 miRNAs regulating ABCA1 gene expression

miRNA	Stimulus/source	Effects	Species examined	References
miRNA-10b	Dietary Anthocyanies	↑ miRNA-10b, ↑ RCT, ↓ atherosclerosis	Human, mouse	[156]
miRNA-19b	Diosgenin	↓ miRNA-19b, ↑ ABCA1, ↓atherosclerosis	Human, mouse	[152]
miRNA-26	LXR Ligands	Not examined	Human, mouse	[183]
miRNA-27a	miRNP derived, chromosome 19	Targets 3′ end of ABCA1 and LPL; ↑ cholesterol efflux to apo A-I in THP-1 cells	Human	[184]
miRNA-27b	AOPEP (putative), chromosome 9	Targets 3′ end of ABCA1 and LPL; ↑ cholesterol efflux to apo A-I in THP-1 cells	Human	[184]
miRNA-33a	Intronic region SREBP2, Sterols, LXR Ligands, Insulin	↑ HDL, ↑ RCT, ↓ atherosclerosis	Human, mouse	[185]
miRNA-33b	Intronic region SREBP1, Sterols, LXR Ligands, Insulin	↑ HDL, ↑ RCT, ↓ atherosclerosis	Human, mouse	[185]
miRNA-34a	Long non-coding RNA MIR34AHG	Macrophage-specific knockout ↓ atherosclerosis in apo $E^{-/-}$ and $LDL^{-/-}$ knockout mice; ↓ ABCA1, ↓ ABCG1, ↓ LXRα	Human, mouse	[186]
miRNA-106b	Intronic miRNA encoded by MCM7 gene on chromosome 7	Not examined	Human, mouse	[187]
miRNA-128-1	Intronic miRNA encoded by R3HDM1 gene	↓ Obesity, protected from insulin resistance	Human, mouse	[188]
miRNA-144	LXR, FXR Ligands	↑ HDL	Mouse	[189, 190]
miRNA-145	Chromosome 5, putative lncRNA	Not examined	Human	[191]
miRNA 148a	Intergenic region of chromosome 7	Knockdown ↓ LDL, ↑ HDL	Human, mouse, Rhesus monkey	[192]
miRNA-206	Increased in HepG2 cells by LXR Ligands; In THP-1 cells, decreased by oxLDL, and VLDL; increased by LPS and TNFα	↓ ABCA1 expression in HepG2 cells, ↑ ABCA1 in THP-1, ↑ cholesterol efflux in THP-1 cells and mouse MPMs	Human, mouse	[193]
miRNA-328-5P	Decreased HDAC3 expression increasing ABCA1 expression	↑ ABCA1 in THP1 and cholesterol efflux; ↓ expression in oxLDL-treated macrophage cells	Human	[194]
miRNA-758	Sterols	Not Examined	Human, mouse	[195]

ABCA1 ATP binding cassette protein A1, *ABCG1* ATP binding cassette protein G1, *AOPEP* aminopeptidase O, *apo A-I* apolipoprotein A-I, *BMM* bone-marrow-derived macrophage, *BREC* bovine retinal endothelial cells, *FXR* farnesoid- X-receptor, *HDAC3* histone deacetylase 3, *HDL* high-density lipoprotein, *HSMC* human skeletal muscle cells, *LDL* low-density lipoprotein, *LPL* lipoprotein lipase, *LPS* lipopolysaccharide, *LXR* liver-X-receptor, *oxLDL* oxidized low-density lipoprotein, *R3HDM1* R3H Domain Containing 1, *MCM7* minichromosome maintenance complex component 7, *miRNP* miRNA protein complex, *MPMs* murine peripheral macrophages, *PBMCs* porcine brain capillary endothelial cells, *PM* peripheral macrophages, *RCT* reverse-cholesterol transport, *SREBP1* sterol responsive element binding protein 1, *SREBP2* sterol responsive element binding protein 2, *TNFα* tumor necrosis factor α, *VLDL* very low-density lipoprotein

cells would be the primary cells to target with each therapy, the means to target each therapeutic modality may be important to limit side effects. Targeting the asialoglycoprotein receptor, which is expressed only in the liver, by conjugating galactose to various therapeutics may prove effective in targeting the liver. Other macrophage-specific cell surface receptors that are internalized after ligand binding may be used to specifically target this cell population.

Other therapeutic targets remain to be discovered. The observation that elevated ABCA1 levels are not always associated with increased cholesterol efflux indicates that there are cellular and/or environmental factors that regulate ABCA1 cholesterol transport. A range of mechanisms can be envisioned to account for this, including post-translational modifications, steric hinderance due to intracellular binding to other membrane-associated or cytoplasmic proteins, or decreases in OSBP and/or ORP expression/activity affecting the delivery of cholesterol to the plasma membrane. Once these targets are identified, therapeutic agents may be available or developed to increase ABCA1 expression and activity.

Another therapeutic modality that may bypass the need to enhance ABCA1 gene expression is HDL or apo A-I mimetic infusion. In a double-blind, randomized, multicenter trial evaluating ten weekly injections of CER-100, a pre- β HDL mimetic containing apo A-I and sphingomyelin (3 mg/kg; $n = 135$), or placebo ($n = 137$) had no effect on coronary atherosclerosis (measured by intravascular ultrasonography) in statin-treated patients with acute coronary syndrome and high plaque burden [198]. In a recent trial using CER-100 and targeting 30 patients with familial hypoalphalipoproteinemia due to ABCA1 and/or apo A-I loss-of-function variants [199], Patients were randomized to treatment (8

mg/kg CER-100) or placebo (2:1 ratio) with nine weekly infusions followed by infusions every 2 weeks for a total of 24 weeks. Mean vessel wall area was measured by 3T-MRI and arterial wall inflammation was measured by ^{18}F-FDG/CT. Unfortunately, there were no differences in mean vessel wall area or arterial wall inflammation between the treatment group and those given placebo. Another HDL mimetic containing recombinant apo A-I Milano (MDCO-216) did not promote plaque regression in patients with acute coronary artery syndrome taking a statin [200]. This double-blind, randomized, multicenter trial treated patients with 20 mg/kg MDCO-216 ($n = 59$) or placebo ($n = 67$) weekly for 5 weeks. The primary outcome, percent atheroma volume, was measured by intravascular ultrasound. Another clinical trial phase 1/II trial examining the safety/tolerability, pharmacokinetics, and pharmacodynamics of the apo A-I mimetic peptide D-4F [201]. The compound was well tolerated and importantly, rendered the patients HDL less inflammatory. Unfortunately, ABCA1-mediated cholesterol efflux was not assessed in any of the studies described above. Future studies will have to address the effect of various therapeutic agents on cholesterol efflux.

Declarations

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this article.

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References

1. Schmitz G, Langmann T. Structure, function and regulation of the ABC1 gene product. Curr Opin Lipidol. 2001;12:129–40. https://doi.org/10.1097/00041433-200104000-00006.
2. Wang N, Silver DL, Thiele C, Tall AR. ATP-binding cassette transporter A1 (ABCA1) functions as a cholesterol efflux regulatory protein. J Biol Chem. 2001;276:23742–7. https://doi.org/10.1074/jbc.M102348200.
3. Singaraja RR, Fievet C, Castro G, James ER, Hennuyer N, Clee SM, Bissada N, Choy JC, Fruchart JC, McManus BM, Staels B, Hayden MR. Increased ABCA1 activity protects against atherosclerosis. J Clin Investig. 2002;110:35–42. https://doi.org/10.1172/JCI15748.
4. Bodzioch M, Orso E, Klucken J, Langmann T, Böttcher A, Diederich W, Drobnik W, Barlage S, Büchler C, Porsch-Ozcürümez 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;22:347–51. https://doi.org/10.1038/11914.
5. 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;22:336–45. https://doi.org/10.1038/11905.
6. 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;22:352–5. https://doi.org/10.1038/11921.
7. Tamehiro N, Shigemoto-Mogami Y, Kqkeya T, Okuhira K, Suzuki K, Sato R, Nagao T, Nishimaki-Mogami T. Sterol regulatory element-binding protein-2 and liver X receptor-driven dual promoter regulation of hepatic ABC transporter A1 gene expression: mechanism underlying the unique response to cellular cholesterol status. J Biol Chem. 2007;282:21090–9. https://doi.org/10.1074/jbc.M701228200.
8. Costet P, Luo Y, Wang N, Tall AR. Sterol-dependent transactivation of the ABC1 promoter by the liver X receptor/retinoid X receptor. J Biol Chem. 2000;275:28240–5. https://doi.org/10.1074/jbc.M003337200.
9. Schwartz K, Lawn RM, Wade DP. ABC1 gene expression and apo A-I-mediated cholesterol efflux are regulated by LXR. Biochem Biophys Res Commun. 2000;274:794–802. https://doi.org/10.1006/bbrc.2000.3243.
10. Field FJ, Watt K, Mathur SN. TNF-α decreases ABCA1 expression and attenuates HDL cholesterol efflux in the human intestinal cell line Caco-2. J Lipid Res. 2010;51:1407–15. https://doi.org/10.1194/jlr.M002410.
11. Broccardo C, Luciani M, Chimini G. The ABCA subclass of mammalian transporters. Biochim Biophys Acta. 1999;1461:395–404. https://doi.org/10.1016/s0005-2736(99)00170-4.
12. 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 USA. 2000;97:7987–92. https://doi.org/10.1073/pnas.97.14.7987.
13. Hozoji M, Munehira Y, Ikeda Y, Makishima M, Matsuo M, Kioka N, Ueda K. Direct interaction of nuclear liver X receptor-beta with ABCA1 modulates cholesterol efflux. J Biol Chem. 2008;283:30057–63. https://doi.org/10.1074/jbc.M804599200.
14. Lee JY, Parks JS. ATP-binding cassette transporter A1 and its role in HDL formation. Curr Opin Lipidol. 2005;16:19–25. https://doi.org/10.1097/00041433-200502000-00005.
15. Mooradian AD, Haas MJ. Targeting high-density lipoproteins: increasing de novo production versus decreasing clearance. Drugs. 2015;75:713–22. https://doi.org/10.1007/s40265-015-0390-1.
16. Wang J, Burnett JR, Neasr S, Young K, Zinman B, Hanley AJ, Connelly PW, Harris SB, Hegele RA. Common and rare ABCA1

