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SR-B1: A Unique Multifunctional Receptor for Cholesterol Influx and Efflux

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Abstract

The scavenger receptor, class B type 1 (SR-B1), is a multiligand membrane receptor protein that functions as a physiologically relevant high-density lipoprotein (HDL) receptor whose primary role is to mediate selective uptake or influx of HDL-derived cholesteryl esters into cells and tissues. SR-B1 also facilitates the efflux of cholesterol from peripheral tissues, including macrophages, back to liver. As a regulator of plasma membrane cholesterol content, SR-B1 promotes the uptake of lipid soluble vitamins as well as viral entry into host cells. These collective functions of SR-B1 ultimately affect programmed cell death, female fertility, platelet function, vasculature inflammation, and diet-induced atherosclerosis and myocardial infarction. SR-B1 has also been identified as a potential marker for cancer diagnosis and prognosis. Finally, the SR-B1–linked selective HDL-cholesteryl ester uptake pathway is now being evaluated as a gateway for the delivery of therapeutic and diagnostic agents. In this review, we focus on the regulation and functional significance of SR-B1 in mediating cholesterol movement into and out of cells.

INTRODUCTION

Cholesterol comprises approximately 25% of animal cell plasma membranes (PMs) and is required to maintain cell membrane integrity and fluidity (1, 2). Cholesterol is embedded in the membrane through the interaction between the hydroxyl group on cholesterol with the polar heads of membrane phospholipids and sphingolipids, as well as through the interaction of the bulky steroid and hydrocarbon chain embedded in the membrane alongside the nonpolar fatty-acid chain of the other membrane lipids. This dynamic arrangement of cholesterol increases cell membrane packing and allows for greater membrane fluidity at low temperatures and stabilization of fluidity at high temperatures, while still maintaining membrane integrity (3).

In all nucleated cells cholesterol is synthesized de novo within the endoplasmic reticulum (ER), starting from two molecules of acetate through the mevalonate pathway and activity of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase as the rate-limiting enzyme. Approximately 20% of total daily cholesterol production occurs in the liver; other sites of high synthetic rates include the intestines, adrenal glands, and reproductive organs. De novo biosynthesis of cholesterol accounts for slightly less than half of cholesterol in the body, with the remainder derived from dietary sources through absorption in the small intestine, primarily the duodenum and proximal jejunum (1, 2).

In addition to de novo synthesis, a major source of cholesterol for cells is the uptake of cholesterol transported inside lipoprotein particles as free cholesterol or cholesteryl esters (CEs). There are five major classes of lipoproteins that differ from each other by their physicochemical properties (4). In order of increasing density, lipoproteins consist of (*a*) chylomicrons, (*b*) very low-density lipoprotein (VLDL), (*c*) intermediate-density lipoprotein (IDL), (*d*) low-density lipoprotein (LDL), and (*e*) high-density lipoprotein (HDL). The liver is the major site for lipoprotein production, at least for VLDL and LDL. Any surplus cholesterol in the liver, whether derived from de novo synthesis or from dietary sources, that exceeds hepatic needs is normally secreted from the liver as VLDL particles and then transported to peripheral tissues after conversion to LDL in the circulation. Besides being packaged into lipoprotein particles for secretion, hepatic cholesterol can also be metabolized into bile acids, which are secreted along with free cholesterol as bile into the intestine for excretion (1, 5). Likewise, lipoprotein-derived CEs in steroidogenic cells of the adrenal glands and gonads are utilized for either tissue-specific steroid hormone production or storage in the form of lipid droplets (LDs).

There are several different lipoprotein receptors, including the scavenger receptor, class B type 1 (SR-B1), each displaying unique ligand specificities and mechanisms for delivering cholesterol to cells (6, 7). For circulating LDL, cholesterol is delivered to cells following binding and endocytosis of the holo-particle via the LDL receptor (LDL-R). The CEs carried in by endocytosed LDL are hydrolyzed within lysosomes by lysosomal acid lipase, releasing unesterified (free) cholesterol that traffics to the ER, where it is either re-esterified to CEs and stored within cytoplasmic LDs or transported from the ER to the PM or mitochondria. Binding of HDL particles is quite distinct from that of LDL-R–mediated internalization of the entire CE-rich lipoprotein particle after binding to its receptor. Instead, HDL particles bind to SR-B1 on the cell surface, and CEs are selectively delivered to the interior of the cell without any internalization of the whole lipoprotein particle. Any CE delivered in this fashion is then hydrolyzed by hormone-sensitive lipase (HSL) into free cholesterol before being utilized. This mechanism is used in steroidogenic cells that rely on cholesterol as the precursor for steroidogenesis. CE-rich LDs are prominently found in steroidogenic cells and can supply cholesterol for steroidogenesis following hydrolysis of CEs to free cholesterol via the actions of HSL (8, 9). Interestingly, the activity of HSL is regulated by tropic hormones via the cyclic AMP (cAMP)/PKA signaling pathway. Indeed, the fact that LDs are rapidly depleted following hormone stimulation of steroidogenesis suggests that this

