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Brothers in Arms: ABCA1- and ABCG1-Mediated Cholesterol Efflux as Promising Targets in Cardiovascular Disease Treatment[S]

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***Abstract*——Atherosclerosis is a leading cause of cardiovascular disease worldwide, and hypercholesterolemia is a major risk factor. Preventive treatments mainly focus on the effective reduction of low-density lipoprotein cholesterol, but their therapeutic value is limited by the inability to completely normalize atherosclerotic risk, probably due to the disease complexity and multifactorial pathogenesis. Consequently, high-density lipoprotein cholesterol gained much interest, as it appeared to be cardioprotective due to its major role in reverse cholesterol transport (RCT). RCT facilitates removal of cholesterol from peripheral tissues, including atherosclerotic plaques, and its subsequent hepatic clearance into bile. Therefore, RCT is expected to limit plaque formation and progression. Cellular cholesterol efflux is initiated and propagated by the ATP-binding cassette (ABC) transporters ABCA1 and ABCG1. Their expression and function are expected to be rate-limiting for cholesterol efflux, which makes them interesting targets to stimulate RCT and lower atherosclerotic risk. This systematic review discusses the molecular mechanisms relevant for RCT and ABCA1 and ABCG1 function, followed by a critical overview of potential pharmacological strategies with small molecules to enhance cellular cholesterol efflux and RCT. These strategies include regulation of ABCA1 and ABCG1 expression, degradation, and mRNA stability. Various small molecules have been demonstrated to increase RCT, but the underlying mechanisms are often not completely understood and are rather unspecific, potentially causing adverse effects. Better understanding of these mechanisms could enable the development of safer drugs to increase RCT and provide more insight into its relation with atherosclerotic risk.**

***Significance Statement*——Hypercholesterolemia is an important risk factor of atherosclerosis, which is a leading pathological mechanism underlying cardiovascular disease. Cholesterol is removed from atherosclerotic plaques and subsequently cleared by the liver into bile. This transport is mediated by high-density lipoprotein particles, to which cholesterol is transferred via ATP-binding cassette transporters ABCA1 and ABCG1. Small-molecule pharmacological strategies stimulating these transporters may provide promising options for cardiovascular disease treatment.**

I. Introduction

A. The Importance of Plasma Cholesterol for Cardiovascular Disease

Cardiovascular disease (CVD) comprises a wide range of disorders, including myocardial infarction and stroke, for which atherosclerosis is the major pathologic mechanism. CVD is associated with severe morbidity and one of the leading causes of mortality worldwide, with 17.5 million annual deaths accounting for almost one-third of all deaths (WHO, 2008, 2014; Taylor et al., 2011). The etiology of atherosclerosis is complex and multifactorial, but hypercholesterolemia and particularly increased low-density lipoprotein (LDL) cholesterol (LDL-C) levels are acknowledged as major risk factors (Levine et al., 1995; De Backer et al., 2003; Taylor et al., 2011; Ridker, 2014; Piepoli et al., 2016). Together with very LDL (VLDL) and intermediate-density lipoprotein particles, cholesterol- and triglyceride-loaded LDL particles facilitate lipid and cholesterol transport from the

ABBREVIATIONS: ABC, ATP-binding cassette; AC, adenylate cyclase; AICAR, 5-aminoimidazole-4-carboxyyamide ribonucleoside; AMPK, AMP-activated protein kinase; apo, apolipoprotein; CETP, cholesteryl ester transfer protein; CVD, cardiovascular disease; DMHCA, *N,N*-dimethyl-3β-hydroxycholenamide; ERK, extracellular signal-regulated kinase; GPR, G protein–coupled receptor; HDL, high-density lipoprotein; HDL-C, HDL cholesterol; HMG-CoA, 3-hydroxy-3-methylglutaryl-coenzyme A; HO-1, heme oxygenase-1; IDL, intermediate density lipoprotein; IMM-H007, triacetyl-3 hydroxyphenyl-adenosine; LDL, low-density lipoprotein; LDL-C, LDL cholesterol; LDLR, LDL receptor; LXR, liver X receptor; LXRE, LXR response element; MAPK, mitogen-activated protein kinase; MC1-R, melanocortin 1 receptor; miRNA, microRNA; NBD, nucleotide binding domain; Nrf, nuclear factor-like; ox-LDL, oxidized LDL; PDE, phosphodiesterase; PEST, Pro-Glu-Ser-Thr; PKA, protein kinase A; PKC, protein kinase C; PKD, protein kinase D; PPAR, peroxisome proliferator-activated receptor; RA, retinoic acid; RAR, retinoid-activated receptor; RCT, reverse cholesterol transport; RXR, retinoid X receptor; SR-B1, scavenger receptor B1; SREBP-1c, sterol regulatory-binding element protein 1c; TMD, transmembrane domain; TNF, tumor necrosis factor; TTNPB, 4-[(E)-2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphtalenyl)-1-propenyl]benzoic acid; VLDL, very LDL.

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liver to peripheral tissues (Hegele, 2009; Kingwell et al., 2014) (Fig. 1). Hepatic lipases and lipoprotein lipases mediate the formation of LDL particles from VLDL particles, the latter containing high triglycerides, but moderate cholesterol and phospholipid concentrations (Fig. 1, right panels), whereas LDL particles contain high cholesterol and moderate phospholipid concentrations and almost no triglycerides (Kwiterovich, 2000;

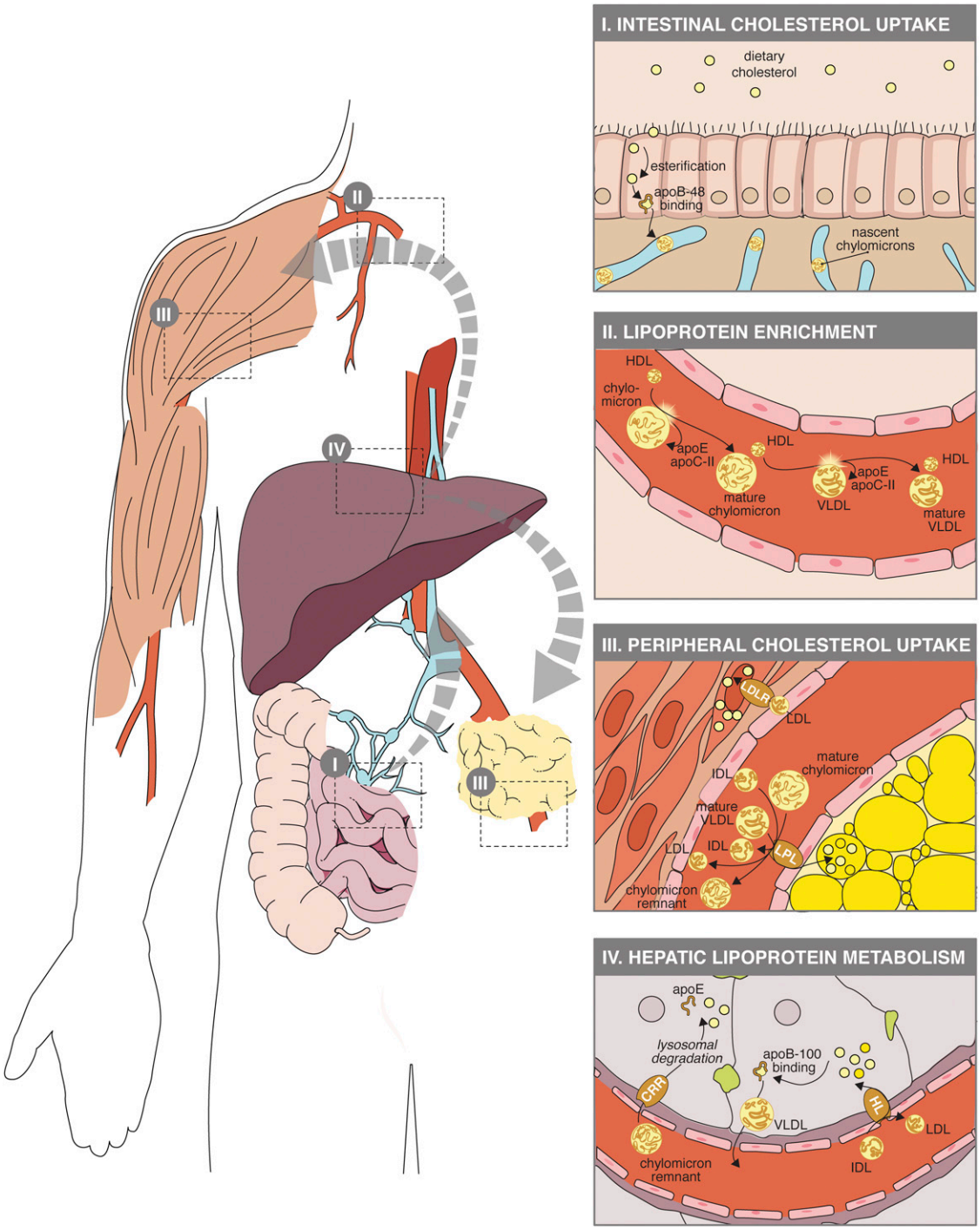

Fig. 1. Cholesterol uptake, distribution, and peripheral utilization. (I) Schematic overview illustrating intestinal cholesterol (light yellow spheres) uptake by enterocytes, including cholesterol esterification and apoB-48 binding, which facilitates cholesterol efflux to the lymphatic system. (II) The resulting nascent chylomicrons are subsequently transported to the blood, where they collide with HDL particles that transfer apoE and apoC-II to chylomicrons, leading to their maturation. (III) Mature chylomicrons can be converted to chylomicron remnants by endothelial lipoprotein lipase (LPL) activated by apoC-II, which releases free fatty acids (yellow spheres) for uptake in peripheral tissues (e.g., muscles and fat) and apoC-II for translocation to HDL. (IV) Next, chylomicron remnants are imported into hepatocytes via the chylomicron remnant receptor (CRR), which releases the remaining cholesterol and apoE by lysosomal degradation. The resulting hepatic free cholesterol, which may also originate from de novo synthesis, can be exported as VLDL particles upon binding to apoB-100. (III) Removal of triglycerides by endothelial LPL converts VLDL particles into intermediate density lipoprotein (IDL) particles. They can collide with HDL to acquire apoE. (IV) Hepatic lipase (HL) subsequently hydrolyzes the remaining triglycerides in IDL, which forms LDL particles (III) that can also be formed by LPL (III) out of IDL particles, and that are able to release cholesterol to peripheral tissues via LDLR.

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Guyton and Hall, 2011). Once formed, circulating LDL particles are removed from the plasma via the interaction of apolipoprotein (apo)B-100 (i.e., one of the LDL particle lipoproteins) with LDL receptors (LDLRs) mainly expressed on liver, but also various other tissues (e.g., lungs, kidneys, urinary bladder, gastrointestinal tract, and adipose tissue). However, if the plasma levels of LDL particles increase, they may accumulate in the arterial wall, where they become proinflammatory by enzymatic oxidation. Subsequently, these proinflammatory LDL particles stimulate endothelial cells and smooth muscle cells in the *tunica intima* (i.e., the innermost arterial layer) to express adhesion molecules and chemoattractants for the recruitment of monocytes, lymphocytes, and neutrophils. In addition, oxidized LDL (ox-LDL) particles can also directly induce a proinflammatory state in monocytes (i.e., inflammatory priming) and accelerate the formation of foam cells (Bekkering et al., 2014). This is preceded by macrophage formation from monocytes, after they have entered the arterial wall guided by chemoattractants. These macrophages recognize and engulf cholesterol, finally yielding foam cells (Insull, 2009; Libby et al., 2011; Maiolino et al., 2013; Bentzon et al., 2014). Consequently, these lipid-loaded macrophages can result in atherosclerotic plaque formation, contributing to an increased risk of CVD (Levine et al., 1995; Kwiterovich, 2000; De Backer et al., 2003; Guyton and Hall, 2011; Taylor et al., 2011; Ridker, 2014; Piepoli et al., 2016).

B. Statins as the Cornerstone of Cardiovascular Disease Treatment

The strong association between high LDL-C levels, atherosclerotic plaque formation, and CVD led to the development of multiple LDL-lowering therapies. To date, statins are among the most widely used LDL-C–lowering therapies (Downs et al., 1998; Baigent et al., 2005; Karalis, 2009; Piepoli et al., 2016), leading to a decrease of 22% in CVD risk with every millimole per liter LDL-C reduction, as quantified in a meta-analysis (Baigent et al., 2010). Statins inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is the rate-limiting enzyme in cholesterol synthesis that mediates the conversion of HMG-CoA into mevalonate (Sacks et al., 1996; Taylor et al., 2011; Cruz et al., 2013). Because statins effectively reduce LDL-C, they comprise the cornerstone of atherosclerosis prevention strategies. Although generally well-tolerated, statin-induced muscle complaints are observed in 7%–29% of all users (Bitzur et al., 2013; Wilkinson et al., 2014; Stroes et al., 2015), which contribute significantly to the high discontinuation rate observed with statin therapy. Myopathic symptoms range from very rare cases of rhabdomyolysis to muscle complaints with normal or minimally elevated creatine kinase levels (Bitzur et al., 2013; Wilkinson et al., 2014; Stroes et al., 2015). These complaints are expected to result from a combination of drug-related (e.g., relative potency, statin metabolism, drug–drug interactions, dose, and lipophilicity) and patient-related (e.g., age, comorbidities, ethnicity, and gender) factors. At the molecular level, many mechanisms have been proposed, with a pivotal role for mitochondrial dysfunction (Schirris et al., 2015a; Stroes et al., 2015). This is supported by the recent discovery of the first statin off-target associated with these muscle complaints, demonstrating that statins in their pharmacologically inactive lactone form inhibit the third complex of the mitochondrial respiratory chain (Schirris et al., 2015a). The cholesterol-lowering statin acid is converted into the lactone form by uridine 5′-diphospho-glycoronyltransferases in the liver (Schirris et al., 2015b). Besides a low adherence due to muscle complaints, statin treatment does not completely normalize the risk of LDL-associated CVD, despite effective LDL reduction (Kuhnast et al., 2015), as demonstrated by several multiple large controlled clinical trials, and follow-up trials illustrated that CVD events persist after treatment in two-thirds of all patients (Sacks et al., 1996; Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group, 1998; Pedersen et al., 2004; Libby, 2005). Similar effects were observed in a subset of patients with coronary heart disease, coronary heart disease risk equivalents, and diabetes mellitus, in which there was a failure to sufficiently lower plasma LDL-C levels (Davidson et al., 2005). More recently, monoclonal antibody proprotein convertase subtilisin/kexin type 9 inhibitors have been introduced (i.e., evolocumab and alirocumab) that drastically reduce LDL-C up to 59% (Sabatine et al., 2017). Contradictory to the large LDL-C reduction, treatment of patients suffering from atherosclerotic CVD with the proprotein convertase subtilisin/kexin type 9 inhibitor evolocumab still resulted in a residual cardiovascular event incidence of 9.8% (Sabatine et al., 2017). This gives rise to the idea that lowering LDL-C cholesterol alone is not sufficient to fully prevent CVD and warrants the exploration of novel therapies to interfere with the pathologic mechanism underlying atherosclerosis.

C. High-Density Lipoprotein and Cardiovascular Disease: High-Density Lipoprotein Levels Are a Poor Reflection of Reverse Cholesterol Transport Capacity

In contrast to blood LDL-C levels, high-density lipoprotein (HDL) cholesterol (HDL-C) levels have been inversely correlated to atherosclerotic events (Tang and Oram, 2009; Uehara and Saku, 2014; Westerterp et al., 2014; Kuhnast et al., 2015). HDL particles have a high protein and low cholesterol and phospholipid content and are involved in the reverse cholesterol transport (RCT) pathway, explaining the beneficial effects of these particles in atherosclerosis (Murphy et al., 2013; Kingwell et al., 2014; Kuhnast et al., 2015).

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However, the concept that increased HDL cholesterol levels do uniformly translate into reduced myocardial infarction risk is challenged by a Mendelian randomization study (Voight et al., 2012). The RCT pathway consists of cholesterol transport by HDL particles from peripheral tissue to the liver, where cholesterol is subsequently excreted into the bile by the ATP-binding cassette (ABC) transporters ABCG5 and ABCG8 (Zanlungo et al., 2004; Kingwell et al., 2014) (Fig. 2). As HDL particles are the key players of RCT, they have the potential to degrade atherosclerotic plaques and prevent the formation of new plaques. At the site of the atherosclerotic plaque, cholesterol is transferred to HDL particles by macrophages, which after engulfment transfer cholesterol to HDL via ABC transporter–mediated efflux across the plasma membrane by ABCA1 and ABCG1 (Fig. 2). In addition, the inverse correlation between HDL-C levels and atherosclerotic events has been associated with anti-inflammatory, antioxidant, antiplatelet, and vasodilatory effects (Murphy et al., 2013; Kingwell et al., 2014; Kuhnast et al., 2015; Ramasamy, 2016). Consequently, stimulation of HDL particle levels as well as RCT provides interesting treatment strategies for atherosclerosis. In contrast to previous studies (Fazio and Linton, 2003), recent clinical trials evaluating the infusion of apo mimetics did not show atherosclerotic protection (Karalis and Jukema, 2018). This indicates that increasing HDL levels alone may not be sufficient to stimulate RCT and lower atherosclerotic risk. This also initiated the development of cholesteryl ester transfer protein (CETP) inhibitors, which increase HDL-C levels by reducing the transfer of cholesterol from HDL particles to LDL particles and triglyceride-loaded lipoprotein particles (Barter et al., 2015). However, next to the involvement of CETP in the heterotypic cholesterol transfer pathway (i.e., cholesterol and triglyceride (TG) movement between VLDL or LDL and HDL), it also contributes to the homotypic cholesterol transfer pathway (Lagrost et al., 1990; Rye et al., 1999; Niesor et al., 2010; Barter and Rye, 2012; Mohammadpour and Akhlaghi, 2013; Lauer et al., 2016). In the homotypic pathway, CETP induces the formation of pre-βHDL and cholesterol efflux between subparticles of HDL, including HDL3 and HDL2 (Lagrost et al., 1990; Rye et al., 1999; Niesor et al., 2010). The effect of CETP inhibitors on the heterotypic and homotypic cholesterol transfer pathway depends on the type of inhibitor, which most likely explains their difference in efficacy to reduce cardiovascular risk. For instance, both the homotypic and heterotypic transfer are inhibited by torcetrapib, evacetrapib, and anacetrapib, whereas dalcetrapib more selectively inhibited the heterotypic transfer without affecting the homotypic transfer (Hewing and Fisher, 2012; Mohammadpour and Akhlaghi, 2013). To date, development of CETP inhibitors has been discontinued due to adverse events or lack of efficacy (Tall and Rader, 2018). The latter also substantiates the notion that functionality of HDL, rather than its absolute HDL-C level, determines effectivity of reducing atherosclerotic risk. Consequently, stimulation of ABCA1- and ABCG1-mediated cellular cholesterol efflux to HDL particles could, due to its pivotal role in RCT, provide a more effective strategy to stimulate RCT and decrease atherosclerotic risk.

D. Systematic Review: Scope and Methodology

In this review, we discuss the major players of RCT as well as therapeutic strategies explored to stimulate them. A systematic literature search was conducted using both Medline and Embase, which resulted in 2928 abstracts (Fig. 3; Supplemental Tables 1 and 2). Removal of duplicates resulted in 2809 unique publications that were independently evaluated for their relevance by two reviewers. First, all publications not involving cholesterol efflux stimulation were excluded based on the title (i.e., title screen, Fig. 3). Following strict exclusion criteria, 175 publications remained, based on their abstract for a more in-depth study and inclusion in this review (Fig. 3), including publications describing the effects on cholesterol efflux of endogenous compounds, natural compounds, apolipoprotein mimetics, microRNAs (miRNAs), as well as nonresearch publications and publications of which only the abstract or no English version was available.

We first provide an overview of the main players involved in RCT, focusing on the crucial role of ABCA1 and ABCG1 cholesterol efflux transporters in the initiation and propagation of this process. We conclude with a critical discussion of small-molecule pharmaceutical interventions that could affect RCT beneficially.