variants affecting plasma HDL cholesterol. Arterioscler Thromb Vasc Biol. 2000;20:1983–9. https://doi.org/10.1161/01.atv.20.8.1983.
17. 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 JJ, Kastelein JJ, Hayden MR. Common genetic variation in ABCA1 is associated with altered lipoprotein levels and a modified risk for coronary artery disease. Circul. 2001;103:1198–205. https://doi.org/10.1161/01.cir.103.9.1198.
18. Harada T, Imai Y, Nojiri T, Morita H, Hayashi D, Maemura K, Fukino K, Kawanami D, Nishimura G, Tsushima K, Monzen K, Yamazaki T, Mitsuyama S, Shintani T, Watanabe N, Seto K, Sugiyama T, Nakamura F, Ohno M, Hirata Y, Yamazaki T, Nagai R. A common Ile 823 Met variant of ATP-binding cassette transporter A1 gene (ABCA1) alters high density lipoprotein cholesterol levels in Japanese population. Atherosclerosis. 2003;169:105–12. https://doi.org/10.1016/s0021-9150(03)00135-7.
19. Tregouet DA, Ricard S, Nicaud V, Arnould I, Soubigou S, Rosier M, Duverger N, Poirer O, Mace S, Kee F, Morrison C, Denefle P, Tiert L, Evans A, Deleuze JF, Cambien F. In-depth haplotype analysis of ABCA1 gene polymorphisms in relation to plasma apoAI levels and myocardial infarction. Arterioscler Thromb Vasc Biol. 2004;24:775–81. https://doi.org/10.1161/01.ATV.0000121573.29550.1a.
20. Frikke-Schmidt R, Nordestgaard BG, Jensen GB, Steffensen R, Tybaerg-Hansen A. Genetic variation in ABCA1 predicts ischemic heart disease in the general population. Arterioscler Thromb Vasc Biol. 2007;28:180–6. https://doi.org/10.1161/ATVBAHA.107.153858.
21. Hamjane N, Benyahya F, Nourouti NG, Mechita MB, Barakat A. Cardiovascular diseases and metabolic abnormalities associated with obesity: what is the role of inflammatory responses? A systematic review. Microvasc Res. 2020;131: 104023. https://doi.org/10.1016/j.mvr.2020.104023.
22. Motillo S, Filion KB, Genest J, Joseph L, Pilote L, Poirier P, Rinfret S, Schiffrin EL, Eisenberg MJ. The metabolic syndrome and cardiovascular risk: a systematic review and meta-analysis. J Am Coll Cardiol. 2010;56:1113–32. https://doi.org/10.1016/j.jacc.2010.05.034.
23. Kraus BR, Hartman AD. Adipose tissue and cholesterol metabolism. J Lipid Res. 1984;25:97–110.
24. Schreibman PH, Dell RB. Human adipocyte cholesterol. Concentration, localization, synthesis and turnover. J Clin Investig. 1975;55:986–93. https://doi.org/10.1172/JCI108028.
25. Yu BL, Zhao SP, Hu JR. Cholesterol imbalance in adipocytes: a possible mechanism of adipocyte dysfunction in obesity. Obes Rev. 2010;11:560–7. https://doi.org/10.1111/j.1467-789X.2009.00699.x.
26. Choramanska B, Mysliwiec P, Hady HR, Dadan J, Mysliwiec H, Bonda T, Chabowski A, Miklosz A. The implication of adipocyte ATP-binding cassette A1 and G1 transporters in metabolic complications of obesity. J Physiol Pharm. 2019;70:143–52. https://doi.org/10.26402/jpp.2019.1.14.
27. deHaan W, Bhattacharjee A, Ruddle P, Kang MH, Hayden MR. ABCA1 in adipocytes regulates adipose tissue lipid content, glucose tolerance, and insulin sensitivity. J Lipid Res. 2014;55:516–23. https://doi.org/10.1194/jlr.M045294.
28. Umemoto T, Han CY, Mitra P, et al. Apolipoprotein A1 and high-density lipoprotein have anti-inflammatory effects on adipocytes via cholesterol transporters: ATP-binding cassette A-1, ATP-binding cassette G-1, and scavenger receptor B-1. Circ Res. 2013;112:1345–54. https://doi.org/10.1161/CIRCRESAHA.111.300581.
29. Sparrow CP, Baffic J, Lam MH, Lund EG, Adams AD, Fu X, Hayes N, Jones AB, Macnaul KL, Ondeyka J, Singh S, Wang J, Zhou G, Moller DE, Wright SD, Menke JG. A potent synthetic LXR agonist is more effective than cholesterol loading at inducing ABCA1 mRNA and stimulating cholesterol efflux. J Biol Chem. 2002;277:10021–7. https://doi.org/10.1074/jbc.M108225200.
30. Quinet EM, Savio DA, Halpern AR, Chen L, Miller CP, Nambi P. Gene-selective modulation by a synthetic oxysterol ligand of the liver X receptor. J Lipid Res. 2004;45:1929–42. https://doi.org/10.1194/jlr.M400257-JLR200.
31. Hammer SS, Beli E, Kady N, Wang Q, Wood K, Lydic TA, Malek G, Saban DR, Wang XX, Hazra S, Levi M, Busik JV, Grant MB. The mechanism of diabetic retinopathy pathogenesis unifying key lipid regulators, sirtuin 1 and liver X receptor. EBioMedicine. 2017;22:181–90. https://doi.org/10.1016/j.ebiom.2017.07.008.
32. Kick E, Martin R, Xie Y, Flatt B, Schweiger E, Wang TL, Busch B, Nyman M, Gu XH, Yan G, Wagner B, Nanao M, Nguyen L, Stout T, Plonowski A, Schulman I, Ostrowski J, Kirchgessner T, Wexler R, Mohan R. Liver X receptor (LXR) partial agonists: biaryl pyrazoles and imidazoles displaying a preference for LXRβ. Bioorg Med Chem Lett. 2015;25:372–7. https://doi.org/10.1016/j.bmcl.2014.11.029.
33. Miao B, Zondlo S, Gibbs S, Cromley D, Hosagrahara VP, Kirchgessner TG, Billheimer J, Mukherjee R. Raising HDL cholesterol without inducing hepatic steatosis and hypertriglyceridemia by a selective LXR modulator. J Lipid Res. 2004;45:1410–7. https://doi.org/10.1194/jlr.M300450-JLR200.
34. Delvecchio CJ, Bilan P, Radford K, Stephen J, Trigatti BL, Cox G, Parameswaran K, Capone JP. Liver X receptor stimulates cholesterol efflux and inhibits expression of proinflammatory mediators in human airway smooth muscle cells. Mol Endocrinol. 2007;21:1324–34. https://doi.org/10.1210/me.2007-0017.
35. Kannisto K, Gafvels M, Jiang Z-Y, Slatis K, Hu X, Jorns C, Steffensen KR, Eggerston G. LXR driven induction of HDL-cholesterol is independent of intestinal cholesterol absorption and ABCA1 protein expression. Lipids. 2014;49:71–83. https://doi.org/10.1007/s11745-013-3853-8.
36. DiBlasio-Smith EA, Arai M, Quinet EM, Evans MJ, Kornaga T, Basso MD, Chen L, Feingold I, Halpern AR, Liu Q-Y, Nambi P, Savio D, Wang S, Mounts WM, Isler JA, Slager AM, Burczynski ME, Dorner AJ, LaVallie ER. Discovery and implementation of transcriptional biomarkers of synthetic LXR agonists in peripheral blood cells. J Transl Med. 2008;6:59. https://doi.org/10.1186/1479-5876-6-59.
37. Quinet EM, Basso MD, Halpern AR, Yates DW, Steffan RJ, Clerin V, Resmini C, Keith JC, Berrodin TJ, Feingold I, Wenyan Zhong W, Hartman HB, Evans MJ, Gardell SJ, DiBlasio-Smith E, Mounts WM, LaVallie ER, Wrobel J, Nambi P, Vlasuket GP. LXR ligand lowers LDL cholesterol in primates, is lipid neutral in hamster, and reduces atherosclerosis in mouse. J Lipid Res. 2009;50:2358–70. https://doi.org/10.1194/jlr.M900037-JLR200.
38. Yan W, Zhang T, Cheng J, Zhou X, Qu X, Hu H. Liver X receptor agonist methyl-3β-hydroxy-5α,6α-epoxycholonate attenuates atherosclerosis in apolipoprotein E knockout mice without increasing plasma triglyceride. Pharmacology. 2010;86:306–12. https://doi.org/10.1159/000321320.
39. Castro Navas FF, Giorgi G, Maggioni D, Pacciarini M, Russo V, Marinozzi M. C24-hydroxylated stigmastane derivatives as liver X receptor agonists. Chem Phys Lipids. 2018;212:44–50. https://doi.org/10.1016/j.chemphyslip.2018.01.005.
40. Marinozzi M, Castro Navas FF, Maggioni D, Carosati E, Bocci G, Carloncelli M, Giorgi G, Cruciani G, Fontana R, Russo V. Side-chain modified ergosterol and stigmasterol derivatives as