mechanism is the preferred source of cholesterol for steroid synthesis, at least initially. However, other evidence makes it apparent that multiple and redundant sources supply cholesterol for steroidogenesis (6, 7, 10). For instance, newly synthesized cholesterol traffics from the ER to the PM and then traffics from the PM to the mitochondria, where the initial step in steroidogenesis, the conversion of cholesterol to pregnenolone, occurs (1, 6, 7, 11). Other than dedicated cells in the adrenal glands and gonads, most peripheral cells cannot metabolize cholesterol. Therefore, to maintain homeostasis, several different mechanisms exist to deal with excess cholesterol, the major mechanism being the efflux of cholesterol out of cells into HDL. Cholesterol extracted by HDL is then esterified by the HDL-associated enzyme lecithin-cholesterol acyltransferase and can be transferred to other lipoproteins such as VLDL or LDL via the action of cholesteryl ester transfer protein. The transport of cholesterol from peripheral cells to the liver is termed reverse cholesterol transport (RCT) (5). In this review, we focus on the role of SR-B1 in facilitating cholesterol trafficking, including both influx as well as efflux from cells and tissues. The reader is referred to several references for more detailed reviews of RCT (12–15).

SR-B1

SR-B1 was first identified by sequence homology to cluster determinant 36 (CD36) (16, 17) as a member of the class B scavenger receptor family, which includes the CD36 family, lysosomal integral membrane protein-2 (LIMP-2, a lysosomal protein), and SR-BII (an isoform of SR-B1 with an alternate C-terminal cytoplasmic tail). SR-B1 is well conserved between species and expressed in many mammalian tissues and cell types, including intestine, macrophages, endothelial cells, smooth muscle cells, keratinocytes, adipocytes, and placenta. SR-B1 has also been identified in livers of amphibians, birds, as well as vertebral and cartilaginous fish species, suggesting that this receptor emerged early in vertebrate evolutionary history (18, 19). Multiple orthologues have also been identified for the SR-B1/CD36 family in invertebrates, including 6 in *Caenorhabditis elegans* (20), 14 in *Drosophila melanogaster* (21), and 13 in the silk worm (*Bombyx mori*) (22). Multiple CD36 homologues have been identified in insects as well, including 8 in Hymenoptera and 12–14 in Diptera (23). Many studies have shown a conserved function of SR-B1 across species, revealing its role as an important regulator for cholesterol efflux and steroid hormone production (reviewed in 19). In addition, insect SR-B1 receptors appear to have an important function in mediating the transport of dietary carotenoids (24–26). In contrast, virtually nothing is known about the function of non-mammalian SR-B1.

Soon after the function of LDL-R was identified in endocytic uptake of cholesterol (27), the existence of a nonendocytic mechanism for the selective uptake of HDL-associated CE was reported (28). However, it would be another decade before the cloning of SR-B1 in 1996 before this protein was identified as the docking receptor for HDL-mediated CE uptake (29). Subsequent studies using mouse models provided insights into SR-B1 function in cholesterol trafficking and validated the importance of SR-B1 as the physiologically functional HDL receptor, as evidenced by global gene ablation of SR-B1. SR-B1 null mice exhibit increases in both the amount and size of HDL–CE that is accompanied by reduced cholesterol in secreted bile and accelerated atherosclerosis (30–32). In contradistinction, mice with overexpression of SR-B1 have decreased HDL–CE and less atherosclerosis (33–35). In addition to HDL, other ligands that can bind and be transported by SR-B1 include lipid-soluble vitamins, such as vitamin E and carotenoids (36–39), as well as silica (40). These mouse models also support a role for SR-B1 in cell inflammatory responses, cell entry of hepatitis C virus (HCV) (41, 42), phagocytosis of apoptotic cells (43), protection against female infertility (44), modulation of platelet reactivity (45, 46), and regulation of HDL-induced signaling in the vasculature (47, 48). More recently, SR-B1 expressed in bone

marrow–derived cells appears to be protective against diet-induced atherosclerosis and myocardial infarction (49).