II. Reverse Cholesterol Transport Pathway

A. Initiation and Propagation of Reverse Cholesterol Transport

Each RCT cycle is initiated by the removal of cellular cholesterol from peripheral tissues, of which the determinants (i.e., HDL size and composition, gender, body mass index, and age) have been reviewed recently by Talbot et al. (2018). Active transport is involved in 70% of all cellular cholesterol efflux pathways (Ono, 2012; Phillips, 2014). Passive bidirectional cholesterol flux between HDL particles and the plasma membrane is mediated by aqueous diffusion and via interaction of HDL particles with scavenger receptor B1 (SR-B1). SR-B1 mediates cholesterol uptake in the cell without endocytic uptake and degradation of HDL particles by ABCG1 (Phillips, 2014). However, the contribution of this mechanism to peripheral cholesterol efflux is expected to be minimal, as SR-B1 is most abundantly expressed in the adrenal gland, and at lower levels in peripheral tissues. Aqueous diffusion includes passive transport through the intervening aqueous phase until collision occurs between cholesterol and an extra- or

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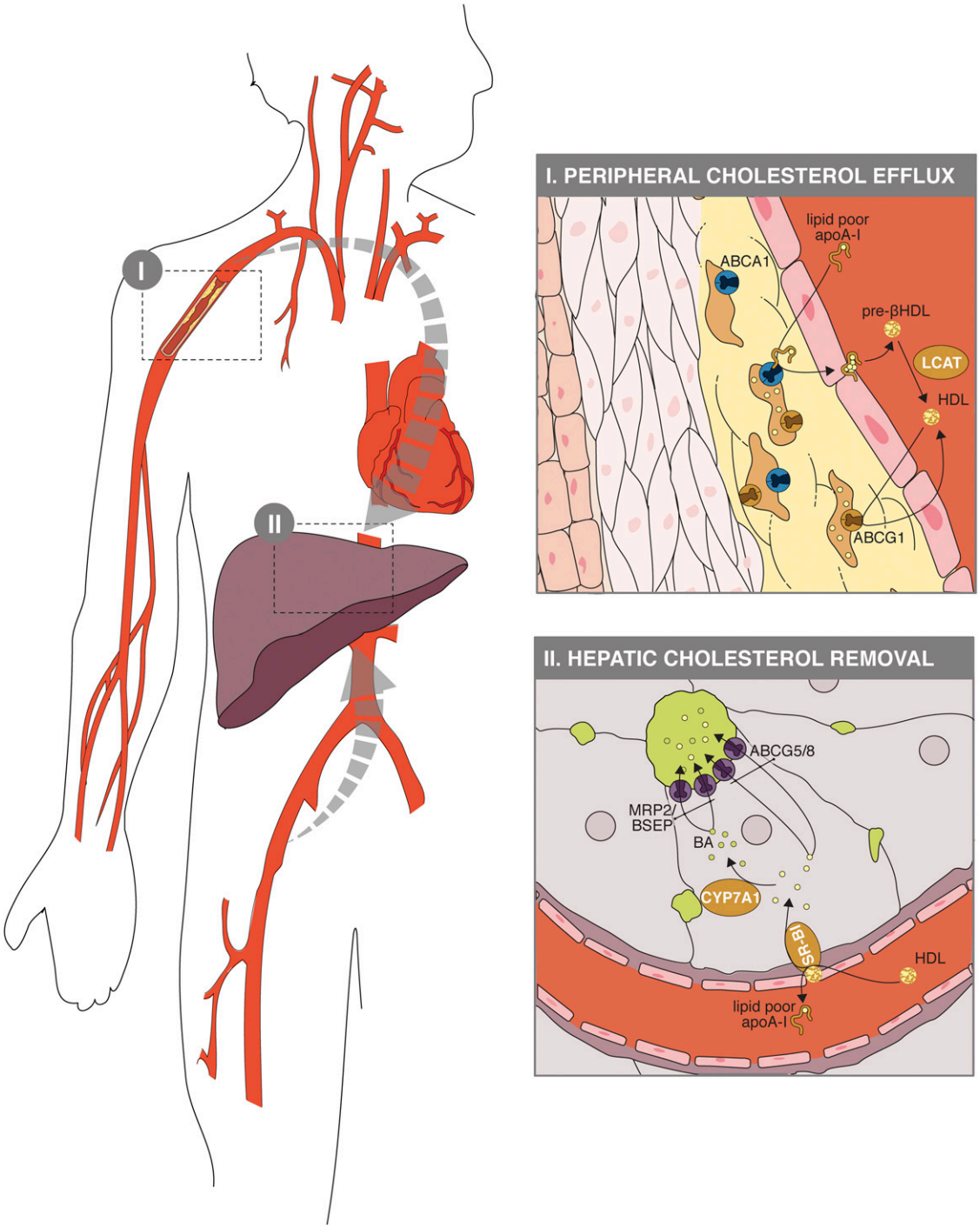

Fig. 2. Reverse cholesterol transport. Schematic overview of reverse cholesterol transport, (I) which is initiated by the efflux of cholesterol (yellow spheres) by ABCA1 and ABCG1 transporters. They are expressed on a variety of peripheral tissues, including macrophages that engulf cholesterol from atherosclerotic plaques (i.e., foam cells). ABCA1-mediated cholesterol efflux transfers cholesterol to lipid-poor apoA-I, leading to the formation of pre-βHDL. These particles can be converted by circulating lecithin:cholesterol acyltransferase (LCAT) into HDL particles, which function as cholesterol acceptor for ABCG1. Cholesterol efflux by ABCG1 is mediated via reorganization of cholesterol in the plasma membrane, which increases plasma membrane cholesterol concentrations. Subsequently, aqueous diffusion could increase the cholesterol efflux out of the cell to HDL without necessity of HDL to bind to the plasma membrane. (II) SR-BI mediates cholesterol influx into hepatocytes without whole HDL particle uptake, allowing unbound apoA-I to circulate and enter a new RCT cycle. Finally, hepatic free cholesterol can be directly removed to bile canaliculi by ABCG5 and ABCG8 transporters, or indirect via conversion by cytochrome P450 (CYP)7A1 into bile acids (green spheres) that can subsequently be transported into bile via the multidrug resistance protein (MRP)2/ABCC2 and bile salt export pump (BSEP/ABCB11) transporters, located on the canalicular membrane.

intracellular cholesterol acceptor (Yancey et al., 2003; Rosenson et al., 2012; Phillips, 2014). ATP-dependent cholesterol efflux is mainly facilitated by ABCA1 and ABCG1 (Fig. 2) (Oram, 2003; Yancey et al., 2003; Yvan-Charvet et al., 2010b; Phillips, 2014; Westerterp et al., 2014). ABCA1-mediated cholesterol and phospholipid efflux is initiated by the interaction of lipid- and cholesterol-free apoA-I particles with ABCA1

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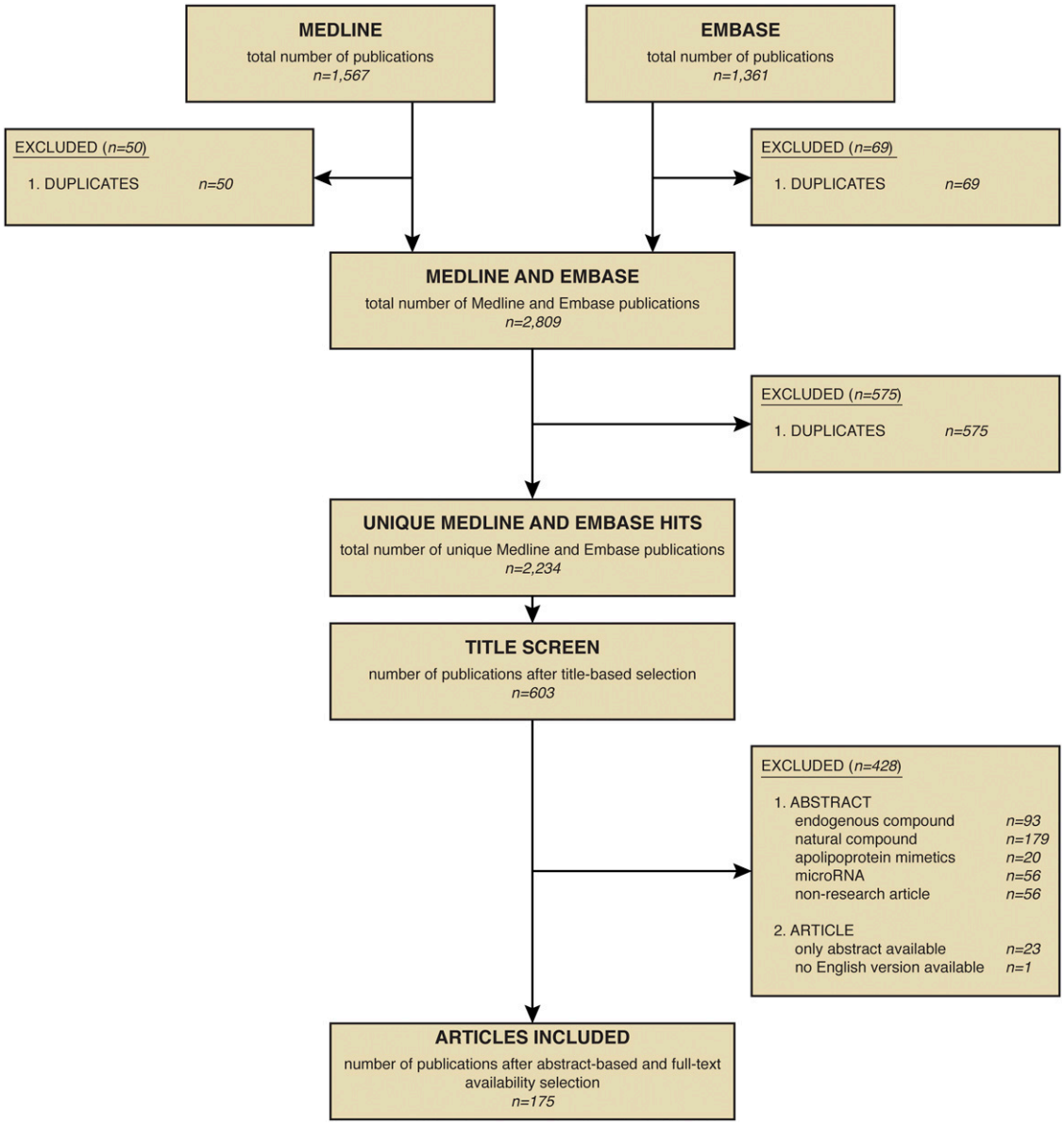

Fig. 3. Flow chart of systematic literature search strategy. Overview of the number of publications retrieved from all MEDLINE and EMBASE searches and exclusion criteria applied to these publications, including removal of duplicates and title- and abstract-based screenings conducted by two independent reviewers. For a detailed overview of the search strategies, see Supplemental Tables 1 and 2.

transporters on peripheral tissue (i.e., highest expression in macrophages and foam cells) and hepatocytes (Fig. 2). This results in the formation of lipid-poor pre-βHDL particles, which upon rapid esterification by lecithin: cholesterol acyltransferase are converted into lipid-rich HDL particles (Morgado et al., 2005). These particles mediate cellular cholesterol efflux via interaction with ABCG1, thereby further facilitating transport of cholesterol from peripheral tissues toward the liver, followed by uptake into hepatocytes via SR-B1 (Tall and Yvan-Charvet, 2015). As the final step of RCT, cholesterol is secreted into the bile via an ABCG5/8 heterodimer complex present at the canalicular membrane (Thomas et al., 2003; Roglans et al., 2004; Zanlungo et al., 2004; Valasek et al., 2007; Lee et al., 2016). These two ABCG transporters are only expressed in hepatocytes, gallbladder epithelium, and enterocytes (Tauscher and Kuver, 2003; Wang et al., 2015a; Patel et al., 2018). Formation of a heterodimer of ABCG5 and ABCG8 in the endoplasmic reticulum is required before the complex can be translocated to the apical membrane, where it facilitates sterol transport into the bile or gut lumen (Graf et al., 2003; Yu et al., 2014). The bilairy excretion rate of cholesterol is associated with the level of hepatic ABCG5 and ABCG8 expression (Yu et al., 2005). Consequently, the ABCG5/G8 complex is important in the correction of high plasma and hepatic cholesterol and sterol levels (Yu et al., 2002, 2014).

B. ATP-Binding Cassette A1 and ATP-Binding Cassette G1 as Master Effectors of Cholesterol Efflux

ABCA1 plays a crucial role in the cellular cholesterol efflux, and its importance is illustrated by Tangier

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disease, which is characterized by a severe deficiency in plasma HDL and cholesterol caused by autosomal recessive mutations in the *ABCA1* gene (Brooks-Wilson et al., 1999; Langmann et al., 1999; Rust et al., 1999; Oram, 2000; Uehara et al., 2011; Phillips, 2018). The human *ABCA1* gene has a total length of 149 kb, including a 1,453-bp promoter, 146,581 bp of introns and exons, and a 1-kb 3′ flanking region. Of the exons, 58 are comprised in the *ABCA1* gene, and multiple bindings sites for transcription factors are detected in the promoter region (Gene, 1982–2019a; Santamarina-Fojo et al., 2000). Like many other transporters of the ABCA subfamily, ABCA1 is a full transporter, which contains 2,261 amino acids and is integrated into the membrane via two transmembrane domains (TMDs) that both comprise six transmembrane helices. In addition, ABCA1 has two nucleotide binding domains (NBDs), which contain the conserved Walker-A and Walker-B peptide motifs (Langmann et al., 1999; Santamarina-Fojo et al., 2000; Uehara et al., 2011). The tissue distribution of ABCA1 is ubiquitous, and expression is especially high in placenta, liver, small intestine, macrophages, adrenal glands, lung, and fetal tissues (Langmann et al., 1999; Uehara et al., 2011). ABCA1 initiates cellular cholesterol efflux and RCT to the lymph and bloodstream via a specific interaction with apoA-I, allowing cellular phospholipids and cholesterol to bind to these apolipoproteins, which almost exclusively mediates HDL biosynthesis and is therefore seen as its rate-limiting step (Lee et al., 2002; Murthy et al., 2002; Ohama et al., 2002; Mulligan et al., 2003; Singaraja et al., 2003). It remains, however, unknown whether phospholipid and cholesterol binding occurs at the plasma membrane surface or whether apoA-I is internalized and targeted to late endosomes after binding to ABCA1 at the plasma membrane, where it forms complexes with lipids that are subsequently released by exocytosis (Takahashi and Smith, 1999; Neufeld et al., 2001; Vaughan and Oram, 2003; Denis et al., 2008; Lorenzi et al., 2008; Azuma et al., 2009; Tang and Oram, 2009; von Eckardstein and Rohrer, 2009; Yvan-Charvet et al., 2010b; Westerterp et al., 2014; Du et al., 2015a) (Fig. 4). This is also supported by the localization of ABCA1 on early and late endosome and lysosome membranes, next to its plasma membrane localization, and in line with its reuptake to regulate cholesterol efflux rates, as described in the next section (Neufeld et al., 2001; Tang and Oram, 2009; von Eckardstein and Rohrer, 2009; Uehara and Saku, 2014; Westerterp et al., 2014; Du et al., 2015a). However, the majority of apoA-I lipidation is expected to occur at the plasma membrane (Denis et al., 2008; Faulkner et al., 2008). The exact modes of interaction between apoA-I and ABCA1 still need to be elucidated. At least six mechanisms have been proposed, as follows: 1) direct apoA-I binding to phosphatidylserine, which is translocated outward by ABCA1 floppase activity (Chambenoit et al., 2001; Alder-Baerens et al., 2005); 2) direct binding of apoA-I to extracellular ABCA1 loop domains (Wang et al., 2001; Fitzgerald et al., 2004); 3) apoA-I binding to protrusions as a result of ABCA1 floppase activity (Vedhachalam et al., 2007a); 4) outward translocation of phosphatidylinositol 4,5-bisphosphate mediated by ABCA1 floppase activity, which allows apoA-I to bind and unfold, followed by microsolubilization of the membrane (Gulshan et al., 2016); 5) low-affinity apoA-I binding to ABCA1 and high-affinity binding to cholesterol (Hassan et al., 2007; Vedhachalam et al., 2007b); 6) apoA-I binding to extracellular domains of ABCA1 dimers that have been formed from two ABCA1 monomers. These monomers have undergone a conformational change as a result of the translocation of phosphatidylcholine and cholesterol leading to dimer formation (Ishigami et al., 2018). Although ABCA1 mainly interacts with apoA-I, it can also associate with lipid-free apoE, which is most efficient when these apolipoproteins originate from small and dense HDL subfractions like HDL3b and HDL3c (Neufeld et al., 2001; Tang and Oram, 2009; von Eckardstein and Rohrer, 2009; Uehara and Saku, 2014; Westerterp et al., 2014; Du et al., 2015a).

In contrast to ABCA1, ABCG1 has a larger ambiguity regarding its lipid acceptors, which include HDL, LDL, and phospholipid vesicles (Wang et al., 2004; Vaughan and Oram, 2005; Kobayashi et al., 2006; Sankaranarayanan et al., 2009; Yvan-Charvet et al., 2010b; Phillips, 2014; Westerterp et al., 2014). Unlike ABCA1, ABCG1 is a half transporter, which only contains a single TMD comprising of six transmembrane helices and a single NBD at the C terminus of the TMD that is responsible for ATP binding and hydrolysis (Kerr et al., 2011; Uehara et al., 2011). Therefore, the ABCG1 protein needs to either homo- or heterodimerize with other ABCG proteins to become functional. The human *ABCG1* gene comprises 23 exons spanning 98 kb (Gene, 1982–2019b; Kennedy et al., 2001). Eight different isoforms of ABCG1 are produced by alternative splicing, with a length varying between 644 and 785 amino acids. The ABCG1 protein is expressed in many cell types, including macrophages, neurons, astrocytes, endothelial, and epithelial cells, and in many tissues, such as the liver, intestine, kidney, spleen, lung, and brain (Nakamura et al., 2004; Kennedy et al., 2005; Wang et al., 2008; Bojanic et al., 2010). Although the precise cellular localization of ABCG1 needs to be elucidated, the transporter was detected in the plasma membrane and membranes of the Golgi apparatus and endosomes of ABCG1-overexpressing HEK293 cells and macrophages (Kobayashi et al., 2006; Wang et al., 2006; Tarling and Edwards, 2011; Neufeld et al., 2014; Phillips, 2014; Westerterp et al., 2014). It has been demonstrated that cholesterol efflux facilitated by ABCG1 does not increase lipoprotein binding to the cell surface (Wang et al., 2004; Kobayashi et al., 2006; Sankaranarayanan et al., 2009; Yvan-Charvet et al., 2010b; Phillips, 2014), which makes a mechanism similar to

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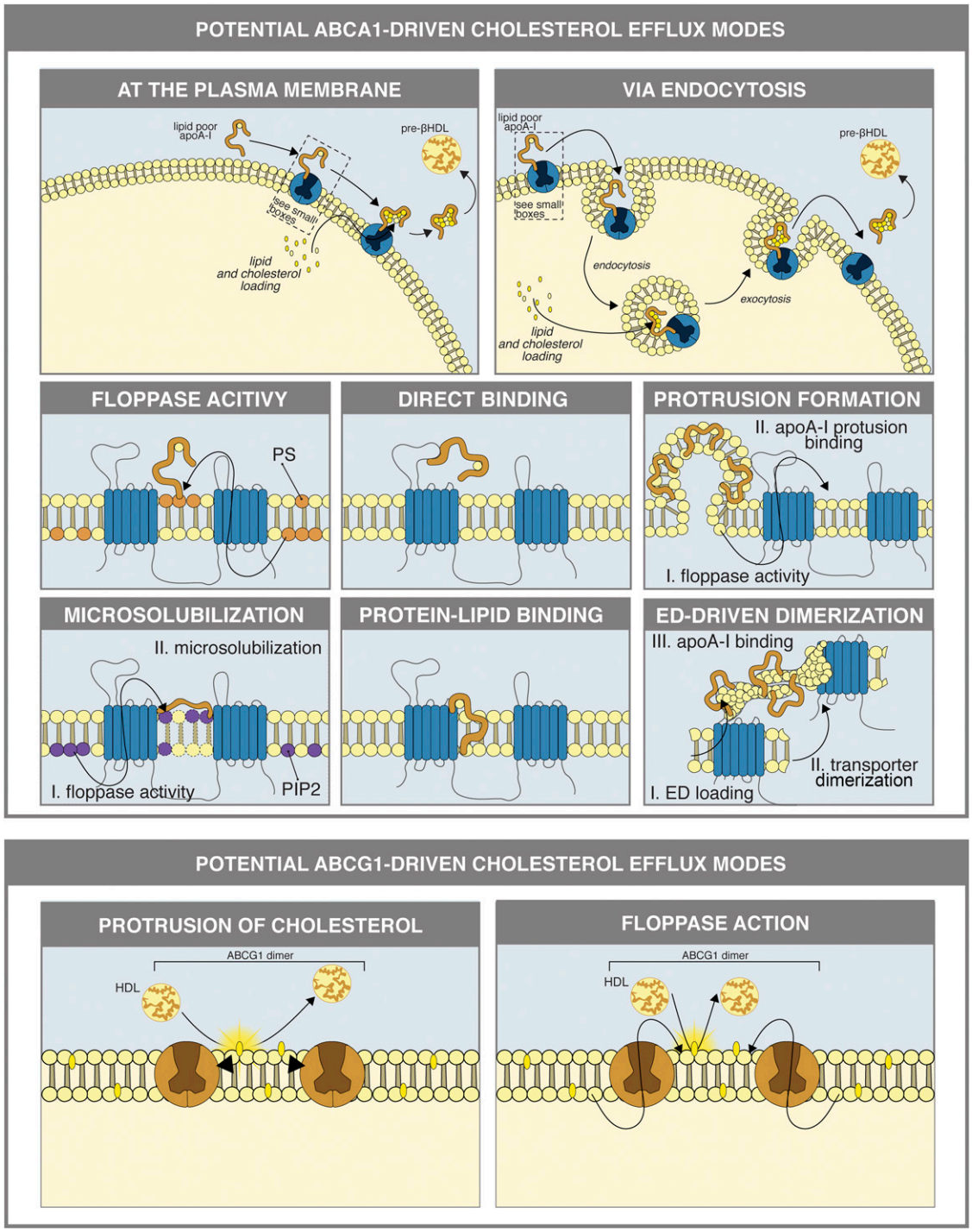

Fig. 4. Potential ABCA1- and ABCG1-driven cholesterol efflux modes. ABCA1-driven cholesterol efflux to lipid-poor apoA-I is hypothesized to occur either at the plasma membrane (upper left panel), or via endocytosis of the apoA-I–bound ABCA1 transporter, followed by intracellular lipid loading and exocytosis (upper right panel). ABCA1 is ubiquitously expressed, particularly at high levels in liver, small intestine, macrophages, adrenal glands, lungs, placenta, and fetal tissue. The transporter initiates cellular cholesterol efflux to the lymph and bloodstream via a specific interaction with apoA-I. Six different mechanisms have been proposed for the interaction between apoA-I and ABCA1 (small boxes), including the following: outward translocation of phosphatidylserine (PS) by ABCA1 floppase activity allowing apoA-I binding; direct binding of apoA-I to extracellular ABCA1 loop domains; ABCA1 floppase activity leading to the formation of protrusions facilitating apoA-I binding; ABCA1 floppase activity leading to the outward translocation of phosphatidylinositol 4,5-bisphosphate (PIP2), allowing apoA-I to bind and unfold, followed by microsolubilization of the membrane; low-affinity binding to ABCA1 and high-affinity binding to cholesterol; dimerization of ABCA1 transporter proteins is initiated by loading of the extracellular loop domains with cholesterol, followed by apoA-I binding to the dimerized cholesterol-loaded extracellular loop domains (ED). ABCG1-driven cholesterol efflux to HDL particles in the bloodstream or lymph is expected to be the result of a collision of these particles with cholesterol molecules that protrude from the plasma membrane (lower left panel), mediated either by a direct effect of the ABCG1 dimer on the membrane structure or by outward translocation via ABCG1 floppase activity (lower right panel). ABCG1 is expressed in many cell types, including macrophages, neurons, astrocytes, endothelial and epithelial cells, and many tissues (e.g., liver, intestine, kidney, spleen, lung, and brain), where it mediates basolateral cholesterol efflux.