liver X receptor agonists. J Med Chem. 2017;60:6548–62. https://doi.org/10.1021/acs.jmedchem.7b00091.
41. Fukomoto 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 beta levels. J Biol Chem. 2002;277:48508–13. https://doi.org/10.1074/jbc.M209085200.
42. Terasaka N, Hiroshima A, Koieyama T, Ubukata N, Morikawa Y, Nakai D, Inaba T. T-0901317, a synthetic liver X receptor ligand, inhibits development of atherosclerosis in LDL receptor-deficient mice. FEBS Lett. 2003;536:6–11. https://doi.org/10.1016/s0014-5793(02)03578-0.
43. Beyer TP, Schmidt RJ, Foxworthy P, Zhang Y, Dai J, Bensch WR, Kauffman RF, Gao H, Ryan TP, Jiang XC, Karathanasis SK, Eacho PI, Cao G. Coadministration of a liver X receptor agonist and a peroxisome proliferator activator receptor-alpha agonist in mice: effects of nuclear receptor interplay on high-density lipoprotein and triglyceride metabolism in vivo. J Pharmacol Exp Ther. 2004;309:861–8. https://doi.org/10.1124/jpet.103.064535.
44. Quinet EM, Savio DA, Halpern AR, Chen L, Schuster GU, Gustafson J-A, Basso MD, Nambi P. Liver X receptor (LXR)-beta regulation in LXRalpha-deficient mice: implications for therapeutic targeting. Mol Pharmacol. 2006;70:1340–9. https://doi.org/10.1124/mol.106.022608.
45. 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;38:1314–29. https://doi.org/10.1016/j.biocel.2006.01.013.
46. Dai X-Y, Ou X, Hao X-R, Cao D-L, Tang Y-L, Hu Y-W, Li X-X, Tang C-K. The effect of T0901317 on ATP-binding cassette transporter A1 and Niemann-Pick type C1 in apo $E^{-/-}$ mice. J Cardiovasc Pharmacol. 2008;51:467–75. https://doi.org/10.1097/FJC.0b013e31816a5be3.
47. Zannotti I, Poti F, Pedrelli M, Favari E, Moleri E, Franceschini G, Calabresi L, Bernini F. The LXR agonist T0901317 promotes the reverse cholesterol transport from macrophages by increasing plasma efflux potential. J Lipid Res. 2008;49:954–60. https://doi.org/10.1194/jlr.M700254-JLR200.
48. Larrede S, Quinn CM, Jessup W, Frisdal E, Olivier M, Hsieh V, Kim M-J, Van Eck M, Couvert P, Carrie A, Giral P, Chapman MJ, Guerin M, Le Goff W. Stimulation of cholesterol efflux by LXR agonists in cholesterol-loaded human macrophages is ABCA1-dependent but ABCG1-independent. Arterioscler Thromb Vasc Biol. 2009;29:1930–6. https://doi.org/10.1161/ATVBAHA.109.194548.
49. Vershuren L, de Vries-van der Weij J, Zadelaar S, Kleemann R, Koostra T. LXR agonist suppresses atherosclerotic lesion growth and promotes lesion regression in apo E*3Leiden mice: time course and mechanisms. J Lipid Res. 2009;50:301–11. https://doi.org/10.1194/jlr.M800374-JLR200.
50. Maejima T, Sugano T, Yamazaki H, Yoshinaka Y, Doi T, Tanabe S, Nishimaki-Mogami T. Pitavastatin increases ABCA1 expression by dual mechanisms: SREBP2-driven transcriptional activation and PPARα-dependent protein stabilization but without activating LXR in rat hepatoma McARH7777 cells. J Pharmacol Sci. 2011;116:107–15. https://doi.org/10.1254/jphs.10241fp.
51. Honzumi S, Shima A, Hiroshima A, Koieyama T, Terasaka N. Synthetic LXR agonist inhibits the development of atherosclerosis in New Zealand White rabbits. Biochim Biophys Acta. 2011;1811:1136–45. https://doi.org/10.1016/j.bbalip.2011.08.009.
52. Chen J, Zhao L, Sun D, Narsinh K, Li C, Zhang Z, Qi S, Wei G, Li W, Guo W, Cao F. Liver X receptor activation attenuates plaque formation and improves vasomotor function of the aortic artery in atherosclerotic apoE(−/−) mice. Inflamm Res. 2012;61:1299–307. https://doi.org/10.1007/s00011-012-0529-4.
53. Ma AZS, Song ZY, Zhang Q. Cholesterol efflux is LXRα isoform dependent in human macrophages. BMC Cardiovasc Disord. 2014;14:80. https://doi.org/10.1186/1471-2261-14-80.
54. Kirchgessner TG, Martin R, Sleph P, Grimm D, Liu X, Lupisella J, Smalley J, Narayanan R, Xie Y, Ostrowsk J, Cantor GH, Mohan R, Kick E. Pharmacological characterization of a novel liver X receptor agonist with partial LXRα activity and a favorable window in nonhuman primates. J Pharmacol Exp Ther. 2015;352:305–14. https://doi.org/10.1124/jpet.114.219923.
55. Manna PR, Sennoune SR, Martinez-Zaguilan R, Slominski AI, Pruitt K. Regulation of retinoid-mediated cholesterol efflux involves liver X receptor activation in mouse macrophages. Biochem Biophys Res Commun. 2015;2015(464):312–7. https://doi.org/10.1016/j.bbrc.2015.06.150.
56. Tamehiro N, Park MH, Hawxhurst V, Nagpal K, Adams K, Zannis VI, Colenbock DT, Fitzgerald ML. LXR agonism upregulates the macrophage ABCA1/syntrophin protein complex that can bind apoA-I and stabilized ABCA1 protein, but complex loss does not inhibit lipid efflux. Biochem. 2015;54:6931–41. https://doi.org/10.1021/acs.biochem.5b00894.
57. Carter AY, Letronne F, Fitz NF, Mounier A, Wolfe CM, Nam KNM, Reeves VL, Kamboh H, Lefterov I, Koldamova R. Liver X receptor agonist treatment significantly affects phenotype and transcriptome of APOE3 and APOE4 Abca1 haplo-deficient mice. PLoS ONE. 2017;12:e0172161. https://doi.org/10.1371/journal.pone.0172161.
58. Kaseda R, Tsuchida Y, Yang HC, Yancey PG, Zhong J, Tao H, Bian A, Fogo AB, Linton MRF, Fazio S, Ikizler TA, Kon V. Chronic kidney disease alters lipid trafficking and inflammatory responses in macrophages: effects of liver X receptor agonism. BMC Nephrol. 2018;18:17. https://doi.org/10.1186/s12882-018-0814-8.
59. Katz A, Udata C, Ott E, Hickey L, Burczynski ME, Burghart P, Vesterqvist O, Meng X. Safety, pharmacokinetics, and pharmacodynamics of single doses of LXR-623, a novel liver X-receptor agonist, in healthy participants. J Clin Pharm 2009;49:643–9. https://doi.org/10.1177/0091270009335768.
60. LaClair KD, Manaye KF, Lee DL, Allard JS, Savonenko AV, Troncoso JC, Wong PC. Treatment with bexarotene, a compound that increases apolipoprotein E, provides no cognitive benefit in mutant APP/PS1 mice. Mol Neurodegener. 2013;8:18. https://doi.org/10.1186/1750-1326-8-18.
61. Kuntz MM, Candela P, Saint-Pol J, Lamartiniere Y, Boucau MC, Sevin E, Fenart L, Gosselet F. Bexarotene promotes cholesterol efflux and restricts apical-to-basolateral transport of amyloid-β peptides in an in vitro model of the human blood-brain barrier. J Alzheimer's Dis. 2015;48:849–62. https://doi.org/10.3233/JAD-150469.
62. Tachibana M, Shinohara M, Yamazaki Y, Liu C-C, Roger J, Bu G, Kanekiyo T. Rescuing effects of RXR-agonist bexarotene on aging-related synapse loss depend on neuronal LRP1. Exp Neuro. 2016;277:1–9. https://doi.org/10.1016/j.expneurol.2015.12.003.
63. Nishimaki-Mogami T, Tamehiro N, Sato Y, Okuhira K, Sai K, Kagechika H, Shudo K, Abe-Dohmae S, Yokoyama S, Ohno Y, Inoue K, Sawada J-I. The RXR agonists PA024 and HX630 have different abilities to activate LXR/RXR and to induce ABCA1 expression in macrophage cell lines. Biochem Pharmacol. 2008;76:1006–13. https://doi.org/10.1016/j.bcp.2008.08.005.
64. Claudel T, Leibowitz MD, Fievet C, Tailleux A, Wagner B, Repa JJ, Torpier G, Lobaccaro JM, Paterniti JR, Mangelsdorf DJ, Heyman RA, Auwerx J. Reduction of atherosclerosis in apolipoprotein E knockout mice by activation of the retinoid X receptor.