GENE ORGANIZATION AND DOMAIN STRUCTURE

The human *SCARB1* gene encoding the SR-B1 protein is located on a segment that spans more than 86 kb on chromosome 12 and comprises 13 exons and 12 introns (50). Predictions from the amino acid (aa) sequences using UniProt indicate that five protein variants may be produced by alternative splicing of human *SCARB1* mRNA. Isoform 3 (Q8WTV0-1) is the longest variant with 552 residues and is annotated as the canonical sequence. Isoform 1 (Q8WTV0-2) differs from isoform 3 at the C-terminal from aa 468 to 552. It has 509 residues and was the first isoform identified and named SR-B1. Isoform 2 (Q8WTV0-3) has 409 residues and the same C-terminal as isoform 1, but it is missing aa 43–142. Isoform 4 (Q8WTV0-4; also known as SR-BIII) has 474 residues, with a different N-terminal at aa 1–42 and the same C-terminal as isoform 1. Finally, isoform 5 (Q8WTV0-5; also known as SR-BII and later termed SR-B1.1) has 506 residues, with another unique C-terminal at aa 468–552. It is noteworthy that the common C-terminal sequence (aa 468–552) shared by isoforms 1, 2, and 4 includes the VLQEAKL motif required to bind the PDZ domain–containing protein (PDZK1) (51). This motif is also found in the mouse sequence (**Figure 1**).

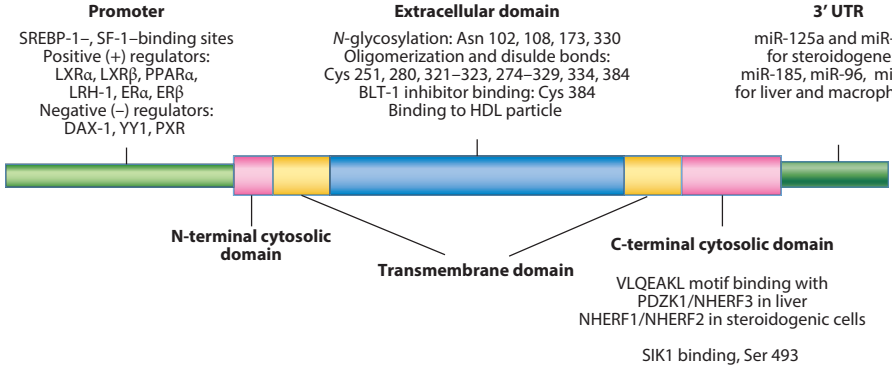

Figure 1

Functional domains and regulation of SR-B1. A schematic depiction of SR-B1 is displayed showing the untranslated promoter and 3′ UTR, as well as the structural domains of the translated protein. SR-B1 has two short intracellular domains at the N- and C-termini of the protein and has two transmembrane domains. Most of the protein is located extracellularly as an ectodomain. The promoter region of SR-B1 contains binding sites for transcription factors SREBP-1 and SF-1, is positively regulated by LXRα, LXRß, PPARα, LRH-1, ERα, and ERß, and is negatively regulated by DAX-1, YY1, and PXR. Micro (mi)RNAs 125a, 455, 185, 96, and 223 have been shown to interact with the 3′UTR and modulate SR-B1 expression. The extracellular or ectodomain, which is responsible for binding HDL, contains four proven *N*-glycosylation sites and several cysteine residues that form disulfide bridges that are important for structural integrity and function, including a cysteine that binds a synthetic inhibitor of SR-B1, known as BLT-1. The C-terminal cytosolic domain contains a motif that mediates the binding of SR-B1 with PDZ-containing proteins, which posttranslationally modulate SR-B1 expression. The C-terminal cytosolic domain also contains a serine that is phosphorylated by the kinase SIK-1, which increases SR-B1 efficiency for cholesteryl ester uptake. Abbreviations: Asn, asparagine; BLT-1, block lipid transport 1; Cys, cysteine; DAX-1, nuclear receptor NR0B1; ER, estrogen receptor; HDL, high-density lipoprotein; LRH-1, liver receptor homolog 1; LXR, liver X receptor; NHERF, Na^+/H^+ exchanger regulatory factor; PDZK1, PDZ domain–containing protein 1; PPARα, peroxisome proliferator-activated receptor alpha; PXR, pregnane X receptor; Ser, serine; SF-1, steroidogenic factor 1; SIK1, salt-inducible kinase 1; SR-B1, scavenger receptor, class B type 1; SREBP-1, sterol response element–binding protein 1; UTR, untranslated region; YY1, Yin Yang 1.