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ABCA1 unlikely. Several pathways have been suggested to explain the ABCG1-mediated cellular cholesterol efflux mechanism (Yvan-Charvet et al., 2010b; Neufeld et al., 2014; Phillips, 2014). One of the proposed mechanisms suggests that ABCG1 facilitates protrusion of cholesterol from the membrane pool into the hydrophilic water layer lining the plasma membrane (Fig. 4). Subsequently, cholesterol uptake by an acceptor occurs after transient collision (Small, 2003; Yvan-Charvet et al., 2010b; Neufeld et al., 2014; Phillips, 2014). A second model suggests that ABCG1 promotes changes in the organization of plasma membrane phospholipids functioning as a phospholipid floppase, which leads to a redistribution of sterols to the plasma membrane (Yvan-Charvet et al., 2010b; Phillips, 2014). This could result in an increased efflux of cholesterol out of the cell by aqueous diffusion because of increased cholesterol concentrations at the plasma membrane (Sankaranarayanan et al., 2009; Yvan-Charvet et al., 2010b; Phillips, 2014).

In summary, ABCA1- and ABCG1-mediated cholesterol efflux is indispensable in cholesterol and phospholipid loading of apolipoproteins and thereby the maturation of HDL particles, which makes both ABC transporters essential for the initiation of RCT (Tang and Oram, 2009; Phillips, 2014; Uehara and Saku, 2014; Westerterp et al., 2014). Consequently, stimulation of cellular cholesterol removal via ABCA1 and ABCG1 could provide a promising target to enhance RCT.

C. Regulation of ATP-Binding Cassette A1– and ATP-Binding Cassette G1–Mediated Cholesterol Efflux

Cholesterol efflux by ABCA1 and ABCG1 is regulated by a variety of different mechanisms. Serum HDL and its key apoA-I are key regulators of the cholesterol efflux rate, in which high apolipoprotein levels are associated with high cellular cholesterol efflux rates. Cellular mechanisms mainly regulate ABCA1- and ABCG1-mediated cholesterol efflux by controlling the plasma membrane expression of both transporters. This is accomplished by various mechanisms. First, the nuclear receptors retinoid X receptor (RXR), peroxisome proliferator-activated receptors (PPARs), and liver X receptor (LXR) regulate the transcription of the genes encoding *ABCA1* and *ABCG1* (Fig. 5). Second, the stability of *ABCA1* and *ABCG1* mRNA can be influenced by their protein expression. Third, the expression of the transporter on the plasma membrane is regulated via modulation of its internalization, degradation, and recycling. Finally, activity and localization are enhanced by cAMP-mediated transporter phosphorylation and the stimulatory role of extracellular ATP thereon (Lee et al., 2011). The different cellular mechanisms influencing ABCA1- and ABCG1-mediated cholesterol efflux are discussed in more detail below, along with an overview of small-molecule treatment strategies known to influence these mechanisms.

III. Apolipoprotein A-I and Apolipoprotein E Mimetics

Although we focus on small-molecule therapies that enhance ABCA1- and ABCG1-mediated cholesterol efflux, we will briefly address recent promising progress in the development of recombinant apolipoproteins to stimulate cholesterol efflux by ABCA1 and ABCG1 (Zhang et al., 2003; Tall et al., 2008; Bielicki et al., 2010; Khera et al., 2011), which was extensively reviewed by others (Sherman et al., 2010; White et al., 2014; Stoekenbroek et al., 2015; Cao et al., 2017). Many efforts have been directed to mimic or overexpress apoA-I as potential atherosclerosis treatment strategy, which is a promising therapy for several reasons. First, apoA-I is the major functional and most abundant structural lipoprotein in HDL, which accounts for approximately two-thirds of the total HDL protein content (Zhang et al., 2003; Tall et al., 2008; Bielicki et al., 2010; Getz and Reardon, 2011; Khera et al., 2011; Uehara and Saku, 2014; Kontush et al., 2015). Moreover, formation of cholesterol-loaded apoA-I by ABCA1 is considered to be the rate-limiting step of HDL particle biogenesis. Consequently, increasing apoA-I levels using apoA-I mimetics (i.e., short synthetic peptides that share structural and biologic features of native apolipoproteins) is expected to stimulate cholesterol transport. The potential of this strategy is demonstrated in several in vitro and in vivo studies, in which treatment with apoA-I mimetics increased plasma HDL levels and reduced atherosclerotic lesions (Zhang et al., 2003; Tall et al., 2008; Bielicki et al., 2010; Khera et al., 2011; Osei-Hwedieh et al., 2011; Uehara and Saku, 2014; Kuhnast et al., 2015). More recently, clinical trials evaluating the infusion of these apoA-I mimetics, including the potent mimetic apoA-I Milano, did not show atherosclerotic protection (Karalis and Jukema, 2018). This also substantiates the notion that not the HDL levels, but other parts of RCT, like ABCA1- and ABCG1-mediated cholesterol efflux, contribute to the inverse correlation between HDL-C levels and atherosclerotic events.

Besides apoA-I mimetics, compounds that act like apoE are of great interest for the treatment of atherosclerosis. ApoE possesses antiatherogenic properties by its cholesterol-reducing potential. These effects are mediated via the clearance of plasma apoB-containing lipoprotein remnants (e.g., VLDL and chylomicrons) by apoE LDLR-binding domain (Sharifov et al., 2011; Xu et al., 2016). Moreover, they are involved in the initiation of RCT from peripheral tissue and macrophages upon lipid binding (Sharifov et al., 2011; Xu et al., 2016) and binding to ABCG1 to facilitate cholesterol efflux by this transporter. Several in vivo studies revealed that apoE mimetics have cholesterol-lowering, anti-inflammatory, and atheroprotective properties (Nayyar et al., 2012; Handattu et al., 2013; Xu et al., 2016). Moreover,

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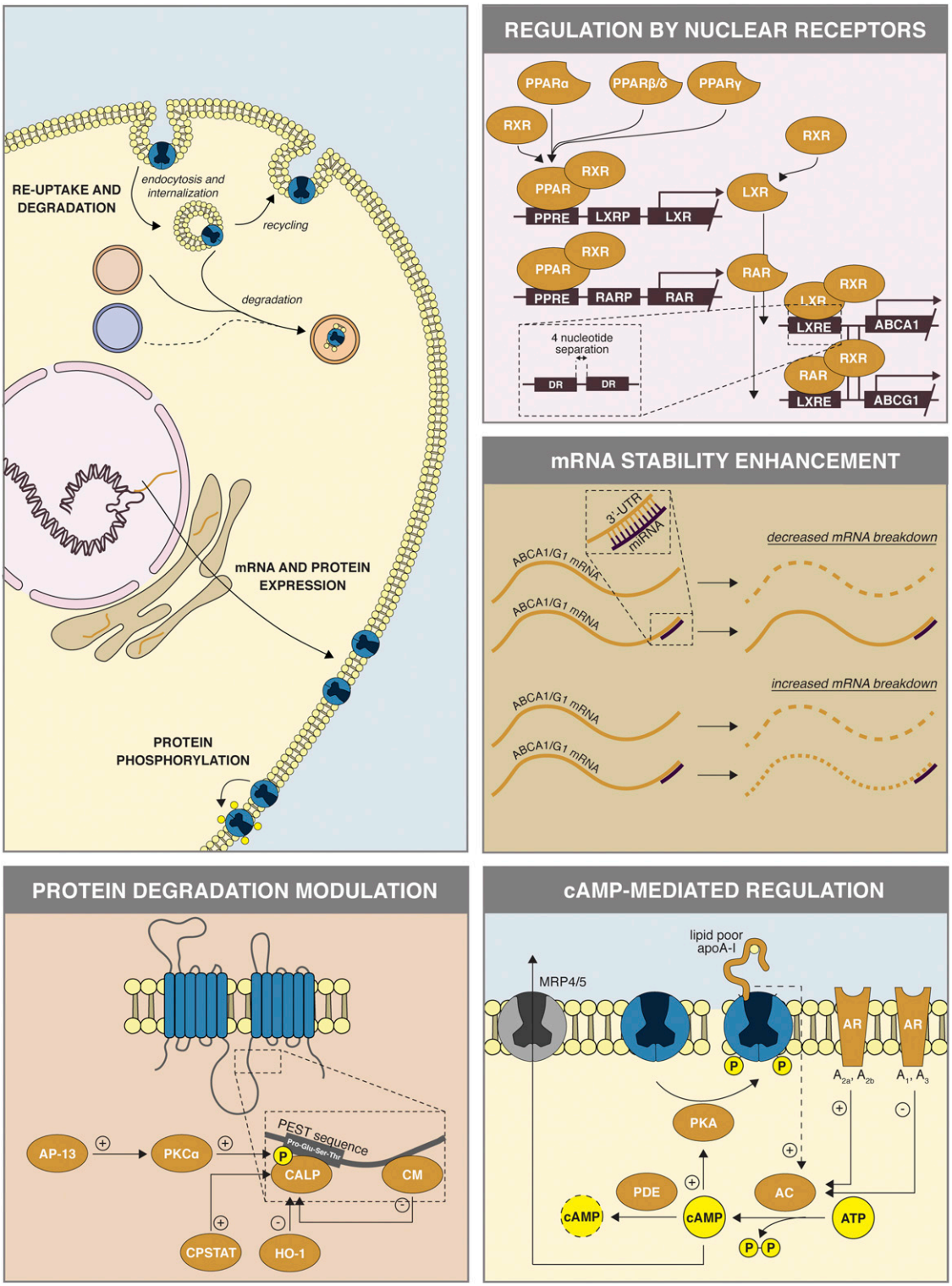

Fig. 5. Cellular regulation of ABCA1 and ABCG1 transporter expression. Expression of ABCA1 and ABCG1 transporters is increased by stimulation of the nuclear PPAR, which upon dimerization with RXR (i.e., another nuclear factor) bind to the PPAR-responsive element (PPRE), leading to the transcription of the nuclear LXR and RAR, respectively (right upper panel). Next, dimerization of LXR or RAR with RXR enables binding to the LXRE, inducing the transcription of *ABCA1* and *ABCG1*, respectively. Once transcribed, the stability of *ABCA1* and *ABCG1* mRNA can either be enhanced or decreased upon binding of miRNAs, of which an overview is provided in Table 4 (right middle panel). ABCA1 and ABCG1 plasma membrane expression is also mediated via modulation of its lysosomal (blue vesicle) or endosomal (orange vesicle) degradation. The latter is stimulated by phosphorylation of the PEST sequence by apelin-13 (AP-13) via PKCα (left lower panel). Upon phosphorylation, calpain (CALP) can bind and initiate proteolysis, a process that is stimulated by calpastatin (CPSTAT), and negatively affected by calmodulin (CM) or by the HO-1 axis. Finally, the ability of ABCA1 and ABCG1 to bind lipid poor apoA-I is stimulated upon transporter phosphorylation by PKA at Ser-1042 and Ser-2054, located in the nucleotide binding domain of ABCA1. PKA is positively regulated by cAMP levels that depend on the balance of cAMP breakdown by PDE, formation by adenosine receptor–stimulated AC, and efflux by multidrug resistance protein (MRP) 4 and 5 (right lower panel).

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a hybrid peptide containing properties of both apoA-I and apoE improved arterial endothelial function and protected against atherogenesis in vivo (Gupta et al., 2005).

Although these apolipoprotein mimetics showed promising results for the treatment of atherosclerosis, their peptide nature may make them less favorable to administer as compared with orally available small-molecule drugs. ABCA1 and ABCG1 transporters provide an interesting target for small molecules to stimulate RCT, as their expression and function are expected to be rate-limiting for cellular cholesterol efflux (Oram, 2003; Tall et al., 2008; Yvan-Charvet et al., 2010b; Phillips, 2014; Westerterp et al., 2014).

IV. Regulation and Pharmacological Manipulation of Nuclear Receptor–Mediated ATP-Binding Cassette A1 and ATP-Binding Cassette G1 Expression

A. Nuclear Receptors Are Important Regulators of ATP-Binding Cassette A1 and ATP-Binding Cassette G1 Expression

Multiple nuclear receptors are involved in the regulation of *ABCA1* and *ABCG1* mRNA expression, of which the two LXR isoforms, LXRα and LXRβ, have demonstrated to play an important role in the cholesterol homeostasis, including RCT (Zhao and Dahlman-Wright, 2010; Hong and Tontonoz, 2014). LXRα is predominantly expressed in metabolically active tissue (e.g., liver, kidney, macrophages, adipose tissue, and small intestine), whereas LXRβ has a more ubiquitous distribution and is in particular highly expressed in the developing brain (Zhao and Dahlman-Wright, 2010; Li et al., 2016). LXRs act as cellular cholesterol sensors, as they are activated by accumulation of oxysterols, oxidized derivatives of cholesterol, which subsequently induce transcription of genes involved in the protection of cells against cholesterol overload (Zhao and Dahlman-Wright, 2010; Di et al., 2012). After activation by oxysterols, LXRα and LXRβ form heterodimers with isoforms of RXRs, including RXRα, RXRβ, or RXRγ (Di et al., 2012; Hong and Tontonoz, 2014) (Fig. 5). After heterodimerization, LXR/RXR initiate transcription of target genes (e.g., genes involved in lipid synthesis and metabolism, including, but not limited to, the following: *ABCA1*, *ABCG1*, *ABCG5*, *ABCG8*, *SREBP-1C*, and *FAS*) by binding to the LXR response element (LXRE), which consists of two direct repeats (i.e., a AGGTCA sequence) separated by four nucleotides (Edwards et al., 2002; Zhao and Dahlman-Wright, 2010; Jakobsson et al., 2012; Hong and Tontonoz, 2014; Li et al., 2016). These LXREs are found in the proximal promotors of genes involved in fatty acid, bile acid, cholesterol, and glucose regulation, but also of genes with high relevance to RCT, including *ABCA1* and *ABCG1* (Zhao and Dahlman-Wright, 2010; Di et al., 2012; Hong and Tontonoz, 2014). Combined with its high expression in macrophages, LXRα is an important regulator in the initiation of RCT via modulation of ABCA1 and ABCG1 expression.

Another class of nuclear receptors involved in the regulation of *ABCA1* and *ABCG1* expression is PPAR, which comprises the following three isoforms: PPARα, PPARβ/δ, and PPARγ (Berger et al., 2005; Ogata et al., 2009). PPARα is mainly expressed in liver, kidney, heart, muscle, and other metabolically active tissues that rely predominantly on fatty acid β-oxidation. PPARβ/δ is ubiquitously expressed (e.g., cardiovascular, urinary, respiratory, digestive, endocrine, nervous, and hemato organ system), whereas PPARγ is mainly found in adipose tissue, skeletal and cardiac muscles, and human monocytes (Escher et al., 2001; Berger et al., 2005; Higashiyama et al., 2007; Ogata et al., 2009). Like LXR, PPARs form obligate heterodimers with RXR upon activation by their ligands (e.g., fatty acid metabolites), which bind to isotype-specific peroxisome proliferator response elements in target genes (Berger et al., 2005; Grygiel-Górniak, 2014) (Fig. 5). Targets of PPARα and PPARγ include genes involved in lipid metabolism (e.g., *SLC25A20*, *APOA1*, *LXRα*, and *SCD-1*) and glucose metabolism (e.g., *G6PC*, *PCK*, and *PDK4*) (Muoio et al., 2002; Li and Glass, 2004; Rakhshandehroo et al., 2010). PPARs have been associated with an increased ABCA1 expression and consequently enhanced HDL biogenesis in vitro and in vivo (Chinetti et al., 2001; Ogata et al., 2009). All three PPAR isoforms mediate these effects via LXRα. However, only PPARγ is known to directly affect LXRα expression via interaction with a peroxisome proliferator response element proximal to the LXRα promotor (Chawla et al., 2001), whereas the exact mechanism remains unknown for the other isotypes and is expected to be indirect (e.g., via effects on its endogenous ligands) (Ogata et al., 2009).

In addition to RXR, retinoid-activated receptors (RARs; i.e., another group of retinoid nuclear receptors) play a role in cholesterol homeostasis. RARs are expressed in a wide variety of tissues and, like other retinoid nuclear receptors, also need to form a heterodimer with RXR (Matsumoto et al., 2007; Jung et al., 2010; Kuntz et al., 2015; Manna et al., 2015; Zhou et al., 2015). For all retinoid nuclear receptors, this heterodimerization allows them to bind to a response element in the promoter region of their target genes, including *ABCA1*, *ABCG1*, *APOA1*, *GCK*, *UCP1* and *UCP3*, and *FGF21* (Puigserver et al., 1996; Solanes et al., 2000; Balmer and Blomhoff, 2002; Cadoudal et al., 2008; Nishimaki-Mogami et al., 2008; Cui et al., 2011; Ayaori et al., 2012; Li et al., 2013; Zhang et al., 2013a, 2015b; Kuntz et al., 2015). PPAR/RXR, LXR/RXR, and RAR/RXR can be activated by agonists for either RXR and any other nuclear receptor (Nishimaki-Mogami et al., 2008; Cui et al., 2011; Kuntz et al., 2015) (Fig. 5). Consequently, RXR exerts pleiotropic effects due to crosstalk of RXR with other nuclear receptors, resulting in the simultaneous activation of multiple converging

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signaling pathways (Matsumoto et al., 2007; Nishimaki-Mogami et al., 2008). Both retinoic nuclear receptors are activated by their endogenous ligand retinoic acid (RA; i.e., all-*trans*-RA and 9-*cis*-RA) (Costet et al., 2003; Koldamova et al., 2003; Nishimaki-Mogami et al., 2008; Zhou et al., 2015). Recently, the relevance of this pathway for RCT was demonstrated in a mouse model of atherosclerosis (*apoE*$^{-/-}$ mice on a high-fat diet) by the LXRE-dependent stimulatory effects of 9-*cis*-RA on macrophage ABCA1 and ABCG1 expression, cholesterol efflux, and HDL-C levels (Zhou et al., 2015). Consequently, RXR as well as the other nuclear factors are important effectors of the cellular cholesterol homeostasis, which makes them valuable targets to induce *ABCA1* and *ABCG1* expression and to eventually enhance cellular cholesterol efflux and RCT.