Proc Natl Acad Sci USA. 2001;98:2610–5. https://doi.org/10.1073/pnas.041609298.
65. Chawla A, Boisvert WA, Lee CH, Laffitte BA, Barak Y, Joseph SB, Liao D, Nagy L, Edwards PA, Curtiss LK, Evans RM, Tontonoz P. A PPAR gamma-LXR-ABCA1 pathway in macrophages is involved in cholesterol efflux and atherogenesis. Mol Cell. 2001;7:161–71. https://doi.org/10.1016/s1097-2765(01)00164-2.
66. 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;289:1524–9. https://doi.org/10.1126/science.289.5484.1524.
67. Chen X, Zhao Y, Guo Z, Zhou L, Okoro EU, Yang H. Transcriptional regulation of ATP-binding cassette transporter A1 expression by a novel signaling pathway. J Biol Chem. 2011;286:8917–23. https://doi.org/10.1074/jbc.M110.214429.
68. Cui H, Okuhira K, Ohoka N, Naito M, Kagechika H, Hirose A, Nishimaki-Mogami T. Tributylin chloride induces ABCA1 expression and apolipoprotein A-1-mediated cellular cholesterol efflux by activating LXRα/RXRα. Biochem Pharmacol. 2011;81:819–24. https://doi.org/10.1016/j.bcp.2010.12.023.
69. Sun Y, Fan J, Zhu Z, Guo X, Zhou T, Duan W, Shen X. Small molecule TBTC as a new selective retinoid X receptor α agonist improves behavioral deficit in Alzheimer's disease model mice. Eur J Pharmacol. 2015;762:202–13. https://doi.org/10.1016/j.ejphar.2015.05.050.
70. Costet P, Lalanne F, Gerbod-Giannone MC, Molina JR, Fu X, Lund EG, Gudas LJ, Tall AR. Retinoic acid receptor-mediated induction of ABCA1 in macrophages. Mol Cell Biol. 2003;23:7756–66. https://doi.org/10.1128/MCB.23.21.7756-7766.2003.
71. Chen J, Costa LG, Guizzeti M. Retinoic acid isomers up-regulate ATP binding cassette A1 and G1 and cholesterol efflux in rat astrocytes: implications for their therapeutic and teratogenic effects. J Pharmacol Exp Ther. 2011;338:870–8. https://doi.org/10.1124/jpet.111.182196.
72. Arora A, Taskinen JH, Olkkonen VM. Coordination of interorganelle communication and lipid fluxes by OSBP-related proteins. Prog Lipid Res. 2022;86: 101146. https://doi.org/10.1016/j.plipres.2022.101146.
73. van der Kant R, Zondervan I, Janssen L, Neefjes J. Cholesterol-binding molecules MLN64 and ORP1L mark distinct late endosomes with transporters ABCA3 and NPC1. J Lipid Res. 2013;54:2153–65. https://doi.org/10.1194/jlr.M037325.
74. Zhao K, Ridgway ND. Oxysterol-binding protein-related protein 1L regulates cholesterol egress from the endo-lysosomal system. Cell Rep. 2017;19:1807–18. https://doi.org/10.1016/j.celrep.2017.05.028.
75. Lee S, Wang PY, Jeong Y, Mangelsdorf DJ, Anderson RG, Michaely P. Sterol-dependent nuclear import of ORP1S promotes LXR regulated trans-activation of apoE. Exp Cell Res. 2012;318:2128–42. https://doi.org/10.1016/j.yexcr.2012.06.012.
76. Wright MB, Santos JV, Kemmer C, Maugeais C, Carralot J-P, Roever S, Molina J, Ducasa GM, Mitrofanova A, Sloan A, Ahmad A, Pedigo C, Ge M, Pressly J, Barisoni L, Mendez A, Sgrignani J, Cavalli A, Merscher S, Prunotto M, Fornoni A. Compounds targeting OSBPL7 increase ABCA1-dependent cholesterol efflux preserving kidney function in two models of kidney disease. Nat Commun. 2021;12:4662. https://doi.org/10.1038/s41467-021-24890-3.
77. Miranda van Eck M, Bos IST, Kaminski WE, Evelyn Orsó E, Gregor Rothe G, Jaap Twisk J, Alfred Böttcher A, Edwin S, Van Amersfoort ES, Trudy A, Christiansen-Weber TA, Wai-Ping Fung-Leung W-P, Theo JC, Van Berkel TJC, Gerd Schmitz G. Luekocyte ABCA1 controls susceptibility to atherosclerosis and macrophage recruitment into tissues. Proc Natl Acad Sci USA. 202;99:6298–303. https://doi.org/10.1073/pnas.092327399.
78. Zhou W, Lin J, Chen H, Wang J, Liu Y, Xia M. Retinoic acid induces macrophage cholesterol efflux and inhibits atherosclerotic plaque formation in apoE-deficient mice. Br J Nutr. 2015;114:509–18. https://doi.org/10.1017/S0007114515002159.
79. Lasch A, Alarcan J, Lampen A, Braeuning A, Lichtenstein D. Combinations of LXR and RXR agonists induced triglyceride accumulation in human HepaRG cells in a synergistic manner. Arch Toxicol. 2020;94:1303–20. https://doi.org/10.1007/s00204-020-02685-7.
80. Suzuki Y, Shimada J, Shudo K, Matsumura M, Crippa MP, Kojima S. Physical interaction between retinoic acid receptor and Sp1: mechanism for induction of urokinase by retinoic acid. Blood. 1999;1999(93):4264–76. https://doi.org/10.1182/blood.V93.12.4264.
81. Huang YC, Chen JY, Hung WC. Vitamin D3 receptor/Sp2 complex is required for the induction of p27Kip1 expression by vitamin D3. Oncogene. 2004;23:4856–61. https://doi.org/10.1038/sj.onc.1207621.
82. Sun G, Porter W, Safe S. Estrogen-induced retinoic acid receptor alpha 1 gene expression: role of estrogen receptor-Sp1 complex. Mol Endocrinol. 1998;12:882–90. https://doi.org/10.1210/mend.12.6.0125.
83. Thymiakou E, Zannis VI, Kardassis D. Physical and functional interactions between liver X receptor/retinoid X receptor and Sp1 modulate the transcriptional induction of the human ATP binding cassette transporter A1 gene by oxysterols and retinoids. Biochem. 2007;46:11473–83. https://doi.org/10.1021/bi700994m.
84. Meyers CD, Kamanna VS, Kashyap ML. Niacin therapy in atherosclerosis. Curr Opin Lipidol. 2004;15:659–65. https://doi.org/10.1097/00041433-200412000-00006.
85. Carlson LA. Nicotinic acid and other therapies for raising high-density lipoprotein. Curr Opin Cardiol. 2006;21:336–44. https://doi.org/10.1097/01.hco.0000231404.76930.e9.
86. AIM-High Investigators, Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med. 2011;365:2244–67. https://doi.org/10.1056/NEJMoa1107579.
87. Shepherd J, Packard CJ, Patsch JR, Gotto AM Jr, Taunton OD. Effects of nicotinic acid therapy on plasma high density lipoprotein subfraction and composition and on apolipoprotein A metabolism. J Clin Investig. 1979;63:858–67. https://doi.org/10.1172/JCI109385.
88. Grundy SM, Mok HY, Zech L, Berman M. Influence of nicotinic acid on metabolism of cholesterol and triglycerides in man. J Lipid Res. 1981;22:24–36. https://doi.org/10.1016/S0022-2275(20)34737-4.
89. Lamon-Fava SM, Diffenderfer MR, Barrett PH, Buchsbaum A, Nyaku M, Horvath KV, Asztalos BF, Otokozawa S, Ai M, Matthan NR, Lichtenstein AH, Dolnikowski GG, Schaefer EJ. Extended-release niacin alters the metabolism of plasma apolipoprotein (apo) A-I and ApoB-containing lipoproteins. Arterioscler Thromb Vasc Biol. 2008;28:1672–8. https://doi.org/10.1161/ATVBAHA.108.164541.
90. Haas MJ, Alamir A-R, Sultan S, Chehade JM, Wong NCW, Mooradian AD. Nicotinic acid induces apolipoprotein A-I gene expression in HepG2 and Caco-2 cell lines. Metabolism. 2011;60:1790–6. https://doi.org/10.1016/j.metabol.2011.05.005.
91. Zhang L-H, Kamanna VS, Ganji SH, Xiong X-M, Kashyap ML. Niacin increases HDL biogenesis by enhancing DR4-dependent transcription of ABCA1 and lipidation of apolipoprotein A-I in HepG2 cells. J Lipid Res. 2012;53:941–50. https://doi.org/10.1194/jlr.M020917.