The major gene product is aa 509 SR-B1 (isoform 1), which is produced from exons 1–12. The alternative spliced SR-B1.1 (isoform 5) has a distinct cytoplasmic carboxyl-terminal tail that lacks the PDZK1 binding site. This form of SR-B1.1 lacks the transcripts from exon 12 but includes exon 13. Although SR-B1 and SR-B1.1 have identical extracellular domains and ligand binding, SR-B1 is more abundant in all tissues and more efficient at selective HDL-cholesterol (HDL-C) uptake, thus accounting for virtually all selective HDL-C uptake in vivo by liver and steroidogenic tissues. Although other variants of SR-B1 have been reported, no functional significance has been associated with them (50, 52). Recently, a very short variant containing only the last two exons of *SCARB1* was detected by next-generation sequencing in nonmalignant adrenal glands and livers at relatively high levels (53); however, the physiological significance of this short variant remains unclear.

SR-B1 has a predicted molecular weight of 56.9 kDa; however, due to posttranslational modifications, it is usually detected as an 82-kDa protein on sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) (17). Sequence analysis shows that it possesses nine *N*-linked glycosylation sites, and glycoproteomic analysis confirmed glycosylation at two sites on asparagine (Asn) 102 and 330 for human SR-B1 (54). Mutational studies of the putative *N*-linked glycosylation sites in human SR-B1 demonstrate that mutation of Asn 108 or Asn 173 results in failure of SR-B1 to locate to the PM and marked reduction in transfer of lipid from HDL to cells (55). SR-B1 has at least one phosphorylation site [serine (Ser) 493 for isoform 1, Ser 393 for isoform 2, and Ser 458 for isoform 4], and large-scale mass spectrometry analysis of phosphoproteins confirmed the presence of the phosphorylated form in human liver (56). SR-B1 has two short intracellular domains at the N- (aa 1–11) and C-termini (aa 462–509) of the protein and has two transmembrane domains (aa 12–32 and 441–461). Most of the protein is located extracellularly as an ectodomain.

Some of the structural features of SR-B1 have been demonstrated to be important for its function. The N-terminal transmembrane glycine (Gly) dimerization motif (Gly 15_Gly 18_Gly 25) is required for normal receptor oligomerization and lipid transport (57). The recently obtained crystal structure of LIMP-2, a homologue of SR-B1, has provided a structural framework for this family of proteins and showed that the main ectodomain of the protein contains an antiparallel β-barrel core with many short α-helical segments (58). Two disulfide bridges stabilize the β-barrel fold. The disulfide bridge pattern for LIMP-2 [cysteine (Cys) 274–329 and Cys 312–318] is similar to that predicted for SR-B1 (Cys 321–323, Cys 274–329) and that of CD36 (Cys 313–322, Cys 272–333), and is consistent with experimental data (59–61). Nearly all (7 of 8) cysteines are conserved among many species, including the mouse, hamster, rabbit, pig, cow, and human, and four of these cysteines in the ectodomain (Cys 280, 321, 323, and 334) are required for SR-B1 (HDL) binding activity, selective CE uptake, and trafficking to the cell surface (61). Another cysteine, Cys 384, helps create a binding site for block lipid transport 1 (BLT-1), a synthetic inhibitor of SR-B1 (62).