B. Liver X Receptor Activation to Induce ATP-Binding Cassette A1 and ATP-Binding Cassette G1 Expression

The increased understanding about the pivotal role of LXR target genes in cholesterol metabolism, including *ABCA1* and *ABCG1*, has enhanced the interest to pharmacologically modulate LXR signaling. One of the first discovered synthetic steroidal LXR agonists, T0901317, a full and potent agonist of both LXRα and LXRβ, appeared to protect against atherosclerotic development in vitro and in animal studies (Terasaka et al., 2003; Thomas et al., 2003; Beyer et al., 2004; Quinet et al., 2004; Wang et al., 2006; Dai et al., 2008; Sato et al., 2008; Larrede et al., 2009; Verschuren et al., 2009; Yan et al., 2010; Honzumi et al., 2011; Chen et al., 2012; Kirchgessner et al., 2015; Manna et al., 2015; Jiang and Li, 2017) (Table 1). T0901317 enhanced the in vitro and in vivo expression of LXR target genes, including *ABCA1* and *ABCG1*, leading to increased cholesterol efflux to apoA-I and HDL and decreased foam cell and atherosclerotic plaque formation (Fukumoto et al., 2002; Murthy et al., 2002; Terasaka et al., 2003; Thomas et al., 2003; Beyer et al., 2004; Miao et al., 2004; Quinet et al., 2004, 2006; Wu et al., 2004; Panzenboeck et al., 2006; Wang et al., 2006; Delvecchio et al., 2007, 2008; Fujiyoshi et al., 2007; Dai et al., 2008; DiBlasio-Smith et al., 2008; Sato et al., 2008; Zanotti et al., 2008; Larrede et al., 2009; Verschuren et al., 2009; Mogilenko et al., 2010; Morrow et al., 2010; Yan et al., 2010; Honzumi et al., 2011; Maejima et al., 2011; Chen et al., 2012; Di et al., 2012; Elali and Hermann, 2012; Jiang et al., 2012; Ma et al., 2014; Kaneko et al., 2015; Kirchgessner et al., 2015; Manna et al., 2015; Tamehiro et al., 2015; Carter et al., 2017; Jiang and Li, 2017; Marinozzi et al., 2017; Monzel et al., 2017; Kaseda et al., 2018). Unfortunately, T0901317 was associated with enhanced lipogenesis, resulting in elevated serum triglyceride levels and hepatic steatosis, which is most likely explained by LXRα-induced activation of the sterol regulatory-binding element protein 1c (SREBP-1c) pathway (Terasaka et al., 2003; Thomas et al., 2003; Beyer et al., 2004; Miao et al., 2004; Quinet et al., 2004, 2006; Delvecchio et al., 2008; DiBlasio-Smith et al., 2008; Sato et al., 2008; Verschuren et al., 2009; Yan et al., 2010; Honzumi et al., 2011; Chen et al., 2012; Kaneko et al., 2015; Kirchgessner et al., 2015; Manna et al., 2015; Carter et al., 2017; Marinozzi et al., 2017). A nonsteroidal LXR agonist, GW3965, also protected against atherosclerosis development (Ruan et al., 2003), but less effectively as T091317 (Sparrow et al., 2002; Bennett et al., 2006; Brunham et al., 2006; Naik et al., 2006; Quinet et al., 2006; Delvecchio et al., 2007; DiBlasio-Smith et al., 2008; Di et al., 2012; Kannisto et al., 2014). Moreover, it amplified *SREBP-1c* expression leading to increased hepatic and plasma triglyceride levels (Sparrow et al., 2002; Quinet et al., 2004). Various other LXR agonists, including acetyl-podocarpic dimer, LXR-623 (i.e., also known as WAY-252623), ritonavir (i.e., an antiretroviral drug), side-chain modified sterol, ergosterol derivatives, and C24-hydoxylated stigmastane derivatives, also effectively increased *ABCA1* expression (Sparrow et al., 2002; DiBlasio-Smith et al., 2008; Pou et al., 2008; Quinet et al., 2009; Marinozzi et al., 2017; Castro Navas et al., 2018). However, they all produced unwanted effects on plasma triglyceride levels by stimulation of *SREBP-1c* gene transcription and LXR-623 enhanced plasma triglyceride levels, yet all to a lower extent than T0901317 (Sparrow et al., 2002; DiBlasio-Smith et al., 2008; Pou et al., 2008; Quinet et al., 2009; Marinozzi et al., 2017; Castro Navas et al., 2018).

Although the adverse effects limit the clinical use of these LXR agonists, they raised great interest in LXR stimulation as a potential target to stimulate RCT. Novel LXR agonists have been developed, like *N,N*-dimethyl-3β-hydroxycholenamide (DMHCA), a synthetic oxysterol that has the potential to enhance cholesterol transport in an LXR-dependent manner without increasing plasma triglyceride levels. Moreover, hepatic *SREBP-1c* mRNA expression was only slightly increased by DMHCA in rat aortic endothelial cells, whereas in macrophages *SREBP-1c* was reduced (Quinet et al., 2004; Kratzer et al., 2009; Hammer et al., 2017). The potential of this type of LXR agonist was emphasized by methyl-3β-hydroxy-5α,6α-epoxy-cholanate, a compound with similar structure and effects as DMHCA (Yan et al., 2010), and a novel analog of *N,N*-disubstituted 2,8-diazaspiro [4.5]decane, also known as IMB-151 (Li et al., 2014). This compound also upregulated ABCA1 and ABCG1 expression in RAW264.7 macrophages in an LXRα-dependent manner, whereas SREBP-1c protein expression levels in HepG2 cells were only slightly increased (Li et al., 2014). Other LXR-agonists, ibrolipim (also known as NO-1886) and BMS-779788, increased *ABCA1* expression and cellular cholesterol efflux and reduced *SREBP-1c* expression in vitro and markedly lowered plasma triglyceride levels in vivo (Zhang et al., 2006; Ma et al., 2009; Chen et al., 2010; Tsou et al., 2014; Kick et al., 2015; Kirchgessner et al., 2015). The LXRβ-specific

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TABLE 1
LXR-activating compounds

Overview of compounds that activate LXR, including their primary pharmacological action, effects on ABCA1 and ABCG1 expression (arrows: *mRNA*, protein), and effects on cellular cholesterol efflux. Effects on ABCA1, ABCG1, and cholesterol efflux are presented as follows: (↓) decreased; (=) no effect; (↑) increased. Italicized symbols indicate changes in *ABCA1* and *ABCG1* mRNA levels, whereas nonitalicized symbols indicate protein levels.

Compound	Primary Action	ABCA1	ABCG1	Cholesterol Efflux	Reference
Acetyl-podocarpic dimer	Selective LXR agonist	↗ THP-1 ↗ Caco-2 ↗ Primary hepatocytes[a]	↗ Caco-2 ↗ Primary hepatocytes[a]	THP-1 ↑ apoA-I ↑ Caco-2 ↑ Monocytes[a] Primary fibroblasts[a]: ↑ apoA-I	Sparrow et al., 2002
Baclofen	$GABA_B$ receptor agonist	—	—	MDM = apoA-I = HDL	Yang et al., 2014
Digoxin	Na^+-K^+-ATPase inhibitor	↑ H9c2	—	↑ H9c2	Campia et al., 2012
Disodium ascorbyl phytostanol phosphate (FM-VP4)	MDR1 antagonist	↗ Liver[b] = Small intestine[b]	—	—	Méndez-González et al., 2010
Daunorubicin	Anthracycline antibiotic	= HL-1	= HL-1	—	Monzel et al., 2017
DMHCA	LXRα agonist	↗ THP-1 ↗ J774 ↗ HepG2 ↗↑ BREC ↗ PM[b,c] ↗ Liver[a] = Liver[d] ↗ Ileum[d] ↗ Aorta[d]	↗ BREC ↗ PM[c] ↗ Liver[a,d] ↗ Ileum[d] ↗ Aorta[d]	↑ THP-1	Quinet et al., 2004; Kratzer et al., 2009; Hammer et al., 2017
Doxorubicin	Anthracycline antibiotic	↑ HL-1	↑ HL-1	HL-1 ↑ apoA-I ↑ HDL	Monzel et al., 2017
E17110	Benzofuran-2-carboxylate analog	↗↑ RAW264.7	↗↑ RAW264.7	RAW264.7 ↑ apoA-I ↑ HDL	Li et al., 2016
(E)-1-(e,4-diisopropoxyphenyl)-3-(4-isopropoxy-3-methoxyphenyl-2-en-1-one	Chalcone derivative	↗↑ THP-1	↗ THP-1	—	Teng et al., 2018
Ergosterol derivatives	Ergosterol analog	↑ U937			Marinozzi et al., 2017
Etoposide	DNA topoisomerase II inhibitor	↑ RAW264.7 ↗↑ PM[b] ↑ THP-1 Blood monocyte[a]	↗ PM[b]	↑ PM ↑ RCT[b]	Zhang et al., 2013a
EXEL-04286651/BMS-779788	LXR partial agonist	↗ Murine blood cells	↗ Murine blood cells ↗ Blood cells[e]	—	Kick et al., 2015; Kirchgessner et al., 2015
FTY720-P	Sphingosine-1-phosphate analog	↗ Monocytes[a]	—	↑ Monocytes[a]	Blom et al., 2010
G004	Unknown (synthetic sulfonylurea compound)	↗↑ RAW264.7 ↑ Liver[c]	↗↑ RAW264.7 ↗↑ Liver[c]	↑ RAW264.7 ↑ RCT[c]	Qian et al., 2017
GW3965	LXRα agonist	↗ THP-1 ↗ J774 ↗ HepG2 ↗ haSMC[a] ↗ BMM ↗ PM[b,h,i] ↗↑ Liver[a,h] ↗= Liver[a,h] ↗ Peripheral blood[f] ↗ Spleen[f] ↗↑ Prox small intestine[b] = Prox small intestine[g]	↗ haSMC[a] ↗= Liver[b] ↗ Peripheral blood[f] ↗ Spleen[f] ↗ Prox small intestine[b,g]	↑ THP-1 ↑ RCT[b]	Miao et al., 2004; Quinet et al., 2004, 2006; Brunham et al., 2006; Naik et al., 2006; Delvecchio et al., 2007; DiBlasio-Smith et al., 2008; Kannisto et al., 2014

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TABLE 1—*Continued*

Compound	Primary Action	ABCA1	ABCG1	Cholesterol Efflux	Reference
		↑ Kidney[b,h] ↑ Duodenum[b,h]			
Ibandronate	Osteoclast inhibitor	↑ MM6 ↑ PBMCs[a]	—	↑ MM6	Strobach and Lorenz, 2003
Ibrolipim (NO-1886)	Lipoprotein lipase activator	↑↑ THP-1 ↑↑ Liver[j] ↑↑ Adipose tissue[j] ↑↑ Aorta[j]	↑↑ THP-1	↑ THP-1	Zhang et al., 2006; Ma et al., 2009; Chen et al., 2010
Idarubicin	Anthracycline antibiotic	↑ HL-1	↑ HL-1		Monzel et al., 2017
IMB-151	Unknown	↑↑ RAW264.7	↑↑ RAW264.7	↑ RAW264.7	Li et al., 2014
Infliximab	Anti–TNF-α mAb	↑↑ THP-1	== THP-1	↑ THP-1 (restores effect of TNF-α)	Voloshyna et al., 2014
Lansoprazole	Proton pump inhibitor	↑ H4 neuroglioma cells[a] ↑ U-87 astrocytoma ↑↑ CCF astrocytoma ↑ U-118 astrocytoma ↑ Primary astrocytes[b]	—	—	Cronican et al., 2010
LXR-623	Synthetic LXR agonist	↑ Duodenum[g] = Liver[g] ↑ Spleen[f] ↑ Peripheral blood[a,b,f] ↑↑ PBMCs[a] ↑ Whole blood[a,e]	↑ Duodenum[g] = Liver[g] ↑ Spleen[f] ↑ Peripheral blood[a,b,f] ↑↑ PBMCs[a] ↑ Whole blood[a,e]	—	DiBlasio-Smith et al., 2008; Katz et al., 2009; Quinet et al., 2009
Methyl-3β-hydroxy-5α,6α-epoxycholanate	LXRα agonist	↑ THP-1 ↑ Aorta[c]	—	—	Yan et al., 2010
Omeprazole	Proton pump inhibitor	↑ H4 neuroglioma cells[a]	—	—	Cronican et al., 2010
Pantoprazole	Proton pump inhibitor	↑ H4 neuroglioma cell[a]	—	—	Cronican et al., 2010
Ouabain	Na^+-K^+-ATPase inhibitor	↑ H9c2	—	↑ H9c2	Campia et al., 2012
Ritonavir	Viral proteinase inhibitor	↑↑ THP-1	= THP-1	—	Pou et al., 2008
Sirolimus	FK-binding protein-12 inhibitor	↑ hVSMC	= hVSMC	= hVSMC	Ma et al., 2007
(24S)-stigmasta-5,28-diene-3β,24- ol	LXR agonist	↑ U937			Castro Navas et al., 2018
(24S)-stigmasta-5-ene-3β,24-ol	LXR agonist	↑ U937			Castro Navas et al., 2018
Stigmasterol derivatives	LXR agonist	↑ U937			Marinozzi et al., 2017
T0901317	LXR agonist	↑↑ THP-1 ↑↑ RAW264.7 ↑ J774 ↑ U937 ↑↑ HepG2 ↑↑ Caco-1 ↑ HL-1 ↑↑ pBCECs ↑ TR-CSFB3 ↑↑ SAS ↑↑ haSMC ↑↑ McARH7777 ↑↑ $CD4^+$ T cells[a] ↑↑ Jurkat ↑ Cerebral endothelial cells	↑ THP-1 ↑↑ RAW264.7 ↑ MCF-7 ↑↑ Caco-1 ↑ HL-1 ↑ TR-CSFB3 ↑↑ haSMC[a] ↑ Cerebral endothelial cells ↑↑ Blood-derived macrophages[a] ↑ Aorta endothelial cells[c] ↑ Liver[b,k] ↑ Aorta[i,o] ↑ Peripheral blood[e, f],	↑ THP-1 ↑ HDL ↑ J774 ↑ Caco-1 HL-1 ↑ apoA-I ↑ HDL ↑ SAS ↑ Jurkat ↑ Fu5AH ↑ COS-7 ↑ pBCECs ↑ Monocyte-derived macrophages[a] ↑ $CD4^+$ T cells[a] ↑ HSKMc[a]	Fukumoto et al., 2002; Murthy et al., 2002; Terasaka et al., 2003; Thomas et al., 2003; Beyer et al., 2004; Miao et al., 2004; Quinet et al., 2004, 2006; Wu et al., 2004; Panzenboeck et al., 2006; Wang et al., 2006; Delvecchio et al., 2007, 2008; Fujiyoshi et al., 2007; Sprecher et al., 2007; Dai et al., 2008; DiBlasio-Sato et al., 2008; Smith et al., 2008; Zanotti et al., 2008; Larrede et al., 2009; Verschuren et al., 2009; Mogilenko et al., 2010; Morrow et al., 2010; Yan et al., 2010; Maejima et al., 2011; Honzumi et al., 2011; Chen et al., 2012; Di et al., 2012; El Roz et al., 2012; Elali and Hermann, 2012;

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TABLE 1—*Continued*

Compound	Primary Action	ABCA1	ABCG1	Cholesterol Efflux	Reference
		↑ Murine immortal macrop.		haSMC[a]	Jiang et al., 2012; Ma et al., 2014; Kaneko et al., 2015; Kirchgessner et al., 2015; Manna et al., 2015; Tamehiro et al., 2015; Li et al., 2016; Carter et al., 2017; Jiang and Li, 2017; Marinozzi et al., 2017; Monzel et al., 2017; Kaseda et al., 2018
		↑ Murine neuro2A		= apoA-I	
		↑ Murine BV-2		↑ HDL	
		↑ Rat C6		MCF-7	
		↑↑ Blood-derived macrop[g]		= apoA-I	
		↑ Aorta endothelial cells[c]		↑ HDL	
		↑ Renal glomerular mesangial cells[i]		↑ Murine primary macrop.	
		↑↑ PM[b,d,g,h]		↑ PM[b,d,g,h]	
		↑↑ Liver [b,c,h,i,l,k]		↑ Murine immortal macrop.	
		↑↑ Aorta[b,c,i,k,o]		↑ Renal glomerular mesangial cells[i]	
		↑ Small intestine[c]			
		↑ Kidney[b,h]			
		↑ Duodenum[b,h]			
		↑ Peripheral blood[f]			
		↑ Proximal intestine[k]			
		↑ Distal intestine[k]			
		↑↑ Brain[m,n]			
Tacrolimus	FK-binding protein-12 inhibitor	↑= THP-1	—	—	Jin et al., 2004
Teniposide	DNA topoisomerase II inhibitor	↑ RAW264.7	↑ PM[b]	↑ PM[b]	Zhang et al., 2013a
		↑↑ PM[b]		↑ RCT	
		↑ THP-1			
		↑ Blood monocyte			
Topiramate	GABA-A receptor agonist	↑↑ MDM	↑↑ MDM	MDM	Yang et al., 2014
				↑ apoA-I	
				↑ HDL	
YC-1	Soluble guanylyl cyclase activator	↑↑ J774A.1	= J774A.1	↑ J774A.1	Tsou et al., 2014
		↑ Aorta[c]	= Aorta[c]		

BMM, bone marrow– derived macrophage; BREC, bovine retinal endothelial cells; haSMC, human airway smooth muscle cells; HSKM, human skeletal muscle cells; hVSMC, human vascular smooth muscle cells; macrop, macrophage; MCF-7, Michigan Cancer Foundation-7; MDM, monocyte-derived macrophage; pBCECs, procine brain capillary endothelial cells; PBMC, peripheral blood mononuclear cell; PM, peritoneal macrophages; prox, proximal; SAS, human squamous cell carcinoma cell line.

[a]Human.
[b]C75BL/6 mice.
[c]*apoE*$^{-/-}$ C57BL/6 mice.
[d]*LXRβ*$^{-/-}$ C75BL/6 mice.
[e]Cynomolgus monkeys.
[f]Male long Evans rats.
[g]*LDLR*$^{-/-}$ C75BL/6 mice.
[h]*LXRα*$^{-/-}$ C75BL/6 mice.
[i]New Zealand White rabbits.
[j]Male chine Bama minipigs.
[k]Male SD rats.
[l]129Sv mice.
[m]*APP*/*PS1*Δ9/APOE4$^{+/+}$/ABCA1$^{+/-}$ C57 BL/6 mice.
[n]*APP*/*PS1*Δ9/APOE3$^{+/+}$/ABCA1$^{+/-}$ C57 BL/6 mice.
[o]E3L mice.

agonist E17110 (i.e., a benzofuran-2-carboxylate analog) and LXRα-specific synthetic chalcone derivative, (E)-1-(3,4-di-isopropoxyphenyl)-3-(4-isopropoxy-3-methoxyphenyl)prop-2-en-1-one, both induced ABCA1 expression in macrophages, whereas an enhanced cholesterol efflux was only described after treatment with E17110 (Li et al., 2016; Teng et al., 2018). Moreover, commonly used proton pump inhibitors (i.e., lansoprazole, omeprazole, pantoprazole) demonstrated to act as LXR agonists, of which lansoprazole was most potent (Cronican et al., 2010). By inducing LXR, proton pump inhibitors enhanced *ABCA1* expression in human and mouse cells (Cronican et al., 2010).

Type II DNA topoisomerase inhibitors, which are used as chemotherapeutic medication, also enhanced

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ABCA1 expression in an LXRα-dependent manner (Zhang et al., 2013a; Tsou et al., 2014; Shen et al., 2015). Inhibition of type II DNA topoisomerase by etoposide and teniposide induced in vitro ABCA1 expression, free cholesterol efflux, and in vivo RCT. Teniposide exerted its effect by inhibiting expression of receptor-interacting protein 140, a corepressor of LXR, and consequently mediated its favorable effects at lower concentrations compared with etoposide (Zhang et al., 2013a). Like other LXR agonists, etoposide and teniposide both enhanced FAS expression, indicating that these inhibitors also activate genes involved in lipogenesis, which could limit their use in the treatment of atherosclerosis (Zhang et al., 2013a) in addition to their unfavorable cytostatic effects. In contrast, 3-(5′-hydroxymethyl-2′furyl)-1-benzyl indazole (YC-1), which in addition to LXR also activates soluble guanylyl cyclase, upregulated ABCA1 expression, enhanced cholesterol efflux, and decreased ox-LDL particle accumulation in macrophages in an LXRα-dependent manner, whereas ABCG1, SR-B1, SR-1, and CD36 expression levels were not altered (Tsou et al., 2014).