92. Matsuura F, Oku H, Koseki M, Sandoval JC, Yuasa-Kawase M, Tsubakio-Yamamoto K, Masuda D, Maeda N, Tsujii K-I, Ishigami M, Nishida M, Hirano K-I, Kihara S, Hori M, Shimomura I, Yamashita S. Adiponectin accelerates reverse cholesterol transport by increasing high density lipoprotein assembly in the liver. Biochem Biophys Res Commun. 2007;358:1091–5. https://doi.org/10.1016/j.bbrc.2007.05.040.
93. Liang B, Wang X, Guo W, Yang Z, Bai R, Liu M, Xiao C, Bian Y. Adiponectin upregulates ABCA1 expression through liver X receptor alpha signaling pathway in RAW 264.7 macrophages. Int J Clin Exp Pathol. 2015;8:450–7.
94. Oku H, Matsuura F, Koseki M, Sandoval JC, Yuasa-Kawase M, Tsubakio-Yamamoto K, Masuda D, Maeda N, Ohama T, Ishigami M, Nishida M, Hirano K-I, Kihara S, Hori M, Shimomura K, Yamashita S. Adiponectin deficiency suppresses ABCA1 expression and apo A-I synthesis in the liver. FEBS Lett. 2007;581:5029–33. https://doi.org/10.1016/j.febslet.2007.09.038.
95. Kumada M, Kihara S, Sumitsuji S, Kawamoto T, Matsumoto S, Ouchi N, Arita Y, Okamoto Y, Shimomura I, Kiraoka H, Nakamura T, Funahashi T, Matsuza Y, Osaka CAD Study Group. Coronary artery disease. Association of hypoadiponectinemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol. 2003;23:85–9. https://doi.org/10.1161/01.atv.0000048856.22331.50.
96. Ryo M, Nakamura T, Kihara S, Kumada M, Shibazaki S, Takahashi M, Nagai M, Matsuzawa Y, Funahashi T. Adiponectin as a biomarker of the metabolic syndrome. Circ J. 2004;68:975–81. https://doi.org/10.1253/circj.68.975.
97. Ntalos G, Gatselis NK, Makaritsis K, Dalekos GN. Adipokines as mediators of endothelial function and atherosclerosis. Atherosclerosis. 2013;227:216–21. https://doi.org/10.1016/j.atherosclerosis.2012.12.029.
98. Lee S, Kwak HB. Role of adiponectin in metabolic and cardiovascular disease. J Exerc Rehabil. 2014;10:54–9. https://doi.org/10.12965/jer.140100.
99. Argmann CA, Sawyez CG, McNeil CJ, Hegele RA, Huff MW. Activation of peroxisome proliferator-activated receptor gamma and retinoid receptor results in net depletion of cellular cholesteryl esters in macrophages exposed to oxidized lipoproteins. Arterioscler Thromb Vasc Biol. 2003;23:475–82. https://doi.org/10.1161/01.ATV.0000058860.62870.6E.
100. Wang X, Luo J, Li N, Liu L, Han X, Liu C, Zuo X, Jiang X, Li Y, Xu Y, Si S. E3317 promotes cholesterol efflux in macrophage cells via enhancing ABCA1 expression. Biochem Biophys Res Commun. 2018;504:68–74. https://doi.org/10.1016/j.bbrc.2018.08.125.
101. Silva JC, de Oliveira EM, Turato WM, Trossini GHG, Maltarollo VG, Pitta MGR, Pitta IR, de Las HB, Bosca L, Rudnicki M, Abdalla DSP. GQ-11: a new PPAR agonist improves obesity-induced metabolic alterations in LDLr$^{-/-}$ mice. Int J Obes. 2018;42:1062–72. https://doi.org/10.1038/s41366-018-0011-7.
102. Nakaya K, Ayaori M, Hisada T, Sawada S, Tanaka N, Iwamoto N, Ogura M, Yakushiji E, Kusuhara M. Telmisartan enhances cholesterol efflux from THP-1 macrophages by activating PPARgamma. J Atheroscler Thromb. 2007;14:133–41. https://doi.org/10.5551/jat.14.133.
103. Mogilenko DA, Shavva VS, Dizhe EB, Orlov SV, Perevozhikov AP. PPARγ activates ABCA1 gene transcription but reduces the level of ABCA1 protein in HepG2 cells. Biochem Biophys Res Commun. 2010;2010(402):477–82. https://doi.org/10.1016/j.bbrc.2010.10.053.
104. Tanabe J, Tamasawa N, Yamashita N, Matsuki K, Murakami H, Matsui J, Sugimoto K, Yasujima M, Suda T. Effects of combined PPARgamma and PPARalpha agonist therapy on reverse cholesterol transport in the Zucker diabetic fatty rat. Diabetes Obes Metab. 2008;10:772–9. https://doi.org/10.1111/j.1463-1326.2007.00810.x.
105. Jiang M, Li X. Activation of PPARγ does not contribute to macrophage ABCA1 expression and ABCA1-mediated cholesterol efflux to apoAI. Biochem Biophys Res Comm. 2017;482:849–56. https://doi.org/10.1016/j.bbrc.2016.11.123.
106. Ogata M, Tsujita M, Hossain MA, Akita N, Gonzalez FJ, Staels B, Suzuki S, Fukutomi T, Kumura G, Yokoyama S. On the mechanism for PPAR agonists to enhance ABCA1 gene expression. Atherosclerosis. 2009;205:413–9. https://doi.org/10.1016/j.atherosclerosis.2009.01.008.
107. Ozaka H, Ayaori M, Iizuka M, Terao Y, Uto-Kondo H, Yakushiji E, Takiguchi S, Nakaya KM, Hisada T, Uehara Y, Masatsune Ogura M, Makoto Sasaki M, Komatsu T, Horii S, Mochizuki S, Yoshimura M, Ikewaki K. Pioglitazone enhances cholesterol efflux from macrophages by increasing ABCA1/ABCG1 expression via PPARγ/LXRα pathway: findings from in vitro and ex vivo studies. Atherosclerosis. 2011;219:141–50. https://doi.org/10.1016/j.atherosclerosis.2011.07.113.
108. Wang J-M, Wang D, Tan YY, Zhao G, Ji ZL. 22(R)-hydroxycholesterol and pioglitazone synergistically decrease cholesterol ester via the PPARγ-LXRα-ABCA1 pathway in cholesterosis of the gallbladder. Biochem Biophys Res Commun. 2014;447:152–7. https://doi.org/10.1016/j.bbrc.2014.03.130 (**Epub 2014 Apr 2**).
109. Chinetti G, Lestavel S, Bocher V, Ramaley AT, Neve B, Torra IP, Teissier E, Minnich A, Jaye M, Duverger N, Brewer HB, Fruchart JC, Clavey V, Staels B. PPAR-alpha and PPAR-gamma activators induce cholesterol removal from human macrophage foam cells through stimulation of the ABCA1 pathway. Nat Med. 2001;7:53–8. https://doi.org/10.1038/83348.
110. Li AC, Binder CJ, Gutierrez A, Brown KK, Plotkin CR, Pattison JW, Valledor AF, Davis RA, Wilson TM, Witzum JL, Palinski W, Glass CK. Differential inhibition of macrophage foam-cell formation and atherosclerosis in mice by PPARalpha, beta/delta, and gamma. J Clin Investig. 2004;114:1564–76. https://doi.org/10.1172/JCI18730.
111. Li C, Tu Y, Liu T-R, Guo Z-G, Xie D, Zhong J-K, Fan Y-Z, Lai W. Rosiglitazone attenuates atherosclerosis and increases high-density lipoprotein function in atherosclerotic rabbits. Int J Mol Med. 2015;35:715–23. https://doi.org/10.3892/ijmm.2015.2072.
112. Llaveria G, Rebollo A, Pou J, Vazquez-Carrera M, Sanchez RM, Laguna JC, Alegret M. Effects of rosiglitazone and atorvastatin on the expression of genes that control cholesterol homeostasis in differentiating monocytes. Biochem Pharmacol. 2006;71:605–14. https://doi.org/10.1016/j.bcp.2005.11.022.
113. Cabrero A, Cubero M, Llaverias G, Jove M, Planavila A, Alegret MN, Sanchez R, Laguna JC, Carrera MV. Differential effects of peroxisome proliferator-activated receptor activators on the mRNA levels of genes involved in lipid metabolism in primary human monocyte-derived macrophages. Metabolism. 2003;52:652–7. https://doi.org/10.1053/meta.2003.50100.
114. Lee J, Hong EM, Byun HW, Choi MH, Jang HJ, Eun CS, Kae SH, Choi HS. The effect of PPARalpha and PPARgamma ligands on inflammation and ABCA1 expression in cultured gallbladder epithelial cells. Dig Dis Sci. 2008;53:1707–15. https://doi.org/10.1007/s10620-007-0029-5.
115. Ruan XZ, Moorhead JF, Fernando R, Wheeler DC, Powis SH, Varghese Z. PPAR agonists protect mesangial cells from interleukin 1beta-induced intracellular lipid accumulation by activating the ABCA1 cholesterol efflux pathway. J Am Soc Nephrol. 2003;14:593–600. https://doi.org/10.1097/01.asn.0000050414.52908.da.
116. Guan J-Z, Tamasawa N, Murakami H, Matsui J, Yamato K, Suda T. Clofibrate, a peroxisome-proliferator, enhances reverse cholesterol transport through cytochrome P450 activation and oxysterol