REGULATION OF SR-B1 EXPRESSION

The highest expression of rodent SR-B1 (both transcripts and protein) is in the fetal adrenal gland, where expression is approximately 50 times greater than in the adult. In the adult, SR-B1 mRNA/protein expression is highest in the adrenal gland, placenta, liver, and ovary. In both rodent and human steroidogenic tissues, SR-B1 expression is highly sensitive to trophic hormones (ACTH, FSH, LH/hCG) in a tissue-specific manner. Adrenocorticotropin (ACTH) is able to increase SR-B1 transcripts and protein in vivo (63, 64) and in cultured rodent adrenocortical cells (65, 66). An increase of SR-B1 expression in rat adrenals is observed as early as 1 h after

treatment with ACTH (67), while ACTH treatment also increases SR-B1 expression in cultured human adrenal cells (65, 68–70). Observations in human adenomas also support the idea that regulation of SR-B1 in humans is similar to that of rodents. In human adenomas, low levels of *SCARB1* transcripts are observed in normal adrenal tissue adjacent to adenomas causing Cushing's syndrome, a condition in which plasma ACTH levels are reduced (69). Likewise, mRNA and protein levels of steroidogenic SR-B1 in ovary and testis are also regulated by trophic hormones (LH/hCG, FSH) (71–74). In lower vertebrates and invertebrates, SR-B1 expression is highest during early developmental stages when peak cholesterol flux is required (18).

SR-B1 is also expressed in macrophages, including tissue macrophages, monocyte-derived macrophages, macrophages in atherosclerotic lesions, and macrophage cell lines. The human homolog of SR-B1, CLA-1 (CD36 and LIMP-2 analogous-1), is also expressed in the same tissues and cell types and with the same relative abundance as rodents. CLA-1 expression is relatively high in steroidogenic cells and liver, and is also expressed in macrophages and other cell types. Likewise, CLA-1 mediates selective uptake of HDL–CE with high efficiency. A naturally occurring missense mutation in *SR-B1*, *P297S* has been identified in humans that display elevated HDL-C, decreased cholesterol efflux from monocyte/macrophages, platelet dysfunction, and adrenal steroid hormone (cortisol) deficiency. Taken together, these data support a role for selective HDL–CE uptake in these human tissues (75, 76).

Cloning of human *SCARB1* revealed that the 5′-flanking promoter region is very guanine-cytosine–rich with canonical binding sites for the sterol response element–binding protein 1 (SREBP-1). SREBP-1 regulates *SCARB1* expression in response to altered intracellular sterol levels (77). Steroidogenic factor 1 (SF-1) is one of the major transcription factors involved in cAMP regulation of *SCARB1* (78). Further analysis showed that within the 2.2-kb proximal 5′-flanking region of the *SCARB1* promoter, other binding sites exist for positive and negative regulators. In rodents, positive regulators of *Scarb1* in the liver and white adipose tissue include the liver X receptors α and β, which are responsive to oxysterol stimulation, and the peroxisome proliferator–activated receptor α, which increases human *SCARB1* promoter activity in response to fibrates (79, 80); both the liver X receptors α and β and the peroxisome proliferator-activated receptor α form heterodimers with the retinoid X receptor for transcriptional activity. The liver receptor homolog 1 (81) and the estrogen receptors α and β bind to estrogen-responsive elements and upregulate rat *Scarb1* (82). A negative regulator that directly binds to the *Scarb1* promoter is the nuclear receptor NR0B1 (DAX-1), a protein that plays an important role in adrenal development (83). Other negative transcriptional factors include the Yin Yang 1 transcription factor, which represses the activity of the SR-B1 promoter by inhibiting the binding of SREBP-1a (84), and the pregnane X receptor (PXR), which represses promoter activity in response to the PXR agonists rifampicin and lithocholic acid (85).

Expression of SR-B1 is dramatically altered in steroidogenic tissues after depleting cholesterol pools or when steroid production is triggered, as is the case after ACTH stimulation in the adrenal glands or human chorionic gonadotropin treatment in ovarian granulosa or testicular Leydig cells (65, 66, 68, 86–88). Hormone stimulation of SR-B1 is largely through cAMP-mediated increased binding of SF-1 to the SR-B1 promoter. The SF-1 binding site in the human SR-B1 promoter is located 77 base pairs upstream of the transcription start site and −645 base pairs upstream of the rat SR-B1 promoter. The human and rat binding sites share 75% identity (77, 78), and mutagenesis analysis confirmed the involvement of SF-1 in regulating both the human and rat SR-B1 promoters. It also revealed that hormone treatment increases cellular cAMP levels and increases phosphorylation of SF-1 at Ser 430 by PKA, which enhances SF-1 binding to the SR-B1 promoter. In addition to mediating hormone-dependent transcriptional changes, the same SF-1 binding motif in the rat promoter also regulates basal expression of the *SR-B1* gene.