Indirect activation of LXR by a synthetic sphingosine analog (i.e., 2-amino-2-[2-(4-*n*-octylphenyl)ethyl]-1,3-propanediol hydrochloride, FTY720-P) and a synthetic sulfonylurea compound (i.e., G004) also enhanced in vitro expression of *ABCA1* and *ABCG1* and cholesterol efflux (Blom et al., 2010). FTY720-P upregulated *ABCA1* expression in human macrophages via increased production of the endogenous LXR ligand 27-hydroxycholesterol,which subsequently enhanced LXR activity independent of sphingosine 1-phosphate receptor activation (Blom et al., 2010; Qian et al., 2017). In contrast, G004 increased ABCA1 and ABCG1 expression by targeting sirtuin 1 and thereby acting as an atheroprotective agent in vivo (Qian et al., 2017). Ibandronate, a bisphosphonate, also stimulated LXR indirectly, which was reversed upon addition of geranylgeranyl pyrophosphate, suggesting that low levels of this mevalonate pathway intermediate increased LXR expression via a negative feedback mechanism (Strobach and Lorenz, 2003). Anthracyclines, which are used as chemotherapeutic agents, also demonstrated to indirectly activate LXR-ABCA1/ABCG1 pathway by enhancing several oxysterol and cholesterol precursor levels, although a direct binding between anthracyclines and LXR cannot be excluded. Their clinical use is generally strongly limited due to cardiotoxic effects (Monzel et al., 2017), and their cytostatic effect omits the use of these drugs to stimulate RCT clinically. An indirect stimulatory effect on LXR expression by a yet unknown mechanism has also been observed with disodium ascorbyl phytostanol phosphate (FM-VP4), a potential cholesterol-lowering drug (Méndez-González et al., 2010).

The cardiac glycosides, digoxin and ouabain, stimulated cholesterol efflux via LXR-mediated upregulation of ABCA1 expression in cardiomyocytes, but only slightly increased ABCG1 expression (Campia et al., 2012). They also increased cholesterol and ubiquinone synthesis via upregulation of HMG-CoA reductase expression without affecting the intracellular cholesterol concentration. This could be explained by the stimulation of cholesterol efflux in cardiomyocytes, which might also contribute to the beneficial effect of cardiac glycosides in CVD (i.e., next to their antiarrhythmic effects). However, further research is warranted to demonstrate their antiatherosclerotic potential. Finally, the anti–tumor necrosis factor (TNF)-α monoclonal antibody infliximab was linked to a reduced foam cell formation in THP-1 macrophages induced by TNF-α, which was dependent on the reversal of TNF-α–induced inhibition of cholesterol efflux and LXR-α, ABCA1, and ABCG1 mRNA and protein expression (Voloshyna et al., 2014). This could also provide an explanation for the improved vascular function, as recently observed in patients with rheumatoid arthritis with TNF inhibitor therapy (Rongen et al., 2018). Although Voloshyna et al. (2014) demonstrated a lowering effect of TNF-α on LXR-α and ABCA1 levels in THP-1 monocytes, no differences in the mRNA levels of the LXR-target gene *ABCA1* and apoA-I–dependent cholesterol efflux were reported in TNF-α–treated C57BL/6 mice peritoneal macrophages (Castrillo et al., 2003). The uncertainty about the exact role of TNF-α on LXR-α and ABCA1 expression is further emphasized by different findings in several cell types. TNF-α reduced *LXR*-α expression and LXRE activity level in HK-2 proximal tubular cells and Hep3B liver cells, whereas in Caco-2 cells *ABCA1* was decreased without attenuation of *LXR*-α upon stimulation with TNF-α (Wang et al., 2005; Kim et al., 2007; Field et al., 2010). A stimulatory effect on cellular cholesterol efflux was found after lowering TNF-α production in human macrophages by GABA and the GABA agonist topiramate (Yang et al., 2014). These effects could not be observed with baclofen, another GABA agonist (Yang et al., 2014), which questions the direct involvement of GABA in the previously observed effects with GABA agonists. Interestingly, a reversal of TNF-α–induced cholesterol efflux inhibition could also be observed with the immunosuppressant sirolimus, which increased cholesterol efflux in human vascular smooth muscle cells accompanied by an increased *ABCA1* expression (Ma et al., 2007). Although the structurally related drug tacrolimus did also increase *ABCA1* expression, its effect seemed to be mediated via PPARγ and not via a TNF-α–dependent mechanism (Jin et al., 2004). Because both immunosuppressants have been also associated with elevated plasma cholesterol and triglyceride levels (Wlodarczyk et al., 2005; Kido et al., 2018), their clinical applicability to reduce atherosclerotic risk is limited.

Of all LXR agonists, only two (i.e., BMS-779788, also known as EXEL-04286652 and LXR-623) were studied in a clinical trial (Hong and Tontonoz, 2014). Unfortunately, no published report is available on the completed study of BMS-779788 (Hong and Tontonoz, 2014).

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LXR-623 stimulated *ABCA1* and *ABCG1* expression in peripheral blood cells of healthy individuals, which is expected to result in an enhanced RCT. However, the phase I clinical trial was terminated due to unfortunate neurologic adverse effects at the two highest concentrations tested. It remains unknown whether this effect was LXR-mediated or via other unknown off-target mechanisms of LXR-623 (Katz et al., 2009).

C. Peroxisome Proliferator-Activated Receptor Activation to Enhance ATP-Binding Cassette A1 and ATP-Binding Cassette G1 Expression

Fibrates have been used for decades as cholesterol-lowering drugs, but currently they are mainly administered as comedication with statins to treat severe hypertriglyceridemia (>15 mmol $\times$ l^{-1}). Although fibrates are mainly agonists of PPARα, they stimulate all three PPAR isoforms with different potencies, except for bezafibrate, which is an equipotent agonist of all isoforms. Gemfibrozil, fenofibrate, bezafibrate, and clofibrate all increased ABCA1 mRNA and protein expression upon PPAR activation in vitro (Oliver et al., 2001; Forcheron et al., 2002; Lin and Bornfeldt, 2002; Guan et al., 2003; Ruan et al., 2003; Thomas et al., 2003; Arakawa et al., 2005; Kooistra et al., 2006; Hossain et al., 2008; Tanabe et al., 2008; Ogata et al., 2009; Kobayashi et al., 2011; Jiang and Li, 2017), which was associated with enhanced apoA-I–mediated cholesterol efflux (Oliver et al., 2001; Ruan et al., 2003; Arakawa et al., 2005; Kooistra et al., 2006; Ogata et al., 2009) (Table 2). Next to an effect on peripheral *ABCA1* expression, fenofibrate and gemfibrozil also induced hepatic *ABCA1*, *ABCG1*, and *ABCG5/8* mRNA expression in a PPARα-dependent manner (Hossain et al., 2008; Rotllan et al., 2011). This positive effect on *ABCA1* expression could also in part explain the antiatherosclerotic effects observed with fibrates in clinical trials (Steiner, 2005). The coronary risk reduction found in these trials could also be related to their LDL-C–lowering capacity. However, the therapeutic value of fibrates remains equivocal due to absence of a reduction in total cardiovascular mortality in several trials. Two large-scale intervention studies with fenofibrate (FIELD trial and ACCORD-LIPID trial) in patients with type 2 diabetes mellitus found no differences in coronary events, nonfatal myocardial infarction, and stroke (Keech et al., 2005; Ginsberg et al., 2010). Similar results were reported in two intervention trials with bezafibrate, in which no significant effect was found on both fatal and nonfatal myocardial infarction in the Bezafibrate Infarction Prevention (BIP) study, and no reduction in the incidence of coronary heart disease and of strokes in the LEADER trial (Bezafibrate Infarction Prevention (BIP) Study, 2000; Meade et al., 2002). In contrast, two trials using gemfibrozil [Helsinki Heart Study (HHS) trial and Veterans Affairs–HDL Intervention Trial (VA-HIT) study] showed a significant reduction in the incidence of coronary heart disease and myocardial infarction or cardiovascular death, demonstrating an overall benefit of gemfibrozil treatment (Frick et al., 1987; Rubins et al., 1999).

Like gemfibrozil and fenofibrate, the specific PPARα agonist, Wy14643, enhanced ABCA1 protein expression and apoA-I–mediated cholesterol release in vitro, primarily mediated via LXRα activation (Chinetti et al., 2001; Ruan et al., 2003; Thomas et al., 2003; Beyer et al., 2004; Arakawa et al., 2005; Lee et al., 2008; Maejima et al., 2011). Although beneficial effects on ABCA1 expression and cholesterol efflux were observed after treatment with gemfibrozil, fenofibrate, and Wy14643, all three compounds stimulated PPARα with a relatively low affinity in the micromolar range (Ferri et al., 2017). This initiated the exploration of high-affinity PPARα agonists like GW7647, which effectively increased *ABCA1* mRNA. However, no effect of GW7647 on apoA-I–driven cholesterol efflux was observed in THP-1 macrophages (Oliver et al., 2001; Li et al., 2004; Wang et al., 2010; Nakaya et al., 2011). Another high-affinity PPARα agonist, LY518674, did increase both ABCA1 expression and apoA-I–mediated cholesterol efflux via LXRα activation, resulting in increased HDL biogenesis, whereas Wy14563 only increased cholesterol efflux via PPARα stimulation (Chawla et al., 2001; Hossain et al., 2008; Ogata et al., 2009; Ferri et al., 2017). Surprisingly, high aspirin concentrations ($\geq$250 μM) slightly enhanced ABCA1 expression and cholesterol efflux in macrophages in a PPARα-dependent manner (Viñals et al., 2005; Wang et al., 2010).

Statins most likely also affect ABCA1-dependent cholesterol efflux beneficially via indirect stimulation of PPARα (Zanotti et al., 2004, 2006; Argmann et al., 2005; Kobayashi et al., 2011; Maejima et al., 2011; Song et al., 2011; Shimizu et al., 2014; Nicholls et al., 2015). However, the results of a variety of studies are equivocal and report large differences with different statins in vitro and in vivo (e.g., in various cell types, animal models, and patients). In hepatocytes, only pitavastatin seemed to enhance *ABCA1* mRNA expression at low micromolar concentrations in all studies (Zanotti et al., 2004, 2006; Kobayashi et al., 2011; Maejima et al., 2011; Song et al., 2011). Mechanistically, PPARα activation was seen in all studies, but LXR was activated as well as suppressed in hepatocytes after statin treatment. Moreover, this effect seems to depend on downstream products of the cholesterol synthesis pathway (e.g., mevalonate, geranylgeranyl pyrophosphate), with a major role for Ras homolog gene family member A, which fully reversed statin-mediated *ABCA1* upregulation and ABCA1-mediated cholesterol efflux (Zanotti et al., 2004; Argmann et al., 2005). Not all statins did increase macrophage *ABCA1* expression in vitro (Zanotti et al., 2006), but rosuvastatin exposure in vivo increased total and ABCA1-dependent cholesterol efflux (Shimizu et al.,

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TABLE 2
PPAR-activating compounds

Overview of compounds that activate PPARs, including their primary pharmacological action, effects on ABCA1 and ABCG1 expression (arrows: *mRNA*, protein), and effects on cellular cholesterol efflux. Effects on ABCA1, ABCG1, and cholesterol efflux are presented as follows: (↓) decreased; (=) no effect; (↑) increased. Italicized symbols indicate changes in *ABCA1* and *ABCG1* mRNA levels, whereas nonitalicized symbols indicate protein levels.

Compound	Primary Action	ABCA1	ABCG1	Cholesterol Efflux	Reference
PPARγ-activating compounds					
15d-PGJ2	Prostanoid-specific receptor inhibitor	↗ THP-1 ↗ HMC ↓↓ PM[a]	↑ PM[a]	Lipid-loaded HMC ↑ apoA-I PM[a] ↓ apoA-I ↑ HDL	Ruan et al., 2003; Jiang and Li, 2017
4010B-30	Benzamide analog	↑ RAW264.7 ↑ HepG2	—	RAW264.7 ↑ apoA-I	Du et al., 2015b
Ciglitazone	PPARγ agonist	↗= THP-1	↗ THP-1	↑ THP-1	Argmann et al., 2003, 2005
E3317	PPARγ agonist	RAW264.7 ↗↑ LO2		RAW264.7 ↑ apoA-I	Wang et al., 2018
GQ-11	PPARγ/α agonist	↗ Liver[b]			Silva et al., 2018
GW1929	PPARγ agonist	↗↑ HepG2	—	—	Mogilenko et al., 2010
GW7845	PPARγ agonist	↗ THP-1	—	↑ THP-1	Chawla et al., 2001; Oliver et al., 2001
Propofol	$GABA_B$ receptor agonist	↗↑ THP-1 ↑ RAECs	↗↑ THP-1	↑ THP-1 RAECs ↑ HDL	Ma et al., 2015; Hsu et al., 2018
Lysophosphatidylcholine	Unknown	↗↑ PM[a]	—	↑ PM[a]	Hou et al., 2007
Mycophenolic acid	Inosine-5′-monophosphate dehydrogenase inhibitor	↗↑ HepG2	—	—	Xu et al., 2011
Pioglitazone	PPARγ agonist	↗↑ THP-1 ↑ HepG2 ↗↑ pBCECs ↑ gBECs ↗↑ WI38 fibroblasts ↗ Monocyte-derived macrop[c] ↓↓ PM[a] = Liver[b] ↗ Diabetic patients[c] ↗ Rat cortical neurons	↗↑ THP-1 ↗ Monocyte-derived macrop ↑ PM[a] ↗ Diabetic patients[c] ↗ Rat cortical neurons	THP-1 ↑ apoA-I ↑ HDL ↓ pBCECs ↑ gBECs ↑ WI38 fibroblasts PM[a] ↓ apoA-I ↑ HDL ↑ Diabetic patients[c]	Panzenboeck et al., 2006; Nakaya et al., 2007; Tanabe et al., 2008; Ogata et al., 2009; Cocks et al., 2010; Ozasa et al., 2011; Wang et al., 2014b, 2015b; Jiang and Li, 2017; Silva et al., 2018
Rosiglitazone	PPARγ agonist	↗↑ THP-1 ↗ RAW264.7 ↑ HepG2 == macrop[d] ↑ PM[e] ↗= Hepatocytes[e] = Aorta[d] Aorta lesion[e]	↗↑ THP-1 ↗ macrop[d] ↗ Aorta[d]	↑ THP ↑ RAW264.7 ↑ macrop[d] ↑ PM[e] ↑ Hepatocytes[e]	Chawla et al., 2001; Chinetti et al., 2001; Claudel et al., 2001; Li et al., 2004, 2015; Llaverias et al., 2006
Telmisartan	Angiotensin receptor 1 antagonist	↗↑ THP-1 ↗ Monocyte-derived macrop[c]	↗↑ THP-1 ↗ Monocyte-derived macrop[c]	↑ THP-1	Nakaya et al., 2007
Troglitazone	PPARγ agonist	↗ THP-1 ↓↑ pBCECs ↗↑ gBECs = Monocyte-derived macrop[c] ↓↓ PM[a]	↑ PM[a]	↑ pBCECs PM[a] ↓ apoA-I ↑ HDL	Cabrero et al., 2003; Panzenboeck et al., 2006; Lee et al., 2008; Jiang and Li, 2017
PPARα-activating compounds					
Aspirin	COX-1/2 inhibitor	↑ THP-1 ↗↑ RAW264.7	—	RAW264.7 ↑ apoA-I	Viñals et al., 2005; Wang et al., 2010
Atorvastatin	HMG-CoA reductase inhibitor	↗ THP-1 ↗ McARH7777	↗ THP-1	THP-1 ↑ apoA-I ↑ HDL	Argmann et al., 2005; Maejima et al., 2011; Nicholls et al., 2015, 2017
Bezafibrate	Pan-PPAR agonist	↗↑ THP-1 ↗↑ HepG2 == pBCECs ↗↑ W138 fibroblast ↗ HMC	—	↑ THP-1 ↑ HepG2 = pBCECs ↑ W138 fibroblast	Cabrero et al., 2003; Ruan et al., 2003; Panzenboeck et al., 2006; Hossain et al., 2008; Inaba et al., 2008; Ogata et al., 2009

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TABLE 2—*Continued*

Compound	Primary Action	ABCA1	ABCG1	Cholesterol Efflux	Reference
				Lipid-loaded HMC	
		↑↑ Primary hepatocytes		↑ apoA-I	
		= Monocyte-derived macrop[c]		↑ Primary hepatocytes	
		= aorta[b]			
Clofibrate	PPARα agonist	↑= HepG2	—	—	Guan et al., 2003; Kobayashi et al., 2011
		= Primary hepatocytes[f]			
		↑ Liver[f]			
Fenofibrate	PPARα agonist	↑↑ THP-1	↑ Liver[g]	↑ THP-1	Forcheron et al., 2002; Lin and Bornfeldt, 2002; Cabrero et al., 2003; Thomas et al., 2003; Arakawa et al., 2005; Kooistra et al., 2006; Hossain et al., 2008; Tanabe et al., 2008; Ogata et al., 2009; Jiang and Li, 2017
		↑↑ RAW264.7		↑ RAW264.7	
		↑↑ HepG2		↑ HepG2	
		=↑ pBCECs		= pBCECs	
		↑↑ Balb/3T3		= Balb/3T3	
		↑↑ W138 fibroblast		↑ W138 fibroblast	
		↑↑ Primary hepatocytes		↑ Primary hepatocytes	
		= Monocyte-derived macrop[c]			
		↑ PM[a]			
		↑ Liver[h]			
		↑ Diabetic patients[c]			
		↑ Aorta[i]			
Gemfibrozil	PPARα agonist	↑↑ THP-1	—	↑ THP-1	Hossain et al., 2008; Ogata et al., 2009
		↑↑ HepG2		↑ HepG2	
		↑↑ W138 fibroblast		↑ W138 fibroblast	
		↑↑ Primary hepatocytes		↑ Primary hepatocytes	
GW7647	PPARα agonist	↑ THP-1	= macrop[d]	= THP-1	Oliver et al., 2001; Li et al., 2004; Wang et al., 2010; Nakaya et al., 2011
		↑↑ RAW264.7	= Aorta[d]	RAW264.7	
		== macrop[d]	↑↑ BMM[a]	↑ apoA-I	
		== Atherosclerotic lesion[d]		= macrop[d]	
		↑↑ BMM[a]		↑ BMM[a]	
LY518674	PPARα agonist	↑↑ THP-1	—	↑ THP-1	Hossain et al., 2008; Ogata et al., 2009
		↑↑ HepG2		↑ HepG2	
		↑↑ W138 fibroblast		↑ W138 fibroblast	
		↑↑ Primary hepatocytes		↑ Primary hepatocytes	
Pitavastatin	HMG-CoA reductase inhibitor	↓ J774	—	↓ J774	Zanotti et al., 2004, 2006; Kobayashi et al., 2011; Maejima et al., 2011
		↑ HepG2		↑ Fu5AH	
		↑↑ McARH7777		↓ PM[a,b,d]	
		↑ Liver[f]		= LXR$^{-/-}$ mice	
Pravastatin	HMG-CoA reductase inhibitor	↑↑ 3T3-L1	↓↓ 3T3-L1	↓ 3T3-L1	Maejima et al., 2011; Mostafa et al., 2016
		= McARH7777			
Rosuvastatin	HMG-CoA reductase inhibitor	= Hepatocytes[a]		↑ J774	Shimizu et al., 2014; Mostafa et al., 2016
				↑ BMM[a]	
				↑ RCT[a]	
Simvastatin	HMG-CoA reductase inhibitor	↑ McARH7777	== PM[i]	THP-1	Argmann et al., 2005; Guan et al., 2008; Maejima et al., 2011; Song et al., 2011; Ying et al., 2013; Gong et al., 2014
		↑ Diabetic patients with hyperlipidemia	== Liver[i]	↑ apoA-I	
		== PM[d]		= HDL	
		↑↑ Liver[i]		↑ RAW264.7	
WY14643	PPARα agonist	↑↑ THP-1	↑ THP-1	↑ THP-1	Chinetti et al., 2001; Ruan et al., 2003; Beyer et al., 2004; Arakawa et al., 2005; Lee et al., 2008; Maejima et al., 2011
		↑↑ RAW264.7		↑ RAW264.7	
		↑↑ gBECs		= Balb/3T3	
		↑↑ Balb/3T3		Lipid-loaded HMC	
		= McARH7777		↑ apoA-I	
		↑ Liver[a]			
Wy,14,563	PPARα agonist	—	—	↑ THP-1	Chawla et al., 2001
PPARδ/β-activating compounds					
Carbaprostacyclin (cPGI)	PPARδ agonist	—	—	↑ THP-1	Chawla et al., 2001
GW0742	PPARδ agonist	= Liver[a]	= Liver[a]	↑ BMM[a]	Li et al., 2004; Briand et al., 2009
		= Small intestine[a]	= Small intestine[a]	= macrop[a]	

(*continued*)

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TABLE 2—*Continued*

Compound	Primary Action	ABCA1	ABCG1	Cholesterol Efflux	Reference
		== macrop[d] = Atherosclerotic lesion[d]	= macrop[d] = Aorta[d]		
GW501515	PPARδ agonist	↑↑ THP-1 ↑↑ W138 fibroblast ↑ 1BR3N fibroblast ↑ Intestinal FHS74 ↑ HSKM	= HSKM	↑ THP-1 ↑ W138 fibroblast ↑ 1BR3N fibroblast ↑ Intestinal HSKM	Oliver et al., 2001; Sprecher et al., 2007; Ogata et al., 2009

BMM, bone marrow– derived macrophage; gBECS, gallbladder epithelial cells; HMC, human mast cell; HSKM, human skeletal muscle cell; macrop, macrophage; pBCECs, porcine brain capillary endothelial cells; PM, peritoneal macrophages; RAECs, rat aortic endothelial cells.
[a]C75BL/6 mice.
[b]*LDLR*$^{-/-}$ C75BL/6 mice.
[c]Human.
[d]*LDLR*$^{-/-}$ C75BL/6 hypercholesterolemic mice.
[e]New Zealand White rabbits.
[f]Male Wistar rats.
[g]Male Zucker diabetic fatty rats.
[h]129SV mice.
[i]Female E3L transgenic mice.