generation. Tohoku J Exp Med. 2003;201:251–9. https://doi.org/10.1620/tjem.201.251.
117. Thomas J, Bramlett KS, Montrose C, Foxworthy P, Eacho PI, McCann D, Cao G, Keifer A, McCowan J, Yu K-L, Grese T, Chin WW, Burris TP, Michael LF. A chemical switch regulates fibrate specificity for peroxisome proliferator-activated receptor alpha (PPARalpha) versus liver X receptor. J Biol Chem. 2003;2003(278):2403–10. https://doi.org/10.1074/jbc.M209629200.
118. Forcheron F, Cachefo A, Thevebib S, Pinteur C, Beylot M. Mechanisms of the triglyceride-and cholesterol-lowering effect of fenofibrate in hyperlipidemic type 2 diabetic patients. Diabetes. 2002;2002(51):3486–91. https://doi.org/10.2337/diabetes.51.12.3486.
119. Kooistra T, Verschuren L, de Vries-van der Weij J, Koenig W, Toet K, Princen HMG, Kleemann R. Fenofibrate reduces atherogenesis in ApoE*Leiden mice: evidence for multiple antiatherogenic effects besides lowering plasma cholesterol. Arterioscler Thromb Vasc Biol. 2006;26:2322-30. https://doi.org/10.1161/01.ATV.0000238348.05028.14.
120. Briand F, Naik SU, Fuki I, Millar JS, MacPhee C, Walker M, Billheimer J, Rothblat G, Rader DJ. Both the peroxisome proliferator-activated receptor delta agonist, GW0742, and ezetimibe promote reverse cholesterol transport in mice by reducing intestinal reabsorption of HDL-derived cholesterol. Clin Trans Sci. 2009;2:127–33. https://doi.org/10.1111/j.1752-8062.2009.00098.x.
121. Sprecher DL, Massien C, Pearce G, Billin AN, Perlstein I, Wilson TM, Hassall DG, Ancellin N, Patterson SD, Lobe DE, Johnson TG. Triglyceride: high-density lipoprotein cholesterol effects in healthy subjects administered a peroxisome proliferator activated receptor delta agonist. Arterioscler Thromb Vasc Biol. 2007;27:359–65. https://doi.org/10.1161/01.ATV.0000252790.70572.0c.
122. Oliver WR Jr, Shenk JL, Snaith MR, Russell CS, Plunket KD, Bodkin NL, Lweis MC, Winegar DA, Sznaidman ML, Lambert MH, Xu HE, Sternbach DD, Kliewer SA, Hansen BC, Wilson TM. A selective peroxisome proliferator-activated receptor delta agonist promotes reverse cholesterol transport. Proc Natl Acad Sci USA. 2001;98:5306–11. https://doi.org/10.1073/pnas.091021198.
123. Szanto A, Benko S, Szatmari I, Balint BL, Furtos I, Ruhl R, Molnar S, Csiba L, Ganti R, Calandra S, Larrson H, Diczfalusy U, Nagy L. Transcriptional regulation of human CYP27 integrates retinoid, peroxisome proliferator-activated receptor, and liver X receptor signaling in macrophages. Mol Cell Biol. 2004;2004(24):8154–66. https://doi.org/10.1128/MCB.24.18.8154-8166.2004.
124. Yoshii H, Onuma T, Yamazaki T, Watada H, Matsuhisa M, Matsumoto M, Kitagawa K, Kitakaze M, Yamasaki Y, Kawamori R, PROFIT-J Study Group. Effects of pioglitazone on macrovascular events in patients with type 2 diabetes mellitus at high risk of stroke: the PROFIT-J study. J Atheroscler Thromb 2014;21:563–73. https://doi.org/10.5551/jat.21626.
125. Tsunoda F, Asztalos IB, Horvath KV, Steiner G, Schaefer EJ, Asztalos BF. Fenofibrate, HDL, and cardiovascular disease in type-2 diabets: the DAIS trial. Atheroscler. 2016;247:35–9. https://doi.org/10.1016/j.atherosclerosis.2016.01.028.
126. Triolo M, Annema W, de Boer JF, Tietge UJF, Dullaart RPF. Simvastatin and bezafibrate increase cholesterol efflux in men with type 2 diabetes. Eur J Clin Investig. 2014;44:240–8. https://doi.org/10.1111/eci.12226.
127. Maejima T, Yamazaki H, Aoki T, Tamaki T, Sato F, Kitahara M, Saito Y. Effect of pitavastatin on apolipoprotein A-I production in HepG2 cells. Biochem Biophys Res Commun. 2004;324:835–9. https://doi.org/10.1016/j.bbrc.2004.09.122.
128. Sone H, Shimano H, Shu M, Nakakuki M, Takahashi A, Sakai M, Sakamoto Y, Yokoo T, Matsuzaka K, Okazaki H, Nakagawa Y, Iida KT, Suzuki H, Toyoshima H, Horiuchi S, Yamada N. Statins downregulate ATP-binding-cassette transporter A1 gene expression in macrophages. Biochem Biophys Res Commun. 2004;316:790–4. https://doi.org/10.1016/j.bbrc.2004.02.121.
129. Ando H, Tsuruoka S, Yamamoto H, Takamura T, Kaneko S, Fujimura A. Effects of pravastatin on the expression of ATP-binding cassette transporter A1. J Pharm Exp Therap. 2004;311:420–5. https://doi.org/10.1124/jpct.104.068213.
130. Martin C, Duez H, Blanquart C, Berezowski V, Poulain P, Fruchart JC, Najib-Fruchart J, Glineur C, Staels B. Statin-induced inhibition of the Rho-signaling pathway activates PPARalpha and induces HDL, apoA-I. J Clin Investig. 2001;107:1423–32. https://doi.org/10.1172/JCI10852.
131. Fajas L, Schoonjans K, Gelman L, Kim JB, Najib J, Martin G, Fruchart JC, Briggs M, Spiegelman BM, Auwerx J. Regulation of peroxisome proliferator activated receptor gamma expression by adipocyte differentiation and determination factor 1/sterol regulatory element binding protein 1: implications for adipocyte differentiation and metabolism. Mol Cell Biol. 1999;19:5495–503. https://doi.org/10.1128/MCB.19.8.5495.
132. Lee CJ, Choi S, Cheon DH, Kim KY, Cheon EJ, Ann S-J, Noh H-M, Park S, Kang S-M, Choi D, Lee JE, Lee S-H. Effect of two lipid-lowering strategies on high-density lipoprotein function and some HDL-related proteins: a randomized clinical trial. Lipids Health Dis. 2017;16:49. https://doi.org/10.1186/s12944-017-0433-6.
133. Murao K, Wada Y, Nakamura T, Taylor AH, Mooradian AD, Wong NC. Effects of glucose and insulin on rat apolipoprotein A-I gene expression. J Biol Chem. 1998;273:18959–65. https://doi.org/10.1074/jbc.273.30.18959.
134. Lam JK, Matsubara S, Mihara K, Zheng XL, Mooradian AD, Wong NC. Insulin induction of apolipoprotein AI, role of Sp1. Biochem. 2003;42:2680–90. https://doi.org/10.1021/bi026984h.
135. Nonomura K, Arai Y, Mitani H, Abe-Dohmae S, Yokoyama S. Insulin down-regulates specific activity of ATP-binding cassette transporter A1 for high density lipoprotein biogenesis through its specific phosphorylation. Atherosclerosis. 2011;216:334–41. https://doi.org/10.1016/j.atherosclerosis.2011.02.021.
136. Turcot V, Bouchard L, Faucher G, Tchernof A, Deshaies Y, Perusse L, Bélisle A, Marceau S, Biron S, Lescelleur O, Biertho L, Vohl MC. DPP4 gene DNA methylation in the omentum is associated with its gene expression and plasma lipid profile in severe obesity. Obesity. 2011;19:388–95. https://doi.org/10.1038/oby.2010.198.
137. Bouchard L, Thibaoult S, Guay SP, Santure M, Monpetit A, St-Pierre J, Perron P, Brisson D. Leptin gene epigenetic adaptation to impaired glucose metabolism during pregnancy. Diabetes Care. 2010;33:2436–41. https://doi.org/10.2337/dc10-1024.
138. Tobi EW, Lumey LH, Talens RP, Kremer D, Putter H, Stein AD, Slagboom PE, Heijmans BT. DNA methylation differences after exposure to prenatal famine are common and timing- and age-specific. Hum Mol Genet. 2009;18:4046–53. https://doi.org/10.1093/hmg/ddp353.
139. Talens RP, Boomsma DK, Tobi EW, Kremer D, Jukema JW, Willemson G, Putter H, Slagboom PE, Heijmans BT. Variation, patterns and temporal stability of DNA methylation: considerations for epigenetic epidemiology. FASEB J. 2010;24:3135–44. https://doi.org/10.1096/fj.09-150490.
140. Guay S-P, Brisson D, Munger J, Lamarche B, Gaudet D, Bouchard L. ABCA1 gene promoter DNA methylation is associated with HDL particle profile and coronary artery disease