Adrenal SR-B1 expression is also subject to feedback regulation when glucocorticoid levels are high (89). In a model of corticosterone-insufficiency using corticotrophin-releasing hormone knockout mice, adrenal SR-B1 expression is elevated but is lowered after oral administration of corticosterone. This suppression depends on the glucocorticoid receptor (GR). Further studies revealed that the region between −201 and −62 within the human SR-B1 promoter contains putative binding sites for transcriptional repressors that are involved in mediating glucocorticoid suppression of SR-B1 transcripts. However, suppression failed to reveal direct binding of GR to the SR-B1 promoter, suggesting that GR suppression of SR-B1 in adrenal cells occurs through an indirect mechanism. This recent report is the first to illustrate how high endogenous levels of glucocorticoids can actively suppress SR-B1-mediated HDL-C uptake to maintain steroid hormone homeostasis.

Recently, noncoding RNAs have been implicated in the negative regulation of SR-B1 in the liver and macrophages, including microRNAs miR-185, miR-96, and miR-223 (90). Initial efforts to define the cellular and molecular mechanisms involved in the regulation and function of SR-B1 in steroidogenic cells identified miRNA-125a and miRNA-455 as expressed in adrenal glands, primary ovarian granulosa cells, and cultured Leydig cell lines that were downregulated by ACTH as well as cAMP. When either miRNA-125a or miRNA-455 was overexpressed, the amount of SR-B1 protein expressed on the cell surface was decreased, resulting in a reduction of both HDL-C uptake and steroid hormone synthesis. On the other hand, when these two miRNAs are decreased, one observes an elevation of SR-B1 protein, HDL-C uptake, and steroid hormone synthesis. Furthermore, we demonstrated that both miRNA-125a and miRNA-455 bind to specific sites in the 3′ untranslated regions (UTR) of SR-B1 mRNA to regulate its expression (91). Collectively, these findings suggest that upon hormone stimulation, miRNA-125a and miRNA-455 negatively regulate SR-B1 expression and inhibit steroidogenesis.

POSTTRANSLATIONAL REGULATION OF SR-B1 FUNCTION

The process for SR-B1 selective uptake of CEs from lipid-rich lipoproteins is not completely understood but appears to require two steps. The first step involves the binding of the lipid-rich lipoprotein to the extracellular domain of SR-B1, and the second requires selective transfer of lipid to the PM (92). Further characterization revealed that these two steps are tightly coupled because the K_d for HDL binding and the K_m for CE uptake are similar when measured as a function of HDL concentration (93). Larger HDL particles have enhanced binding and increased selective CE delivery, demonstrating that alterations in the conformation of recognition sites on the surface of HDL influence the ability of HDL to interact with SR-B1 (94).

Analyses of which lipid-rich lipoproteins will bind SR-B1 concluded that all suitable CE donors share class A amphipathic helices that serve as the structural feature that SR-B1 can bind after testing of many CE donors, such as HDL, apoA-1/phospholipid bilayer disks, and lipid-free apoA-1 (95, 96). The extracellular domain of SR-B1 was shown to be essential for efficient CE transfer (97). Further studies also revealed that high-affinity lipid-rich lipoprotein binding to SR-B1 is essential but not sufficient for efficient lipid transfer (98). To reinforce this concept, some compounds that increase CE-rich lipoprotein binding to SR-B1 actually block lipid transfer (62).

The ability of SR-B1 to form dimers and higher-order oligomeric forms facilitates its CE transfer activity. Although SR-B1 exists primarily in a monomeric form in normal rat adrenal tissue, SR-B1 exists as a homodimer in microvilli-enriched adrenal PMs of 17α-ethinyl estradiol–treated rats (64). ACTH stimulation also increases the dimerization of SR-B1 in adrenals and promotes selective CE uptake, whereas dexamethasone-induced loss of ACTH dramatically lowers SR-B1

levels, SR-B1 dimers, and selective HDL–CE uptake by SR-B1. Changes in SR-B1 expression are accompanied by striking architectural changes of the microvillar compartment at the adrenocortical cell surface. Other studies have now established that, similar to early studies carried out in rat adrenal tissue, SR-B1 exists as a dimer and high-order oligomer in all steroidogenic and nonsteroidogenic cells and tissues that are active in selective uptake of HDL–CEs (99–101). More recently, mutating cysteine residues in the ectodomain resulted in robust induction of a SR-B1 dimer, which were rendered nonfunctional because these same residues are likely essential for optimal HDL binding, and hence, selective CE uptake (61).