2014). Although cotreatment with atorvastatin and evacetrapib revealed an enhanced cholesterol efflux, whereas single treatment with atorvastatin resulted in a decreased cholesterol efflux, the clinical relevance is limited, because evacetrapib also increased overall atherogenic risk (Nicholls et al., 2017). Therefore, the absence of an effect or even negative effect of statins on ABCA1-mediated cholesterol efflux in some clinical studies (Nicholls et al., 2015, 2017), as well as the high incidence of dose-dependent muscle complaints associated with these drugs, limits their ability to increase RCT.

Next to compounds that beneficially affect PPARα, a vast number of drugs can stimulate PPARγ. Thiazolidinediones are probably the most well-known and widely used PPARγ agonists, due to their antidiabetic properties. Thiazolidinediones, including pioglitazone, ciglitazone, and rosiglitazone, enhanced LXRα expression, which subsequently induced ABCA1 protein expression and cholesterol efflux toward apoA-I in vitro (Chawla et al., 2001; Chinetti et al., 2001; Claudel et al., 2001; Cabrero et al., 2003; Li et al., 2004, 2015; Llaverias et al., 2006; Panzenboeck et al., 2006; Nakaya et al., 2007; Lee et al., 2008; Tanabe et al., 2008; Ogata et al., 2009; Cocks et al., 2010; Ozasa et al., 2011; Wang et al., 2014b, 2015b; Jiang and Li, 2017) (Table 2). Contradictory to these results with pioglitazone in THP-1 macrophages and J774 macrophages, an attenuated or unaffected ABCA1 expression was found in peritoneal macrophages isolated from 15PGJ2-, troglitazone-, and pioglitazone-treated C57BL/6 mice, and in the liver of pioglitazone-treated *LDLR*$^{-/-}$ C57BL/6 mice (Ruan et al., 2003; Ogata et al., 2009; Ozasa et al., 2011; Zhao et al., 2015; Jiang and Li, 2017; Silva et al., 2018). Clinically, the cardioprotective antiatherosclerotic effects of thiazolidinediones have been heavily debated (Liebson, 2010). Although increased HDL-C levels were observed after pioglitazone and rosiglitazone treatment, increased cardiovascular morbidity and heart failure have been associated with rosiglitazone (Gerstein et al., 2006; Home et al., 2009; Liebson, 2010; Chandra et al., 2017). Although in various clinical trials cardioprotective effects have been observed with pioglitazone (Chandra et al., 2017), its chronic use is limited by the observed association with an increased risk of developing bladder cancer, bone fractures, and congestive heart failure (Tang et al., 2018). Another PPARγ agonist, GW7845, which is an analog of the PPARα agonist GW7647, did not affect apoA-I–mediated cholesterol efflux, whereas *ABCA1* mRNA expression was enhanced (Chawla et al., 2001; Oliver et al., 2001). The PPARγ agonist, GW1929, reduced ABCA1 protein expression in HepG2 cells, whereas *ABCG1* gene expression was increased probably due to an interplay between PPARγ and LXRβ, resulting in dissociation of LXRβ from the ABCA1/LXRβ complex (Mogilenko et al., 2010). In contrast, mycophenolic acid, 4010B-30, telmisartan, propofol, and lysophosphatidylcholine exposure did result in an increased in vitro ABCA1 expression and apoA-I–mediated cholesterol efflux, mediated via the PPARγ–LXRα–ABCA1 axis (Hou et al., 2007; Nakaya et al., 2007; Xu et al., 2011; Du et al., 2015b; Ma et al., 2015; Hsu et al., 2018). Lysophoshatidylcholine treatment enhanced apoE secretion from peritoneal macrophages (Hou et al., 2007) and 4010B-30 enhanced apoA-I production, whereas telmisartan and propofol also enhanced ABCG1 expression in macrophages (Nakaya et al., 2007; Du et al., 2015b; Ma et al., 2015). The clinical antiatherosclerotic applicability of propofol seems limited, because of its sedative effect and risk of hypertriglyceridemia induced by the lipid emulsion formulation (Eddleston and Shelly, 1991). Additionally, E3317 enhanced in vitro ABCA1 expression and apoA-I–dependent cholesterol efflux via PPARγ, and a novel thiazolidine, GQ-11, which is a partial PPARγ and PPARα agonist, increased hepatic *ABCA1*, *APOA-I*, and *HDL* mRNA expression in *LDLR*$^{-/-}$ C57BL/6 mice (Silva et al., 2018; Wang et al., 2018). Thus, PPARγ agonists show controversial results in the stimulation of ABCA1 expression, which could be due to their

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relatively low potency for PPARα and high PPARγ potency.

Although explored to a lesser extent, activation of PPARβ/δ may be promising, as activation with GW501515 promoted RCT by enhancing in vitro apoA-I and HDL levels, *ABCA1* expression, and apoA-I–mediated cholesterol efflux (Oliver et al., 2001; Sprecher et al., 2007; Ogata et al., 2009) (Table 2). Another PPARβ/δ agonist, GW0742, did not affect *ABCA1* or *ABCG1* mRNA expression and only stimulated cholesterol efflux in bone marrow–derived macrophages, but not in peritoneal macrophages from $LDLR^{-/-}$ mice (Li et al., 2004; Briand et al., 2009). Carbaprostacyclin, a PPARβ/δ agonist, only increased cholesterol efflux in macrophages (Chawla et al., 2001).

Combinations of PPAR and LXR agonists were investigated to overcome disadvantages observed with either PPAR or LXR agonists (e.g., increased plasma triglyceride concentrations), which demonstrated to be a promising strategy. Fenofibrate could abolish the LXR-mediated induction of *SREBP1* by T0901317 in THP-1 macrophages without affecting the endogenous *ABCA1* expression (Thomas et al., 2003). Similar results were observed after coadministration of T0901317 and Wy14643, as shown by the attenuation of T0901317-induced increases in serum and plasma triglycerides, without posing an effect on *ABCA1* mRNA levels in C57BL/6 mice (Beyer et al., 2004).

In summary, both PPARα and PPARγ agonists increase ABCA1 and ABCG1 expression in an LXRα-dependent manner, whereas PPARα agonists were more effective inducers of apoA-I levels and apoA-I–mediated cholesterol efflux. Furthermore, coadministration of LXR and PPARα agonists may overcome the adverse effects on plasma triglyceride levels of LXR agonists. However, more studies are needed to elucidate the mechanism and effectivity of such combinatorial strategies for treatment of atherosclerosis.

D. Enhancement of ATP-Binding Cassette A1 and ATP-Binding Cassette G1 Expression by Retinoid X Receptor Agonists

The notion that RXR activates and orchestrates the signaling of other nuclear receptors, including LXR and PPAR, led to the idea that RXR stimulation could be of special interest to stimulate RCT (Costet et al., 2003; Nishimaki-Mogami et al., 2008; Cui et al., 2011; Zhang et al., 2013a; Zhou et al., 2015). Such crosstalk with other nuclear receptors is illustrated by RXR/LXRα heterodimer formation after stimulation of RXR by endogenously synthesized 9-*cis*-RA (Manna et al., 2015; Zhou et al., 2015) and with synthetic RXR agonists, including PA024 and HX630 (Nishimaki-Mogami et al., 2008; Zhou et al., 2015), which all increased *ABCA1* expression (Table 3). In RAW264 cells, PA024, unlike HX630, directly influenced LXRE and positively modified the promoter activity to enhance *ABCA1* mRNA expression, resulting in generation of HDL particles and stimulation of cholesterol efflux (Nishimaki-Mogami et al., 2008). In contrast, HX630 is expected to stimulate *ABCA1* expression by activating PPARγ/RXR heterodimer, leading to an enhanced *LXR* expression in RAW264 cells (Nishimaki-Mogami et al., 2008). Similar mechanisms were observed with two other RXR agonists, tributyltin chloride and LG268, which activated PPARγ/RXR and LXRα/RXR signaling. This treatment modulated cellular lipid homeostasis and cholesterol efflux in RAW264 and THP-1 macrophages via increased expression of *ABCA1* and *ABCG1* (Repa et al., 2000; Chawla et al., 2001; Cui et al., 2011; Sun et al., 2015). Additionally, LG101305 enhanced *ABCA1* mRNA expression and cholesterol efflux in macrophages (Claudel et al., 2001). The RXR agonists, bexarotene and methoprene, enhanced ABCA1 expression and cholesterol efflux in astrocytes and increased the overall cerebral cholesterol efflux into the circulation (LaClair et al., 2013; Kuntz et al., 2015; Tachibana et al., 2016).

However, as RXR interacts with many other nuclear receptors, RXR agonists are associated with a wide spectrum of adverse events (Costet et al., 2003), including enhanced lipogenesis due to LXR/RXR heterodimerization (Manna et al., 2015), which severely limits their therapeutic potential to stimulate RCT.

Compounds that stimulate RAR do not suffer from these adverse mechanisms, as they are less ambiguous in the targets they activate. The RAR agonists, 4-[(E)-2-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphtalenyl)-1-propenyl]benzoic acid (TTNPB) and Am580, enhanced *ABCG1* expression by modulating *ABCG1* promoter activity, especially by interacting with LXRE-B in macrophages (Ayaori et al., 2012). Furthermore, TTNPB stimulated *ABCA1* expression in mouse and human macrophages mediated via a stimulatory effect of RARγ/RXR on the *ABCA1* promoter (Costet et al., 2003). Chen et al. (2011b) found opposite effects of TTNPB in astrocytes, indicating that the effects may be cell-type dependent. The beneficial effects in macrophages are, however, most relevant for a potential antiatherosclerotic effect of RAR agonists, which makes them an interesting class of compounds to target RCT.

V. ATP-Binding Cassette A1 and ATP-Binding Cassette G1 mRNA Stability

A. mRNA Degradation as a Post-Translational Mechanism to Regulate ATP-Binding Cassette A1 and ATP-Binding Cassette G1 Expression

Another mechanism regulating plasma membrane abundance of ABCG1 and ABCA1 transporters is the rapid post-translational degradation of their mRNA transcripts. For ABCG1 this depends on the interaction of the 3′ untranslated region of its transcript with miRNAs, resulting in repression of translation or mRNA degradation (Li et al., 2010; Rayner et al., 2011; Rotllan and Fernandez-Hernando, 2012;

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TABLE 3
Synthetic retinoid nuclear receptor agonists

Overview of retinoid nuclear receptor agonists, including their primary pharmacological action, effects on ABCA1 and ABCG1 expression (arrows: *mRNA*, protein), and effects on cellular cholesterol efflux. Effects on ABCA1, ABCG1, and cholesterol efflux are presented as follows: (↓) decreased; (=) no effect; (↑) increased. Italicized symbols indicate changes in *ABCA1* and *ABCG1* mRNA levels, whereas nonitalicized symbols indicate protein levels.

Compound	Primary Action	ABCA1	ABCG1	Cholesterol Efflux	Reference
RXR agonists					
Bexarotene	pan-RXR agonist	↑↑ BLECs ↑ Cortex[a] ↑ Cortex[b] ↑ Cortex[c]	—	↑ BLECs	LaClair et al., 2013; Kuntz et al., 2015; Tachibana et al., 2016
HX630	RXR agonist	↑ THP-1 ↑ RAW264.7	↑ THP-1	↑ THP-1	Nishimaki-Mogami et al., 2008
LG101305	RXR agonist	↑ RAW264.7	—	↑ RAW264.7	Claudel et al., 2001
LG268	RXR agonist	↑ Small intestine[d] ↑ PM	—	↑ THP-1	Chawla et al., 2001
Methoprene	RXR agonist	↑ Astrocyte	↑ Astrocyte	Astrocyte ↑ apoA-I ↑ HDL	Repa et al., 2000; Chen et al., 2011b
PA024	RXR agonist	↑ THP-1 ↑ RAW264.7	↑ THP-1	↑ THP-1	Nishimaki-Mogami et al., 2008
Tri-butylin chloride	RXRα agonist	↑↑ RAW264.7 ↑↑ Primary mouse astrocyte cells ↑↑ Cortex[c]	↑↑ Primary mouse astrocyte cells ↑↑ Cortex[c]	↑ RAW264.7	Cui et al., 2011; Sun et al., 2015
RAR agonists					
AM580	RARα agonist	—	↑ THP-1	—	Ayaori et al., 2012
TTNPB	Synthetic RAR agonist	↑ THP-1 ↑ HEK293 ↓ Astrocytes = Liver[d] ↑ PM[d]	↑ THP-1 ↓ Astrocytes = Liver[d]	↑ RAW264.7 ↓ Astrocytes	Costet et al., 2003; Chen et al., 2011b; Ayaori et al., 2012

BLEC, bovine lens epithelial cells; PM, peritoneal macrophages.
[a]Lrp1$^{flox/flox}$; αCamKII-Cre$^{-/-}$ mice.
[b]Lrp1$^{flox/flox}$; αCamKII-Cre$^{+/-}$ mice.
[c]APPSWE/PSE1$_{\Delta E}$ mice.
[d]C75BL/6/A129Sv mice.

Lv et al., 2014). Consequently, these small noncoding RNAs appear to be important modulators of gene expression (Rotllan and Fernandez-Hernando, 2012), which upon binding with other mRNA regions can lead to degradation as well as increased mRNA expression and translation (Rotllan and Fernandez-Hernando, 2012) (Fig. 5). Several miRNAs, which are summarized in Table 4, are known to affect *ABCA1* mRNA expression. Although less is known about *ABCG1* regulation, some miRNAs directly decreased *ABCG1* mRNA expression levels (Table 4) Moore et al., 2010; 2011; Fernández-Hernando et al., 2011; Fernández-Hernando and Moore, 2011; Rayner et al., 2011, 2012; Hazen and Smith, 2012; Iatan et al., 2012; Rotllan and Fernandez-Hernando, 2012; Sun et al., 2012; Wang et al., 2012, 2014a; Adlakha et al., 2013; Dávalos and Fernandez-Hernando, 2013; de Aguiar Vallim et al., 2013; Kang et al., 2013; Ramárez et al., 2013; Canfrán-Duque et al., 2014; Goedeke et al., 2014; Mao et al., 2014; DiMarco and Fernandez, 2015; He et al., 2015; Mandolini et al., 2015; Yang et al., 2015; Feinberg and Moore, 2016; Ono, 2016; Rotllan et al., 2016; Aryal et al., 2017).

B. Targeting Post-Transcriptional Regulation of ATP-Binding Cassette A1 mRNA

The therapeutic potential of miRNA in the regulation of cholesterol metabolism will not be further addressed in this review, as this was extensively reviewed by others (Moore et al., 2010, 2011; Fernández-Hernando and Moore, 2011; Rotllan and Fernandez-Hernando, 2012; Dávalos and Fernandez-Hernando, 2013; Canfrán-Duque et al., 2014; Goedeke et al., 2014; DiMarco and Fernandez, 2015; Rotllan et al., 2016; Aryal et al., 2017). In this study, other drugable mechanisms involved in the post-transcriptional regulation of *ABCA1* and *ABCG1* mRNA expression will be discussed (Moore et al., 2011; Rotllan and Fernandez-Hernando, 2012; Dangwal and Thum, 2014; van Rooij and Kauppinen, 2014; Rotllan et al., 2016). One of these mechanisms is mediated by the cellular energy sensor AMP-activated protein kinase (AMPK), through its regulation of cholesterol metabolism. AMPK activation by 5-aminoimidazole-4-carboxyyamide ribonucleoside (AICAR; an AMP mimetic) has led to enhanced ABCG1 mRNA and protein expression, reduced ox-LDL uptake, and enhanced HDL-mediated cholesterol efflux (Table 5). These effects were found to be independent of LXRα, but mediated through *ABCG1* mRNA 3′ untranslated region without affecting ABCA1, SR-A, CD36, and SR-B1 protein expression (Li et al., 2010). In contrast, Kemmerer et al. (2016) demonstrated predominant LXRα-mediated upregulation of *ABCA1* mRNA expression in macrophages after exposure to AICAR and the allosteric AMPK activators A769662 and salicylate (Li et al., 2010). The increased

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TABLE 4
Overview of microRNAs enhancing or reducing ABCA1 and ABCG1 mRNA

Overview of microRNAs, including their effects on ABCA1 and ABCG1 expression. Effects on ABCA1, ABCG1, and cholesterol efflux are presented as follows: (↓) decreased; (=) no effect; (↑) increased.

MicroRNA	ABCA1	ABCG1	Reference
miR-10b	↓	↓	Hazen and Smith, 2012; Wang et al., 2012; Dávalos and Fernandez-Hernando, 2013; Goedeke et al., 2014; Rayner and Moore, 2014; Rotllan et al., 2016; Aryal et al., 2017
miR-17	↓		He et al., 2015
miR-19b	↓		Lv et al., 2014, 2015; DiMarco and Fernandez, 2015
miR-20a/b	↓		Liang et al., 2017
miR-21	↓	↓	Canfrán-Duque et al., 2017
miR-26	↓	↓ (Indirect via LXR)	Sun et al., 2012; Dávalos and Fernandez-Hernando, 2013; Canfrán-Duque et al., 2014; Goedeke et al., 2014; Rayner and Moore, 2014; DiMarco and Fernandez, 2015; Yang et al., 2015; Feinberg and Moore, 2016; Rotllan et al., 2016
miR-27a/b	↓	= (↓ Indirect)	Kang et al., 2013; Canfrán-Duque et al., 2014; Goedeke et al., 2014, 2015b; Zhang et al., 2014; DiMarco and Fernandez, 2015; Yang et al., 2015; Rotllan et al., 2016
miR-33a/33b	↓	↓	Moore et al., 2010, 2011; Fernandez-Hernando et al., 2011; Fernández-Hernando and Moore, 2011; Rayner et al., 2011, 2012; Iatan et al., 2012; Rotllan and Fernandez-Hernando, 2012; Dávalos and Fernandez-Hernando, 2013; Kang et al., 2013; Canfrán-Duque et al., 2014; Goedeke et al., 2014; Mao et al., 2014; Rayner and Moore, 2014; DiMarco and Fernandez, 2015; He et al., 2015; Mandolini et al., 2015; Yang et al., 2015; Feinberg and Moore, 2016; Ono, 2016; Rotllan et al., 2016; Aryal et al., 2017
miR-93	↓		He et al., 2015
miR-96	↓		Moazzeni et al., 2017
miR-101	↓		Zhang et al., 2015a; Aryal et al., 2017
miR-106b	↓		Kim et al., 2012; Rotllan and Fernandez-Hernando, 2012; Dávalos and Fernandez-Hernando, 2013; Goedeke et al., 2014; Rayner and Moore, 2014; Feinberg and Moore, 2016
miR-128-1	↓		Wagschal et al., 2015; Feinberg and Moore, 2016; Rotllan et al., 2016; Aryal et al., 2017
miR-128-2	↓	↓	Adlakha et al., 2013; DiMarco and Fernandez, 2015
miR-130b	↓		Wagschal et al., 2015; Feinberg and Moore, 2016
miR-144	↓	↓ (Indirect via RXR)	de Aguiar Vallim et al., 2013; Kang et al., 2013; Ramírez et al., 2013; Canfrán-Duque et al., 2014; Goedeke et al., 2014; Rayner and Moore, 2014; DiMarco and Fernandez, 2015; Feinberg and Moore, 2016; Rotllan et al., 2016; Aryal et al., 2017
miR-145	↓		Kang et al., 2013; Canfrán-Duque et al., 2014; Goedeke et al., 2014; Sala et al., 2014; DiMarco and Fernandez, 2015
miR-148a	↓		Kang et al., 2013; Goedeke et al., 2015a; Wagschal et al., 2015; Feinberg and Moore, 2016; Rotllan et al., 2016; Aryal et al., 2017
miR-223	↑		DiMarco and Fernandez, 2015; Rotllan et al., 2016
miR-301b	↓		Wagschal et al., 2015; Feinberg and Moore, 2016
miR-302a	↓		DiMarco and Fernandez, 2015; Meiler et al., 2015; Rotllan et al., 2016; Aryal et al., 2017
miR-378		↓ (Indirect)	Wang et al., 2014a; DiMarco and Fernandez, 2015; Yang et al., 2015
miR-613	↓		Zhao et al., 2014; DiMarco and Fernandez, 2015
miR-758	↓		Ramirez et al., 2011; Kim et al., 2012; Rayner et al., 2012; Rotllan and Fernandez-Hernando, 2012; Dávalos and Fernandez-Hernando, 2013; Canfrán-Duque et al., 2014; Goedeke et al., 2014; Rayner and Moore, 2014; DiMarco and Fernandez, 2015; Mandolini et al., 2015; Yang et al., 2015; Feinberg and Moore, 2016

miR, microRNA.