in familial hypercholesterolemia. Epigenetics. 2012;7:464–72. https://doi.org/10.4161/epi.19633.
141. Hogue JC, Lamarche B, Gaudet D, Tremblay AJ, Desperes JP, Bergeron J, Gagné C, Couture P. Association of heterozygous familial hypercholesterolemia with smaller HDL particle size. Atherosclerosis. 2007;190:429–35. https://doi.org/10.1016/j.atherosclerosis.2006.02.023.
142. van der Graaf A, Vissers MN, Gaudet D, Brisson D, Sivapalaratnam S, Roseboom TJ, Jansen AC, Kastelein JJ, Hutten BA. Dyslipidemia of mothers with familial hypercholesterolemia deteriorates lipids in adult offspring. Arterscler Thromb Vasc Biol. 2010;30:2673–7. https://doi.org/10.1161/ATVBAHA.110.209064.
143. Wang D, Hiebel V, Xu T, Ladurner A, Atanasov AG, Heiss EH, Dirsch VM. Impact of natural products on the cholesterol transporter, ABCA1. J Ethnopharm. 2020;249: 112444. https://doi.org/10.1016/j.jep.2019.112444.
144. Wang D, Hievl V, Ladurner A, Latkolik SL, Bucar F, Heiss EH, Dirsch VM, Atanasov AG. 6-Dihydroparadol, a ginger constituent, enhances cholesterol efflux from THP-1-derived macrophages. Mol Nutr Food Res. 2018. https://doi.org/10.1002/mnfr.201800011.
145. Jiang Z, Sang H, Ful X, Liang Y, Li L. Alpinetin enhances cholesterol efflux and inhibits lipid accumulation in oxidized low-density lipoprotein-loaded human macrophages. Biotechnol Appl Biochem. 2015;62:840–7. https://doi.org/10.1002/bab.1328.
146. Wagsater D, Dimberg J, Sirsjo A. Induction of ATP-binding cassette A1 by all-trans retinoic acid: possible role of liver X receptor-alpha. Int J Mol Med. 2003;11:419–23. https://doi.org/10.3892/ijmm.11.4.419.
147. Zhao GJ, Tang SL, Lv YC, Ouyang XP, He PP, Yao F, Chen WJ, Lu Q, Tang YY, Zhang M, Fu Y, Zhang DW, Yin K, Tang CK. Antagonism of betulinic acid on LPS-mediated inhibition of ABCA1 and cholesterol efflux through inhibiting nuclear factor-κB signaling pathway and miR-33 expression. PLoS ONE. 2013;8: e74782. https://doi.org/10.1371/journal.pone.0074782.
148. Zolberg RN, Bechor S, Harari A, Ben-Amotz A, Kamari Y, Harats D, Shaish A. The inhibition of macrophage foam cell formation by 9-cis beta-carotene is driven by BCMO1 activity. PLoS ONE. 2015;10: e115272. https://doi.org/10.1371/journal.pone.0115272.
149. Chen FY, Zhou J, Guo N, Ma WG, Huang X, Wang H, Yuan ZY. Curcumin retunes cholesterol transport homeostasis and inflammation response in M1 macrophage to prevent atherosclerosis. Biochem Biophys Res Commun. 2015;467:872–8. https://doi.org/10.1016/j.bbrc.2015.10.051.
150. Lin XL, Liu MH, Hu HJ, Feng HR, Fan XJ, Zou WW, Pan YQ, Hu XM, Wang Z. Curcumin enhanced cholesterol efflux by upregulating ABCA1 expression through AMPK-SIRT1-LXRalpha signaling in THP-1 macrophage-derived foam cells. DNA Cell Biol. 2015;34:561–72. https://doi.org/10.1089/dna.2015.2866.
151. Saenz J, Alba G, Reyes-Quiroz ME, Geniz I, Jimenez J, Sobrino F, Santa-Maria C. Curcumin enhances LXRalpha in an AMP-activated protein kinase-dependent manner in human macrophages. J Nutr Biochem. 2018;54:48–56. https://doi.org/10.1016/j.jnutbio.2017.11.006.
152. Lv YC, Yang J, Yao F, Xie W, Tang YY, Ouyang XP, He PP, Tan YL, Li L, Zhang M, Liu D, Cayabyab FS, Zheng XL, Tang CK. Diosgenin inhibits atherosclerosis via suppressing the MiR-19b-induced downregulation of ATP-binding cassette transporter A1. Atherosclerosis. 2015;240:80–9. https://doi.org/10.1016/j.atherosclerosis.2015.02.044.
153. Liu XX, Zhang XW, Wang K, Wang XY, Ma WL, Cao W, Mo D, Sun Y, Li XQ. Kuwanon G attenuates atherosclerosis by upregulation of LXRalpha-ABCA1/ABCG1 and inhibition of NFkappaB activity in macrophages. Toxicol Appl Pharmacol. 2018;341:56–63. https://doi.org/10.1016/j.taap.2018.01.007.
154. Li X, Zhou Y, Yu C, Yang H, Zhang C, Ye Y, Xiao S. Paeonol suppresses lipid accumulation in macrophages via upregulation of ATP binding cassette transporter A1 and downregulation of the cluster of differentiation 36. Int J Oncol. 2015;46:764–74. https://doi.org/10.3892/ijo.2014.2757.
155. Zhao JF, Jim Leu SJ, Shyue SK, Su KH, Wei J, Lee TS. Novel effect of paeonol on the formation of foam cells: promotion of LXRalpha-ABCA1-dependent cholesterol efflux in macrophages. Am J Chin Med. 2013;41:1079–96. https://doi.org/10.1142/S0192415X13500730.
156. Wang D, Xia M, Yan X, Li D, Wang I, Xu Y, Jin T, Ling W. Gut microbiota metabolism of anthocyanin promotes reverse cholesterol transport in mic via repressing miRNA-10b. Circ Res. 2012;111:967–81. https://doi.org/10.1161/CIRCRESAHA.112.266502.
157. Li CH, Gong D, Chen LY, Zhang M, Xia XD, Cheng HP, Huang C, Zhao ZW, Zheng XL, Tang XE, Tang CK. Puerarin promotes ABCA1-mediated cholesterol efflux and decreases cellular lipid accumulation in THP-1 macrophages. Eur J Pharmacol. 2017;811:74–86. https://doi.org/10.1016/j.ejphar.2017.05.055.
158. Chang YC, Lee TS, Chiang AN. Quercetin enhances ABCA1 expression and cholesterol efflux through a p-38-dependent pathway in macrophages. J Lipid Res. 2012;53:1840–50. https://doi.org/10.1194/jlr.M024471.
159. Li S, Cao H, Shen D, Jia Q, Chen C, Xing SL. Quercetin protects against oxLDL induced injury via upregulation of ABCA1, LXRalpha, and PCSK9 in RAW264.7 macrophages. Mol Med Rep. 2018;18:799–806. https://doi.org/10.3892/mmr.2018.9048.
160. Liu Z, Wamg K, Huang E, Gao S, Li H, Lu J, Tian K, Little PJ, Shen X, Xu S, Liu P. Tanshinone IIA suppresses cholesterol accumulation in human macrophages: role of heme oxygenase-1. J Lipid Res. 2014;55:201–13. https://doi.org/10.1194/jlr.M040394.
161. Jia LQ, Zhang N, Xu YM, Chen WN, Zhu ML, Song N, Ren L, Cao HM, Wang JY, Yang GL. Tanshinone IIA affect the HDL subfractions distribution, not serum lipid levels: involving in intake and efflux of cholesterol. Arch Biochem Biophys. 2016;592:50–9. https://doi.org/10.1016/j.abb.2016.01.001.
162. Egert S, Bosy-Westphal A, Seiberl J, Kürbitz C, Settler U, Plachta-Danielzik S, Wagner AE, Frank J, Schrezenmeir J, Rimbach G, Wolffram S, Müller MJ. Quercetin reduces systolic blood pressure and plasma oxidised low-density lipoprotein concentrations in overweight subjects with a high-cardiovascular disease risk phenotype: a double-blinded, placebo-controlled cross-over study. Br J Nutr. 2009;102:1065–74. https://doi.org/10.1017/S0007114509359127.
163. Campbell MS, Quyang A, I M K, Charnigo RJ, Westgate PM, Fleenor BS. Influence of enhanced bioavailable curcumin on obesity-associated cardiovascular disease risk factors and arterial function: a double-blinded, randomized, controlled trial. Nutrition 2019;62:135–9. https://doi.org/10.1016/j.nut.2019.01.002.
164. Yang J, Zhang Y, Nia X, Zhao A. β-Carotene supplementation and risk of cardiovascular disease: a systematic review and meta-analysis of randomized controlled trials. Nutrients. 2022;14:1284. https://doi.org/10.3390/nu14061284.
165. Haas MJ, Jurado-Flores M, Hammoud R, Feng V, Gonzales K, Onstead-Haas L, Mooradian AD. The effects of known cardioprotective drugs on proinflammatory cytokine secretion from human coronary artery endothelial cells. Am J Ther. 2019;26:e321–32. https://doi.org/10.1097/MJT.0000000000000648.
166. Maitra U, Li L. Molecular mechanisms responsible for the reduced expression of cholesterol transporters from macrophages

by low-dose endotoxin. Arterioscler Thromb Vasc Biol. 2013;33:24–33. https://doi.org/10.1161/ATVBAHA.112.300049.
167. van Leuven SI, Hezemans R, Levels JH, Snoek S, Stokkers PC, Hovingh GK, Kastelein JJ, Stroes ES, de Groot E, Hommes DW. Enhanced atherogenesis and altered high density lipoprotein in patients with Crohn's disease. J Lipid Res. 2007;48:2640–6. https://doi.org/10.1194/jlr.M700176-JLR200.
168. Palacio C, Alexandraki K, Bertholf RL, Mooradian AD. Transient dyslipidemia mimicking the plasma lipid profile of Tangier disease in a diabetic patient with gram negative sepsis. Ann Clin Lab Sci. 2011;41:150–3.
169. Van Deventer SJ. Tumor necrosis factor and Crohn's disease. Gut. 1997;40:443–8. https://doi.org/10.1136/gut.40.4.443.
170. Wang Y. Mitogen-activated protein kinases in heart development and diseases. Circul. 2007;116:1413–23. https://doi.org/10.1161/CIRCULATIONAHA.106.679589.
171. Sebolt-Leopold JS, Herrera R. Targeting the mitogen-activated protein kinase cascade to treat cancer. Nat Rev Cancer. 2004;4:937–47. https://doi.org/10.1038/nrc1503.
172. Kyriakis JM, Avruch J. Mammalian mitogen-activated protein kinase signal transduction pathways activated by stress and inflammation. Physiol Rev. 2001;81:807–69. https://doi.org/10.1152/physrev.2001.81.2.807.
173. Zhou X, Yin Z, Guo X, Hajjar DP, Han J. Inhibition of ERK1/2 and activation of liver X receptor synergistically induce macrophage ABCA1 expression and cholesterol efflux. J Biol Chem. 2010;285:6316–26. https://doi.org/10.1074/jbc.M109.073601.
174. Kobayashi H, Tomari Y. RISC assembly: coordination between small RNA's and argonaute proteins. Biochim Biophys Acta. 2016;1859:71–81. https://doi.org/10.1016/j.bbagrm.2015.08.007.
175. Finnegan EF, Pasquinelli AE. MicroRNA biogenesis: regulating the regulators. Crit Rev Biochem Mol Biol. 2013;48:51–68. https://doi.org/10.3109/10409238.2012.738643.
176. Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell. 2009;136:215–33. https://doi.org/10.1016/j.cell.2009.01.002.
177. Michell DL, Vickers KC. Lipoprotein carriers of microRNAs. Biochim Biophys Acta. 2016;186:2069–74. https://doi.org/10.1016/j.bbalip.2016.01.011.
178. Garcia-Martin R, Wang G, Brandao BB, Zaontto TM, Shah S, Patel SK, Schilling B, Kahn CR. MicroRNA sequence codes for small extracellular vesicle release and cellular retention. Nature. 2022;601:446–51. https://doi.org/10.1038/s41586-021-04234-3.
179. Rayner KJ, Moore KJ. MicroRNA control of high-density lipoprotein metabolism and function. Circ Res. 2014;114:183–92. https://doi.org/10.1161/CIRCRESAHA.114.300645.
180. Canfran-Duque A, Lin C-S, Goedeke L, Suarez Y, Fernandez-Hernando C. Micro-RNAs and high-density lipoprotein metabolism. Arterioscler Thromb Vasc Biol. 2016;36:1076–84. https://doi.org/10.1161/ATVBAHA.116.307028.
181. Feinberg MW, Moore KJ. MicroRNA regulation of atherosclerosis. Circ Res. 2016;118:703–20. https://doi.org/10.1161/CIRCRESAHA.115.306300.
182. Fernandez-Tussy P, Ruz-Maldonado I, Fernandez-Hernando C. MicroRNAs and circular RNAs in lipoprotein metabolism. Curr Atheroscler Rep. 2021;23:33. https://doi.org/10.1007/s11883-021-00934-3.
183. Sun D, Zhang J, Xie J, Wei W, Chen MM, Zhao. MiR-26 controls LXR-dependent cholesterol efflux by targeting ABCA1 and ARL7. FEBS Lett. 2012;586:1472–9. https://doi.org/10.1016/j.febslet.2012.03.068.
184. Zhang M, Wu JF, Chen WJ, Tang SL, Mo ZC, Tang YY, Li Y, Wang JL, Liu XY, Peng J, Chen K, He PP, Lv YC, Ouyang XP, Yao F, Tang DP, Cayabyab FS, Zhang DW, Zheng XL, Tian GP, Tang CK. MicroRNA-27a/b regulates cellular cholesterol efflux, influx, and esterification/hydrolysis in THP-1 macrophages. Atherosclerosis. 2014;234:54–64. https://doi.org/10.1016/j.atherosclerosis.2014.02.008.
185. Najafi-Shoushtari SH, Kristo F, Li Y, Shioda T, Cohen DE, Gerszten RE, Naar AM. MicroRNA-33 and the SREBP host genes cooperate to control cholesterol homeostasis. Science. 2010;328:1566–9. https://doi.org/10.1126/science.1189123.
186. Xu Y, Xu Y, Zhu Y, Sun H, Juguilon C, Li F, Fan D, Yin L, Zhang Y. Macrophage miR-34a is a key regulator of cholesterol efflux and atherosclerosis. Mol Ther. 2020;28:202–16. https://doi.org/10.1016/j.ymthe.2019.09.008.
187. Kim J, Yoon H, Ramirez CM, Lee SM, Hoe HS, Fernandez-Hernando C. Mir-106b impairs cholesterol efflux and increases abeta levels by repressing abca1 expression. Exp Neurol. 2012;235:476–83. https://doi.org/10.1016/j.expneurol.2011.11.010.
188. Wang L, Sinnott-Armstrong N, Wagschal A, Wark AR, Camporez JP, Perry RJ, Ji F, Sohn Y, Oh J, Wu S, Chery J, Moud BN, Saadat A, Dankel SN, Mellgren G, Tallapragada DSP, Strobel SM, Lee M-J, Tewhey R, Sabeti PC, Schaefer A, Petri A, Kauppinen S, Chung RT, Soukas A, Avruch J, Fried SK, Hauner H, Sadreyev RI, Shulman GI, Claussnitzer M, Näär AM. A microRNA linking human positive selection and metabolic disorders. Cell. 2020;183:684–701. https://doi.org/10.1016/j.cell.2020.09.017.
189. Ramirez CM, Rotllan N, Vlassov AV, Dávalos A, Li M, Goedeke L, Aranda JF, Cirera-Salinas D, Araldi E, Salerno A, Wanschel A, Zavadil J, Castrillo A, Kim J, Suárez Y, Fernández-Hernando C. Control of cholesterol metabolism and plasma high-density lipoprotein levels by micro RNA-144. Circ Res. 2013;112:1592–601. https://doi.org/10.1161/CIRCRESAHA.112.300626.
190. de Aguiar Vallim TQ, Tarling EJ, Kim T, Civelek M, Baldan A, Esau C, Edwards PA. MicroRNA-144 regulates hepatic ATP binding cassette transporter A1 and plasma high-density lipoprotein after activation of the nuclear farnesoid X receptor. Circ Res. 2013;112:1602–12. https://doi.org/10.1161/CIRCRESAHA.112.300648.
191. Hall IF, Climent M, Viviani Anselmi C, Papa L, Tragante V, Lambroia L Farina FM, Kleber ME, Marz W, Bigouri C, Condorelli G, Elia L. rs41291957 controls miR-143 and miR-145 expression and impacts coronary artery disease risk. EMBO Mol Med. 2021;13:e14060. https://doi.org/10.15252/emmm.202114060.
192. Goedeke L, Rotlan N, Canfran-Duque A, Aranda JF, Ramírez CM, Araldi E, Lin C-S, Anderson NN, Wagschal A, de Cabo R, Horton JD, Lasunción MA, Näär AM, Suárez Y, Fernández-Hernando C. Miro-RNA-148a regulates LDL receptor and ABCA1 expression to control circulating lipoprotein levels. Nat Med. 2015;21:1280–9. https://doi.org/10.1038/nm.3949.
193. Vinod M, Chennamsetty I, Colin S, Belloy L, De Paoli F, Schaider H, Graier WF, Frank S, Kratky D, Staels B, Chinetti-Gbaguidi G, Kostner GM. miR-206 controls LXRα expression and promotes LXR-mediated cholesterol efflux in macrophages. Biochim Biophys Acta. 2014;1841:827–35. https://doi.org/10.1016/j.bbalip.2014.02.006.
194. Huang J-W, Jiang X, Li Z-I, Jiang C-R. MicroRNA-328-5P alleviates macrophage lipid accumulation through histone deacetylase 3/ATP-binding cassette transporter A1 pathway. Lipids. 2021;56:301–11. https://doi.org/10.1002/lipid.12297.
195. Ramirez CM, Davalos A, Goedeke L, Salerno AG, Warrier N, Cirera-Salinas D, Suarez Y, Fernandez-Hernando C. MicroRNA-758 regulates cholesterol efflux through posttranslational repression of ATP-binding cassette transporter A1. Arterioscler Thromb Vasc Biol. 2011;31:2707–14. https://doi.org/10.1161/ATVBAHA.111.232066.

196. Rutland JC, Politz F, Zhang T, Pederson T. MicroRNA-206 colocalizes with ribosome-rich regions in both the nucleus and cytoplasm of rat myogenic cells. Proc Natl Acad Sci. 2006;103:18957–62. https://doi.org/10.1073/pnas.0609466103.
197. Truesdell SS, Mortensen RD, Seo M, Schroeder JC, Lee JH, LeTonqueze O, Vasudevan S. MicroRNA-mediated mRNA translation activation in quiescent cells and oocytes involves recruitment of a nuclear microRNP. Sci Rep. 2012;2:842. https://doi.org/10.1038/srep00842.
198. Nicholls SJ, Andrews J, Kastelein JJP, Merkely B, Nissen SE, Ray KK, Schwartz GG, Worthley SG, Keyserling C, Dasseux J-L, Griffith L, Kim SW, Janssan A, Di Giovanni G, Pisaniello AD, Scherer DJ, Psaltis PJ, Butters J. Effect of serial infusions of CER-001, a pre-β high-density lipoprotein mimetic, on coronary atherosclerosis in patients following acute coronary syndromes in the CER-001 atherosclerosis regression acute coronary syndrome trial: a randomized clinical trial. JAMA Cardiol. 2018;3:815–22. https://doi.org/10.1001/jamacardio.2018.2121.
199. Zheng KH, Kaiser Y, van Olden CC, Santos RD, Dasseux J-L, Genest J, Gaudet D, Westerink J, Keyserling C, Verberne HJ, Leitersdorf E, Hegele RA, Descamps OS, Hopkins P, Nederveen AJ, Stroes ESG. No benefit of HDL mimetic CER-001 on carotid atherosclerosis in patients with genetically determined very low HDL levels. Atherosclerosis. 2020;311:13–9. https://doi.org/10.1016/j.atherosclerosis.2020.08.004.
200. Nicholls SJ, Puri R, Ballantyne CM, Jukema JW, Kastelein JJP, Koenig W, Wright RS, Kallend D, Wijngaard P, Borgman M, Wolski K, Nissen SE. Effect of infusion of high-density lipoprotein mimetic containing recombinant apolipoprotein A-I milano on coronary disease in patients with an acute coronary syndrome in the MILANO-PILOT trial: a randomized clinical trial. JAMA Cardiol. 2018;3:806–14. https://doi.org/10.1001/jamacardio.2018.2112.
201. Richard LD, Rajesh M, LeAnne TB, Danielle D, Robert BN, Mohamad N, Alan MF, Daniel JR. Oral apolipoprotein A-I mimetic D-4F lowers HDL-inflammatory index in high-risk patients: a first-in-human multiple-dose, randomized controlled trial. Clin Transl Sci 2007;10:455–69. https://doi.org/10.1111/cts.12487.