ABCA1 expression by A769662 and AICAR was proposed to be mediated via inhibition of extracellular signal-regulated kinase (ERK) or the mammalian target of rapamycin pathways (Kemmerer et al., 2016). Indeed, ERK signaling is described as a negative regulator of ABCA1 protein stability (Mogilenko et al., 2010). Compounds that affect the ERK pathway will be discussed in Section VI.B (Pharmacological Inhibition of ATP-Binding Cassette A1 and ATP-Binding Cassette G1 Protein Degradation). Thus, AMPK agonists could increase cholesterol efflux via a dual mechanism, either by enhancing *ABCG1* mRNA stability or via increased mRNA expression of *ABCG1* and *ABCA1*.

VI. ATP-Binding Cassette A1 and ATP-Binding Cassette G1 Protein Degradation as a Target to Increase Cholesterol Efflux

A. The Role of ATP-Binding Cassette A1 and ATP-Binding Cassette G1 Reuptake and Degradation in the Regulation of Their Plasma Membrane Abundance

Like other plasma membrane transporters and receptors, ABCA1 and ABCG1 protein abundance is dependent on their cellular reuptake and degradation (Yokoyama et al., 2012; Wang et al., 2017). After internalization, ABCA1 is mainly degraded via lysosomal and ubiquitin- or calpain-mediated proteolysis (Yokoyama et al., 2012; Huang et al., 2015; Wang et al., 2017) (Fig. 5). Although the function of lysosomal and ubiquitin-mediated proteolytic degradation in ABCA1 turnover and activity needs to be elucidated, the importance of calpain-mediated ABCA1 breakdown has been established, especially in THP-1 macrophages (Yokoyama et al., 2012; Wang et al., 2017).

ABCA1 proteolysis is initiated by calpain binding to a calpain-specific cleavage sequence [Pro-Glu-Ser-Thr (PEST)] (Iwamoto et al., 2010; Huang et al., 2015; Wang et al., 2017), which is located within the large cytosolic loop of ABCA1 (Reiss and Cronstein, 2012) (Fig. 5). The relevance of this region was illustrated by deletion of the PEST sequence, which prevented the breakdown of ABCA1 (Yokoyama et al., 2012). This region is also important for ABCA1 half-life, which is 1 to 2 hours in the absence of helical apolipoproteins, such as apoA-I, apoA-II, and apoE (Iwamoto et al., 2010; Yokoyama et al., 2012).

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TABLE 5
Compounds enhancing ABCA1 and ABCG1 mRNA stability

Overview of compounds that enhance *ABCA1* and *ABCG1* mRNA stability, including their primary pharmacological action, effects on ABCA1 and ABCG1 expression (arrows: *mRNA*, protein), and effects on cellular cholesterol efflux. Effects on ABCA1, ABCG1, and cholesterol efflux are presented as follows: (↓) decreased; (=) no effect; (↑) increased. Italicized symbols indicate changes in *ABCA1* and *ABCG1* mRNA levels, whereas nonitalicized symbols indicate protein levels.

Compound	Primary Action	ABCA1		ABCG1		Cholesterol Efflux		Reference
AICAR	AMPK agonist	= =	J774.A1	↑↑	J774.A1		J774.A1	Li et al., 2010; Kemmerer et al., 2016
		↑	THP-1	↑↑	PM[a]	↑	HDL	
A769662	Allosteric AMPK agonist	↑↑	THP-1	↑	J774.A1	↑	THP-1	Li et al., 2010; Kemmerer et al., 2016
Salicylate	Allosteric AMPK agonist	↑	THP-1		—		—	Kemmerer et al., 2016

[a]*apoE*$^{-/-}$ C75BL/6 mice.
PM, peritoneal macrophages.

Phosphorylation of the PEST sequence is suggested to reduce ABCA1 half-life (Iwamoto et al., 2010; Yokoyama et al., 2012), whereas apoA-I binding or pre-exposure (i.e., apoA-I presence before internalization of prebiotinylated surface ABCA1 expressed on THP-1) prolongs the half-life by increasing the resistance of ABCA1 calpain-mediated proteolysis (Lu et al., 2008; Iwamoto et al., 2010; Yokoyama et al., 2012). This did not affect ABCA1 internalization in endosomes, but resulted in a larger portion of ABCA1 that is recycled from the endosomes to the plasma membrane. Besides apoA-I, calpain-mediated ABCA1 degradation is regulated by various endogenous ligands, including calmodulin, calpeptin, calpastatin, protein kinase C (PKC)α, and heme oxygenase-1 (HO-1). Calmodulin interacts with a region in the large cytoplasmic loop near the PEST sequence, which protects ABCA1 against calpain-mediated proteolysis (Iwamoto et al., 2010). In contrast to calmodulin, calpastatin and the nuclear factor-like (Nrf)2–HO-1 axis directly inhibit calpain activity and decrease ABCA1 degradation (Tsai et al., 2010; Wissel et al., 2015). Finally, phosphorylation of the PEST region by activation of apelin-13–mediated PKCα also protects ABCA1 against calpain-mediated proteolysis (Liu et al., 2013). In short, inhibition of calpain activity and ABCA1 internalization, or stimulation of its turnover rate, may result in an increased ABCA1-mediated cellular cholesterol efflux and increased HDL biosynthesis.

B. Pharmacological Inhibition of ATP-Binding Cassette A1 and ATP-Binding Cassette G1 Protein Degradation

As proteolytic breakdown of ABCA1 and ABCG1 plays a significant role in the regulation of their plasma membrane abundance, different pharmacological treatments have been investigated and aimed at increasing RCT via this mechanism (Table 6). One is the use of inhibitors of thiol proteases (e.g., calpain), like leupeptin and N-acetyl-leu-leu-norleucinal (ALLN), which both prevented ABCA1 degradation (Arakawa and Yokoyama, 2002; Yokoyama, 2004). In contrast, other thiol protease inhibitors (i.e., pepstatin A, aprotinin, and phosphoramidon) did not affect ABCA1 degradation (Arakawa and Yokoyama, 2002), questioning the specificity of the effect of leupeptin and ALLN. In addition, ABCA1 protein expression levels were not affected by nonspecific protease inhibitors like the proteasome inhibitor lactacystin (Arakawa and Yokoyama, 2002).

The stabilizing role of PKC on ABCA1 also seems to hold for ABCG1, as the ABCG1-dependent cholesterol efflux is decreased by the PKC inhibitors calphostin C and PKC19-36 (Gelissen et al., 2012). As mentioned above, apelin-13, a cleaved peptide from the adipocytokine apelin, phosphorylated ABCA1 in THP-1 macrophages, leading to ABCA1 stabilization and enhanced cholesterol efflux (Liu et al., 2013). Remarkably, several other PKC inhibitors (i.e., Gö6983, Gö6976, rottlerin, and doxazosin) enhanced ABCA1 mRNA and protein expression as well as cholesterol efflux in macrophages via an inhibitory effect on protein kinase D (PKD), with the strongest effect by Gö6983 (Iwamoto et al., 2007, 2008; Tsunemi et al., 2014). This effect is probably mediated by a decreased phosphorylation of activator protein 2α, which represses transcription of *ABCA1* as phosphorylated activator protein 2α binds to the promoter region of *ABCA1* (Iwamoto et al., 2007, 2008; Remaley, 2007). The potential of this promoter region as a target to increase cellular cholesterol efflux is emphasized by pyrrole–imidazole polyamides that bind to this region and enhanced ABCA1 mRNA and protein levels as well as cholesterol efflux in 3T3-L1 adipocytes and RCT in C57BL/6 mice (Tsunemi et al., 2014). In this study, ABCA1 levels were increased via PKD inhibition, which illustrates the importance of the balance between PKC and PKD activity.

A more specific calpain inhibitor, triacetyl-3 hydroxyphenyl-adenosine (IMM-H007), increased ABCA1 plasma membrane expression in THP-1 cells and enhanced ABCA1-mediated cholesterol efflux to apoA-I (Huang et al., 2015). In *apoE*$^{-/-}$ mice, IMM-H007 delayed ABCA1 protein degradation, promoted ABCA1 cell surface localization, enhanced RCT, and suppressed atherosclerotic lesion development (Huang et al., 2015). Interestingly, IMM-H007 activated AMPK, which may have also contributed to these effects via ABCA1 stabilization, as described above. In summary, the adenosine analog IMM-H007 may be a promising candidate to upregulate ABCA1 expression with proven capacity to increase RCT in vivo.

More indirect strategies to inhibit calpain, including the induction of HO-1 production, have also been shown

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TABLE 6
Inhibitors of ABCA1 and ABCG1 protein breakdown

Overview of compounds that inhibit ABCA1 and ABCG1 protein breakdown, including their primary pharmacological action, effects on ABCA1 and ABCG1 expression (arrows: *mRNA*, protein), and effects on cellular cholesterol efflux. Effects on ABCA1, ABCG1, and cholesterol efflux are presented as follows: (↓) decreased; (=) no effect; (↑) increased. Italicized symbols indicate changes in *ABCA1* and *ABCG1* mRNA levels, whereas nonitalicized symbols indicate protein levels.

Compound	Primary Action	ABCA1	ABCG1	Cholesterol Efflux	Reference
Acifran	GPR109A agonist	—	—	—	Gaidarov et al., 2013
Acipimox	GPR109A agonist	—	—	—	Gaidarov et al., 2013
ALLN	Thiol-protease inhibitor	=↑ THP-1	—	↑ THP-1	Arakawa and Yokoyama, 2002; Yokoyama, 2004
Calphostin C	PKC inhibitor	—	—	↓ CHO-K1 ABCG1(+12) ↓ CHO-K1 ABCG1(−12)	Gelissen et al., 2012
Diphenoquinone	Unknown, probucol metabolite	↑ THP-1 ↑ RAW264.7 ↑ HEK293 ↑ Balb/3T3 ↑ MEFs =↑ Liver[a]	↑ RAW264.7	↑ THP-1 RAW264.7 ↑ apoA-I ↑ HDL ↑ Hek293 ↑ MEFs	Arakawa et al., 2009; Lu et al., 2016; Yakushiji et al., 2016
Exendin-4	GLP-1R agonist	↑↑ 3T3-L1 adipocytes ↑↑ glomeruli[b]	↑↑ 3T3-L1 adipocytes	↑ 3T3-L1 adipocytes ↑ glomeruli[b]	Mostafa et al., 2015; Yin et al., 2016
Ezetimibe	NPC1L1 inhibitor	↑ VSCMs ↓↓ Liver[c] ↓↓ Proximal small intestine[c]	—	—	Gong et al., 2014; Kannisto et al., 2014
Gö6976	PKC inhibitor	↑↑ THP-1	—	↑ THP-1	Iwamoto et al., 2008
Gö6983	PKC inhibitor	↑↑ THP-1 ↑↑ Liver[c]	—	↑ THP-1	Iwamoto et al., 2008
IMM-H007	AMPK agonist	↑ THP-1 ↑ Liver[d]	—	↑ J774 ↑ THP-1 ↑ RCT[c]	Huang et al., 2015
LD211	MC1-R agonist	↑ BMDM[d]	↑ BMDM[d]	BMDM[d] ↑ apoA-I ↑ HDL	Rinne et al., 2017
Leupeptin	Thiol-protease inhibitor	=↑ THP-1	—	—	Arakawa and Yokoyama, 2002
MK-0354	GPR109A agonist	= MDM[d]	= MDM[d]	= MDM[d]	Gaidarov et al., 2013
MK-1903	GPR109A agonist	↑ MDM[d]	↑ MDM[d]	↑ MDM[d]	Gaidarov et al., 2013
MSG606	MC1-R agonist	↑ BMDM[d] = Aorta[d] ↑ Liver[d]	↑ BMDM[d] = Aorta[d] ↑ Liver[d]	BMDM[d] ↑ apoA-I ↑ HDL	Rinne et al., 2017
N-acetyl cysteine	Glutathione synthase stimulator	↓ J774	↑ J774	J774 ↓ apoA-I ↑ HDL	Machado et al., 2014
Niacin	GPR109A agonist	↑↑ HepG2 ↑↑ 3T3-L1 adipocytes ↑ MM6sr ↑ MDM[d] ↑ Monocyte[d] ↑↑ Liver[e]	↑ MDM[d]	↑ THP-1 ↑ HepG2 ↑ 3T3-L1 adipocytes ↑ MM6sr ↑ MDM[d]	Rubic et al., 2004; Siripurkpong and Na-Bangchang, 2009; Wu and Zhao, 2009; Yvan-Charvet et al., 2010a; Zhang et al., 2012; Gaidarov et al., 2013
Nicardipine	Calcium channel blocker	—	—	↑ THP-1 ↑ RAW264.7	Suzuki et al., 2004
Nifedipine	Calcium channel blocker	↑↑ RAW264.7 ↑↑ Aorta sinus[f] ↑↑ PM[a]	↑↑ RAW264.7	↑ THP-1 RAW264.7 ↑ apoA-I ↑ HDL	Suzuki et al., 2004; Ishii et al., 2010; Zhang et al., 2013b
PD98059	MEK1/2 inhibitor	↑ THP-1 ↑↑ RAW264.7 ↓ HuH7 ↓ CHO	↑ THP-1 ↑↑ RAW264.7 ↓ CHO ↓ HEK293 ↑↑ Mouse primary macrop ↑ PM[d]	↓ CHO PM[d] ↑ HDL	Zhou et al., 2010; Mulay et al., 2013; Zhang et al., 2016
PKC19-36	PKC inhibitor	—	—	↓ CHO-K1 ABCG1(+12)	Gelissen et al., 2012

(*continued*)

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TABLE 6—*Continued*

Compound	Primary Action	ABCA1	ABCG1	Cholesterol Efflux	Reference
				↓ CHO-K1 ABCG1(−12)	
Rottlerin	PKC inhibitor	↗↑ THP-1	—	= THP-1	Iwamoto et al., 2008
Spiroquinone	Unknown, probucol metabolite	↑ THP-1 ↑ RAW264.7 ↑ HEK293 ↑ Balb/3T3 ↑ MEFs =↑ Liver[a]	↑ RAW264.7	↑ THP-1 RAW264.7 ↑ apoA-I = HDL ↑ Hek293 ↑ MEFs	Yokoyama, 2004; Arakawa et al., 2009; Lu et al., 2016; Yakushiji et al., 2016
Tert-butylhydroquinone	Synthetic phenolic antioxidant	↗↑ THP-1	—	↑ THP-1	Lu et al., 2013
U0126	MEK1/2 inhibitor	↗↑ RAW264.7 ↗↑ HepG2 ↗↑ PM[b] ↗↑ Jurkat	↑ THP-1 ↗↑ RAW264.7 ↗↑ Mouse primary macrop ↑ PM[d] ↗↑ PM[g] ↗↑ Jurkat	RAW264.7 ↑ apoA-I ↑ HDL PM ↑ apoA-I ↑ HDL Jurkat ↑ apoA-I	Mogilenko et al., 2010; Zhou et al., 2010; Mulay et al., 2013; Xue et al., 2016; Zhang et al., 2016; Liu et al., 2019
Verapamil	Calcium channel blocker	↗↑ RAW264.7	↓ RAW264.7	↑ THP-1 ↑ RAW264.7	Suzuki et al., 2004
Vildagliptin	GLP-1R agonist	↗↑ 3T3-L1 adipocytes	↗↑ 3T3-L1 adipocytes	↑ 3T3-L1 adipocytes	Mostafa et al., 2015, 2016

ALLN, *N*-acetyl-leu-leu-norleucinal; GLP-1R, glucagon-like peptide-1 receptor; MDM, monocyte-derived macrophage; MEF, murine embryonic fibroblast; MEK, mitogen-activated protein kinase kinase; NPC1L1, Niemann-Pick C1-like 1; PM, peritoneal macrophages.

[a]New Zealand White rabbits.
[b]*apoE*$^{-/-}$ C75BL/6 diabetic mice.
[c]*apoE*$^{-/-}$ C75BL/6 mice.
[d]C75BL/6 mice.
[e]Golden Syrian Hamster.
[f]C3H/He mice.
[g]Sprague Dawley rats.

to suppress ABCA1 degradation. Tertiary-butylhydroquinone, a synthetic phenolic antioxidant, mediates these effects by activation of Nrf2 via its dissociation from kelch-like ECH-associated protein (Keap) 1, translocation of Nrf2 toward the nucleus, and activation of antioxidant responsive element (ARE)-dependent transcription of *HO-1* gene. The increased production of HO-1, which is an endogenous inhibitor of calpain, resulted in reduced ABCA1 degradation (Lu et al., 2013).

In addition, two oxidative products of probucol, spiroquinone and diphenoquinone, suppressed ABCA1 and ABCG1 degradation both in vitro and in vivo, and thereby increased RCT and reduced lipid deposition in atherosclerotic plaques in vivo (Yokoyama, 2004; Arakawa et al., 2009; Lu et al., 2016; Yakushiji et al., 2016). These effects are expected to be due to disruption of the caveolin-1 interaction with ABCA1 by spiroquinone and diphenoquinone, resulting in the stabilization of ABCA1 protein against degradation (Arakawa et al., 2009). This mechanism is also expected to mediate the increase in ABCA1 abundance by ezetimibe, which lowers caveolin-1 expression through suppression of SREBP-1 expression (Lu et al., 2016). Another mechanism directly affecting ABCA1 stability is the reduction of its disulfide bonds (Bungert et al., 2001), as described with *N*-acetyl-cysteine (Machado et al., 2014). *N*-acetyl-cysteine treatment is, however, associated with an increased cellular cholesterol efflux, which was mediated by increased ABCG1 expression and HDL-dependent cholesterol efflux, whereas ABCA1 expression and apoA-I–dependent cholesterol efflux were decreased in J774 cells (Machado et al., 2014).

Finally, calpain-mediated ABCA1 proteolysis can also be inhibited by alteration of the phosphorylation status of the ABCA1 PEST sequence, as described above (Reiss et al., 2008; Chen et al., 2011a). This could explain the beneficial effects of the ERK1/2 inhibitors, PD98059 and U0126, on ABCA1 and ABCG1 mRNA and protein expression, cholesterol efflux in macrophages, and RCT in *apoE*$^{-/-}$ mice (Mulay et al., 2013; Kemmerer et al., 2016; Xue et al., 2016; Zhang et al., 2016). Besides a direct effect, ERK1/2 inhibition could also increase *ABCA1* and *ABCG1* mRNA stability and expression via an LXRα-dependent mechanism, possibly, by enhancing the LXRα to LXRE-A binding, without affecting PPARγ and LXRα expression (Xue et al., 2016; Liu et al., 2019). In addition to an increased cholesterol efflux, lipid deposition and CD36 expression were suppressed upon U0126 treatment in ox-LDL–stimulated macrophages (Xue et al., 2016). The effect of ERK1/2 inhibition is cell-type dependent, as ABCA1 and ABCG1 protein stability was reduced in CHO and HuH7 cells after ERK1/2 inhibition (Gelissen et al., 2012; Mulay et al., 2013). In addition, the beneficial effect on ABCA1 and ABCG1 expression of zerumbone (i.e., a wild ginger-derived natural compound) and tanshinone IIA was abolished in THP-1 macrophages by ERK inhibitor PD98059 (Liu et al., 2014; Mostafa et al., 2015, 2016; Zhu and Liu, 2015;

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Yin et al., 2016). Moreover, LXRα, PPARα, ABCA1, and ABCG1 expression were not altered after inhibition of c-Jun N-terminal kinase and P38 mitogen-activated protein kinase (MAPK) phosphorylation by SP600125 and SB203580, respectively (Liu et al., 2019). The uncertainty about the precise role of ERK inhibition in cellular cholesterol efflux is emphasized by the observation that stimulation of MAPK/ERK increased LXR-mediated ABCA1 expression, as found for the glucagon-like peptide 1 receptor agonist exendin-4 and the dipeptidyl peptidase-4 inhibitor vildagliptin (Mostafa et al., 2015, 2016; Yin et al., 2016). Similar effects upon MAPK/ERK stimulation were observed using the melanocortin 1 receptor (MC1-R) agonist MSG606, which upregulates cholesterol efflux and ABCA1 and ABCG1 protein levels in bone marrow–derived macrophages, probably via ERK stimulation without increasing cAMP levels (Rinne et al., 2017). The MC1-R agonist, LD211, which stimulated ERK1/2 and p38 MAPK phosphorylation along with a strong increase in cAMP levels, also positively affected cholesterol efflux (Rinne et al., 2017). However, the exact mechanism behind the effect of MC1-R agonists on ERK1/2 is yet unidentified.

Stimulation of the ERK1/2–PPARγ–LXLα axis has been associated with the favorable effects of the G protein–coupled receptor (GPR)109 agonist, niacin, on triglyceride and total, LDL, and HDL cholesterol levels in plasma. Moreover, it has been shown that this first clinically available cholesterol-lowering drug may upregulate ABCA1 expression, stabilize newly produced HDL, and promote cholesterol efflux possibly via cAMP/protein kinase A (PKA) and PPARγ–LXRα pathways (Rubic et al., 2004; Siripurkpong and Na-Bangchang, 2009; Wu and Zhao, 2009; Yvan-Charvet et al., 2010a; Zhang et al., 2012; Connolly et al., 2013; Gaidarov et al., 2013). The GPR109A agonists, acifran and acipimox, but not isoniacin, also activated ERK1/2 and Ca^{2+} flux (Gaidarov et al., 2013). Although niacin exerted beneficial effects, it is also associated with vasodilation and flushing side effects, possibly mediated via the secretion of prostaglandins as a result of activation of GPR109A (Rubic et al., 2004; Gaidarov et al., 2013). Besides niacin, the full GPR109A agonist, MK-1903, gave similar effects on ABCA1- and apoA-I–mediated cholesterol efflux, whereas the effect on *ABCG1* expression was lower compared with niacin (Gaidarov et al., 2013). Another GPR109A agonist, MK-0354, induced neither flushing nor activation of GPR109A signaling in macrophages and HDL modulation (Gaidarov et al., 2013). This suggests that GPR109A agonists that do not cause flushing are probably also unable to exert an antiatherogenic effect.

ERK1/2 inhibition by the commonly used calcium channel blocker nifedipine leads to in vitro anthiatherogenic effects at clinically relevant low nanomolar concentrations via inhibition of monocyte chemoattractant protein-1 and stimulation of ABCA1 expression (Ishii et al., 2010). Two other calcium channel blockers, verapamil and nicardipine, also increased ABCA1- but not ABCG1-mediated cholesterol and phospholipid efflux at suprapharmacological concentrations in the low micromolar range (Suzuki et al., 2004). Verapamil was able to enhance *ABCA1* promotor activity in an LXR-independent manner (Suzuki et al., 2004). In summary, ERK1/2 has the potential to beneficially affect cellular cholesterol efflux, but some of the controversies of this relation will need to be clarified to assess its true therapeutic relevance.

To conclude, inhibition of ABCA1 and ABCG1 degradation has demonstrated to be a promising strategy to enhance their plasma membrane expression, in combination with beneficial in vivo effects on RCT and the progression of atherosclerotic plaque formation. However, many compounds are rather unspecific, which may limit their therapeutic applicability due to adverse effects as a consequence of off-target activities.

VII. ATP-Binding Cassette A1 Function and Cyclic Adenosine Monophosphate

A. cAMP Is a Potent Regulator of ATP-Binding Cassette A1 Function and Expression

ABCA1 expression and function can also be enhanced by increasing cellular cAMP levels (Sakr et al., 1999). The transporter is phosphorylated upon cAMP-mediated activation of PKA, which leads to an increased capacity to interact with apoA-I and subsequent apoA-I–dependent cellular cholesterol efflux (Haidar et al., 2002, 2004) (Fig. 5). PKA has two major phosphorylation sites, Ser-1042 and Ser-2054, which are located at the NBDs of ABCA1 (See et al., 2002). These effects are most likely specific to macrophages (Bortnick et al., 2000; Suzuki et al., 2004). Interestingly, phosphorylation can also be autoregulatory, as apoA-I binding to ABCA1 has been demonstrated to stimulate adenylate cyclase (AC) activity by an unknown mechanism and boost intracellular cAMP levels (Haidar et al., 2002). Besides influencing cholesterol efflux, cAMP is also involved in the regulation of glucose, lipid, and cholesterol metabolism (Haidar et al., 2002, 2004; Tresguerres et al., 2011), and its cellular concentrations are a result of a delicate balance between its production from ATP by AC and its hydrolysis into AMP by phosphodiesterases (PDEs) and cellular efflux by the ABC transporters multidrug resistance protein 4/ABCC4 and multidrug resistance protein 5/ABCC5 (Lin and Bornfeldt, 2002; Wielinga et al., 2003; Copsel et al., 2011; Tresguerres et al., 2011) (Fig. 5). The activity of AC is regulated by different adenosine receptor subtypes, of which A_1 and A_3 receptors have an inhibitory and A_{2a} and A_{2b} a stimulatory effect (Reiss and Cronstein, 2012). Consequently, A_{2a} receptor activation enhanced cAMP levels and promoted RCT via ABCA1-mediated cholesterol efflux (Bingham et al., 2010).

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B. Stimulation of cAMP Levels Enhances ATP-Binding Cassette A1–Mediated Cholesterol Efflux

Treatment with cAMP analogs, 8-bromo-cAMP, 8-(4-chlorophenylthio)adenosine-cAMP, (Bu)2cAMP, and dibutyryl cAMP, stimulated apoA-I–dependent cholesterol efflux in different cell types (Sakr et al., 1999; Abe-Dohmae et al., 2000; Haidar et al., 2002; Lin and Bornfeldt, 2002; Kellner-Weibel et al., 2003; Bingham et al., 2010; Gaidarov et al., 2013; Manna et al., 2015) (Table 7). The 8-bromo-cAMP enhanced cholesterol efflux toward apoA-I, most likely via increased PKA-mediated ABCA1 phosphorylation (Iwamoto et al., 2008; Katz et al., 2009), as PKA inhibition by H89 reversed the beneficial effects of 8-bromo-cAMP on D4-F–mediated cholesterol efflux in RAW264.7 macrophages (Bingham et al., 2010; Xie et al., 2010). Similar results were observed with 8-(4-chlorophenylthio)adenosine-cAMP, which elevated ABCA1 protein expression (Sakr et al., 1999; Haidar et al., 2002; Lin and Bornfeldt, 2002; Kellner-Weibel et al., 2003). A direct PKA agonist, 6-Benz-cAMP, also stimulated ABCA1 protein expression and cellular cholesterol expression, which emphasizes the role of PKA-dependent phosphorylation in enhancing ABCA1-mediated cholesterol efflux capacity (Bingham et al., 2010). Surprisingly, PKA seemed to have contradictory effects on ABCG1 as inhibition of its activity by H89 or KT5720 in CHO-K1 cells enhanced ABCG1-mediated cholesterol efflux and stabilized ABCG1. However, this effect was only observed in cells overexpressing a mutant ABCG1 containing a 12-amino-acid internal segment (Gelissen et al., 2012). Interestingly, treatment with the platelet inhibitor dipyradimole, which increases intracellular cAMP levels, demonstrated antiatherosclerotic effects in the ESPRIT trial (Halkes et al., 2006)).

In line with a central role for cAMP, modulation of AC and PDEs has demonstrated to be another useful strategy to enhance RCT. The AC activator forskolin enhanced RCT via elevated ABCA1 protein levels and phosphorylation (Haidar et al., 2002; Lin and Bornfeldt, 2002). AC stimulation via A_{2a} receptor activation with CGS-21680 and ATL313 enhanced cholesterol efflux and ABCA1 protein expression (Bingham et al., 2010; Voloshyna et al., 2013). Moreover, stimulation with 8-pcPT-2′-O-Me-cAMP of Epac, a signaling molecule downstream of A_{2a} receptor activation, showed similar results. A_{2a} receptor activation decreased foam cell formation in THP-1–derived macrophages by regulation of cholesterol influx and efflux (Bingham et al., 2010). Activation of this adenosine receptor is also associated with an increased *ABCA1* expression in peripheral blood mononuclear cells by methotrexate, which is used to treat cancer and autoimmune diseases (Reiss et al., 2008; Chen et al., 2011a).

Increased cAMP levels as a result of reduced breakdown with PDE4 inhibitors (3-isobutyl-1-methylxanthine (IBMX), rolipram, and cilomast) also resulted in elevated ABCA1 expression levels and apoA-I–dependent cholesterol efflux in macrophages (Haidar et al., 2002; Lin and Bornfeldt, 2002). Similar effects were observed with the PDE3 inhibitor cilostazol through increased ABCA1 and ABCG1 expression and cholesterol efflux in vitro and in vivo (Nakaya et al., 2010).

In summary, cAMP analogs, A_{2a} receptor agonists, and other compounds that increase intracellular cAMP levels have the potential to induce ABCA1 expression, which could increase apoA-I–mediated cholesterol efflux. The involvement of cAMP in many different metabolic pathways (i.e., glucose, lipid, and cholesterol metabolism) may though render these strategies vulnerable to adverse effects.

VIII. Increasing Cellular Cholesterol Efflux via Unknown Mechanisms

Stimulation of cellular cholesterol efflux has also been observed with various other compounds by yet unidentified mechanisms, including four antimicrobial drugs (aclarubicin, daidzein, pratensein, pyrromycin) that upregulated ABCA1 expression in ABCA1-overexpressing HepG2 cells (Table 8). Similar effects were observed with the sphingolipid synthesis inhibitor 1-phenyl-2-decanoylamino-3-morpholino-1-propanol (a potential therapeutic for Gaucher's disease), which was accompanied by an increased ABCA1-dependent cholesterol efflux (Glaros et al., 2005). Although the mechanism remains unknown, a structurally similar sphingolipid synthesis inhibitor, *N*-butyldeoxy-nojirimycin, did not increase cellular cholesterol efflux. Enhanced cholesterol efflux was also observed in macrophages of patients treated with the CETP inhibitors anacetrapib, dalcetrapib and torcetrapib, whereas torcetrapib also increased ABCA1 expression (Yvan-Charvet et al., 2007, 2010a; Brodeur et al., 2017). This is, however, expected to be a result of the increased HDL-C levels due to CETP inhibition. The clinical application of these drugs seems to be limited, as the development of all three CETP inhibitors has been discontinued because of an unfavorable benefit–risk ratio (Tall and Rader, 2018). Upregulation of ABCA1 has also been observed with ibrutinib and MCC950, which decreased ox-LDL uptake in THP-1 macrophages mediated via inhibition of nucleotide binding oligomerization domain receptor family pyrin domain-containing protein (NLRP) 3 inflammasome (Chen et al., 2018). Inhibition of the NLRP3 inflammasome resulted in reduced foam cell formation in macrophages and promoted cholesterol efflux (Chen et al., 2018). Moreover, inhibition of soluble epoxide hydrolase using *trans*-4-[4-(3-Adamanthan-1-yl-uneido)-cyclohexyloxy]-benzoic acid (t-AUCB) increased hepatic ABCA1 expression and cholesterol efflux in $LDLR^{-/-}$ mice via a yet unknown mechanism, whereas hepatic ABCG1 expression was not affected (Shen et al., 2014; Shen et al., 2015). The blood glucose–lowering drug, metformin, which

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TABLE 7
Compounds increasing cAMP levels

Overview of compounds that increase intracellular cAMP levels, including their primary pharmacological action, effects on ABCA1 and ABCG1 expression (arrows: *mRNA*, protein), and effects on cellular cholesterol efflux. Effects on ABCA1, ABCG1, and cholesterol efflux are presented as follows: (↓) decreased; (=) no effect; (↑) increased. Italicized symbols indicate changes in *ABCA1* and *ABCG1* mRNA levels, whereas nonitalicized symbols indicate protein levels.

Compound	Primary Action	ABCA1	ABCG1	Cholesterol Efflux	Reference
6-Benz-cAMP	PKA agonist	↑ THP-1	—	↑ THP-1	Bingham et al., 2010
8-Bromo-cAMP	cAMP analog	=↑ Skin fibroblasts[a] ↗ PM	—	↑ THP-1 ↑ Skin fibroblasts[a]	Haidar et al., 2002; Lin and Bornfeldt, 2002
8-(4-Chlorophenylthio) adenosine-cAMP	cAMP analog	↑ J774.A1	—	= THP-1 ↑ J774.A1 ↑ L cells = CHO = Fu5AH = Skin fibroblasts[a] ↑ Mouse PM	Sakr et al., 1999; Kellner-Weibel et al., 2003
8-pcPT-2′-O-Me-cAMP	Epac agonist	↑ THP-1	—	↑ THP-1	Bingham et al., 2010
ATL313	A2AR agonist	↗↑ THP-1	↗↑ THP-1	—	Voloshyna et al., 2013
$(Bu)_2$cAMP	cAMP analog	↑ RAW264.7	—	↑ RAW264.7	Manna et al., 2015
CGS-21680	A2AR agonist	↗↑ THP-1	↗↑ THP-1	↑ THP-1	Bingham et al., 2010; Voloshyna et al., 2013
Cilomast	PDE4 inhibitor	↑ THP-1 ↑ J774.A1	—	↑ THP-1 ↑ J774.A1	Lin and Bornfeldt, 2002
Cilostazol	PDE3 inhibitor	↗↑ THP-1 ↗↑ RAW264.7 ↑ MDM[a] ↗ PM[b] = Liver[b] = Small intestine[b]	↗↑ THP-1 ↗↑ RAW264.7 ↑ MDM[a]	↑ THP-1 ↑ RAW264.7 ↑ MDM[a] ↑ RCT[b]	Nakaya et al., 2010
Dibutyrl cyclic AMP	cAMP analog	↗ RAW264 ↗ Monocyte-derived macrop[a]	↗ Monocyte-derived macrop[a]	↑ RAW264.7 ↑ Monocyte-derived macrop[a]	Abe-Dohmae et al., 2000; Gaidarov et al., 2013
Doxazosin	α-A1 adrenergic receptor antagonist	↗↑ THP-1 ↗↑ RAW264.7 ↗ NCTC clone 1469 ↗ CHO-K1 ↗↑ Liver[b]	—	↑ THP-1 ↑ RAW264.7	Iwamoto et al., 2007; Tsunemi et al., 2014
Forskolin	Adenylyl cyclase activator	↑ Skin fibroblasts[a]	—	↑ THP-1 ↑ Skin fibroblasts[a]	Haidar et al., 2002; Lin and Bornfeldt, 2002
H89	PKA inhibitor	—	↑ CHO-K1 ABCG1(+12) = CHO-K1 ABCG1(−12)	↑ CHO-K1 ABCG1(+12) = CHO-K1 ABCG1(−12)	Gelissen et al., 2012
IBMX	Nonselective PDE inhibitor	—	—	↑ THP-1 ↑ Skin fibroblasts[a]	Haidar et al., 2002; Lin and Bornfeldt, 2002
KT5720	PKA inhibitor	—	—	↑ CHO-K1 ABCG1(+12) = CHO-K1 ABCG1(−12)	Gelissen et al., 2012
Methotrexate	Dihydrofolate reductase inhibitor	↗ PBMCs[a]	—		Chen et al., 2011a
Rolipram	PDE4-selective inhibitor	↗↑ THP-1 ↑ J774.A1	—	↑ THP-1 ↑ J774.A1	Lin and Bornfeldt, 2002

IBMX, 3-isobutyl-1-methylxanthine; macrop, macrophage; MDM, monocyte-derived macrophage; PBMC, peripheral blood mononuclear cell; PM, peritoneal macrophages.
[a]Human.
[b]C57BL/6 mice.

among other effects is an AMPK activator, did not alter ABCA1 expression and apoA-I–dependent cholesterol efflux, but enhanced ABCG1 expression and HDL-dependent cholesterol efflux in RAW264.7 macrophages (He et al., 2019).

Finally, an experimental xanthone compound, IMB2026791, enhanced the binding between apoA-I and ABCA1 and consequently increased apoA-I–mediated cholesterol in vitro. Although the exact mechanism underlying the effect of this xanthone still needs to be elucidated, it is the only compound to date that directly affects the mechanism of ABCA1 cholesterol efflux (Liu et al., 2012).

IX. Conclusions and Future Directions

The discovery of the inverse association between HDL and risk of atherosclerosis and the consequent potency of ABCA1- and ABCG1-mediated cholesterol transport as cardioprotective therapeutic targets (Tang and Oram, 2009; Kuhnast et al., 2015) started the search for strategies to enhance this transport step and thereby enhance RCT. A decade of research resulted in several lipoprotein mimetics, many natural compounds, and miRNA-based strategies with the ability to increase the cellular cholesterol efflux to HDL and over 100 small-molecule–based approaches discussed in this review.

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TABLE 8
Compounds increasing ABCA1/G1 expression or function by an unknown mechanism

Overview of compounds that increase ABCA1 or ABCG1 expression or function by a yet unknown mechanism, including their primary pharmacological action, effects on ABCA1 and ABCG1 expression (arrows: *mRNA*, protein), and effects on cellular cholesterol efflux. Effects on ABCA1, ABCG1, and cholesterol efflux are presented as follows: (↓) decreased; (=) no effect; (↑) increased. Italicized symbols indicate changes in *ABCA1* and *ABCG1* mRNA levels, whereas nonitalicized symbols indicate protein levels.

Compound	Primary Action	ABCA1	ABCG1	Cholesterol Efflux	Reference
1-Phenyl-2-Decanoylamino-3-morpholino-1-propanol	Glycosylceramide transferase inhibitor	↑↑ Skin fibroblasts[a]	—	↑ Skin fibroblasts[a] ↑ MDM[a]	Glaros et al., 2005
Aclarubicin	Topoisomerase I and II inhibitor	↑↑ HepG2	—	—	Gao et al., 2008
Anacetrapib	CETP inhibitor	—	—	↑ THP-1 ↑ BHK ↑ ABCA1-expressing BHK	Yvan-Charvet et al., 2010a; Brodeur et al., 2017
Daidzein	Mitochondrial aldehyde dehydrogenase inhibitor	↑↑ HepG2	—	—	Gao et al., 2008
Dalcetrapib	CETP inhibitor	—	—	↑ BHK ↑ ABCA1-expressing BHK	Brodeur et al., 2017
Ibrutinib	NLRP3 inflammasome inhibitor	↑ THP-1	= THP-1	THP-1 = apoA-I ↑ HDL	Chen et al., 2018
IMB2026791	Unknown	—	—	↑ THP-1 ↑ CHO-ABCA1 ↑ CHO	Liu et al., 2012
MCC950	NLRP3 inflammasome inhibitor	↑ THP-1	= THP-1	THP-1 = apoA-I ↑ HDL	Chen et al., 2018
Metformin	Antihyperglycemic agent	== RAW264.7	↑↑ RAW264.7	RAW264.7 = apoA-I ↑ HDL	He et al., 2019
N-butyldeoxynojirimycin	Glycosylceramide transferase inhibitor	—	—	= Skin fibroblasts[a]	Glaros et al., 2005
Pratensein	Unknown	↑↑ HepG2	—	—	Gao et al., 2008
Pyrromycin	Microbial protein synthesis inhbitor	↑↑ HepG2	—	—	Gao et al., 2008
t-AUCB	Soluble epoxide hydrolase inhibitor	↑↑ Liver[b]	== Liver[b]	↑ 3T3-L1 adipocytes ↑ Epididymal fatc ↑ RCT[b]	Shen et al., 2015
Torcetrapib	CEPT inhibitor	↑ THP-1		↑ THP-1	Yvan-Charvet et al., 2007

BHK, baby hamster kidney cell; fatc., fat cell; MDM, monocyte-derived macrophage; NLRP3, nucleotide binding oligomerization domain receptor family, pyrin domain-containing protein 3; t-AUCB, *trans*-4-[4-(3-Adamanthan-1-yl-uneido)-cyclonexyloxy]-benzoic acid.
[a]Human.
[b]*LXRα*$^{-/-}$ C75BL/6 mice.

Besides the discovery of a large variety of different experimental compounds and existing drugs that enhance ABCA1- and ABCG1-mediated cholesterol efflux, this quest has also provided us with enhanced insights into the mechanisms that regulate the expression and function of these two key players in the initiation and propagation of RCT. It also demonstrated one of the important challenges in this field, namely to develop specific and potent therapies, which is currently a major limiting factor in the clinical applicability of many compounds described in this review. Most of them are also involved in other mechanisms, including stimulation of lipogenesis by LXR and RXR agonists, and regulation of other metabolic pathways (e.g., lipogenesis, fatty acid β-oxidation, glycolysis) by AMPK and cAMP agonists. In addition, several other drugs that increased ABCA1- or ABCG1-dependent cholesterol efflux can probably not be directly used as cardioprotectants due to their toxic effects. Recent developments though seem to be promising in overcoming these adverse mechanisms, like combining LXR and PPARα agonists (Thomas et al., 2003; Beyer et al., 2004), or the use of novel RAR agonists instead of promiscuous RXR agonists (Costet et al., 2003; Ayaori et al., 2012; Chen et al., 2012).

Interestingly, a high-throughput screening approach searching for compounds that directly affect apoA-I and ABCA1 binding identified the xanthone compound IMB2026791 as a first direct activator of ABCA1-mediated cellular cholesterol efflux (Liu et al., 2012). Along with many other novel experimental as well as existing drugs, such developments indicate that we are heading toward promising compounds for clinical evaluation, as these steps have previously been limited by unforeseen adverse effects due to lack of specificity.

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To conclude, increasing ABCA1- and ABCG1-mediated cellular efflux seems to be a promising strategy to lower cardiovascular risk and, combined with cholesterol-lowering therapies, to reduce mortality and morbidity associated with atherosclerosis.

Authorship Contributions

Participated in research design: Frambach, Schirris.

Performed data analysis: Frambach, Schirris.

Wrote or contributed to the writing of the manuscript: Frambach, de Haas, Smeitink, Rongen, Russel, Schirris.

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