SR-B1 can interact with other accessory proteins, which in turn can regulate the function of SR-B1. PDZK1/Na^+/H^+ exchanger regulatory factor 3 (NHERF3) was shown to regulate hepatic SR-B1 stability and steady-state protein levels. However, PDZK1/NHERF3 is not expressed in steroidogenic cells of the adrenal gland, ovary, or testis (102). Instead, two other NHERF family members, NHERF1 and NHERF2, partner with SR-B1 in steroidogenic cells as well as in the liver, where they negatively regulate both the expression and selective HDL–CE uptake of SR-B1 (103). Another member of the family, NHERF4, had no effect on selective HDL–CE uptake or steroidogenesis. When mRNA levels of SR-B1 are upregulated by cAMP stimulation, NHERF1 and NHERF2 mRNA levels decrease reciprocally. Structure-function analyses revealed that the PDZ and MERM domains within NHERF1 and NHERF2 interact with the C-terminal PDZ recognition motif (EAKL) in SR-B1. Functionally, it is established that overexpression of NHERF1 and NHERF2 inhibits de novo synthesis of SR-B1 (103).

In more recent studies of stimulated steroidogenesis, a cytosolic serine/threonine kinase that belongs to the stress- and energy-sensing AMPK family of kinases, salt-inducible kinase 1 (SIK1), was shown to interact with the cytoplasmic C-terminal domain of SR-B1. This interaction requires both the intact catalytic activity of SIK1 and its PKA-catalyzed phosphorylation and results in phosphorylation of Ser 496 of SR-B1 and increased HDL–CE uptake and steroidogenesis (67). Collectively, these studies suggest that SR-B1 function is under complex regulation and is modulated through several different posttranslational mechanisms.

MECHANISM OF SR-B1 FUNCTION AND THE FUNCTIONAL SIGNIFICANCE OF SR-B1 ACTION IN DIFFERENT TISSUES

Selective Cholesteryl Ester Uptake by SR-B1

As mentioned above, the first step in SR-B1–mediated selective uptake is the binding of CE-rich lipoproteins to the SR-B1 extracellular domain through the amphipathic α-helix domain. Following binding, CEs move down a concentration gradient within the HDL particles to the cell PM. Other lipids in the HDL particle, such as free cholesterol and triglyceride molecules, are also selectively transferred to cells. For CE, rates of uptake are proportional to the amount of CE initially present in the HDL particles. For nonpolar components, such as CEs and triglycerides, transport is more efficient, whereas rates for more polar phospholipids are 5–10 times slower (14, 104). The activation energy for CE uptake from HDL is relatively low at approximately 9 kcal/mol, suggesting that the rate-limiting step in this uptake may involve a nonaqueous pathway (105). A hydrophobic "channel" formed by the extracellular domain of the receptor, from which water is excluded and along which CE molecules diffuse, was proposed to accommodate these activities. Recent publication of the high-resolution crystal structure of the extracellular domain of LIMP-2, in addition to the homology modeling of SR-B1 (58), confirmed the existence of such a channel. The structure revealed an antiparallel β-barrel core and many short helical segments forming a globular structure with protein folds that create a cluster of basic residues to

facilitate binding of the acidic amphipathic α-helices present in an apoA-1 molecule located at the surface of an HDL particle. In addition, there is a hydrophobic tunnel with a 5 × 5-Å opening and a prominent 22 × 11 × 8-Å cavity located at the center of the β-barrel that traverses the entire length of the molecule. The size of this cavity is sufficient to allow the passage of CE and free cholesterol molecules. The recent discovery of a synthetic inhibitor of SR-B1, BLT-1, which can bind to Cys 384 of SR-B1 and prevent CE transfer, is also in agreement with this structure, as Cys 384 was shown to be located in the lumen of the tunnel, where binding with its inhibitor would block passage of lipids (60, 62).

Although selective uptake of CEs is considered to be nonendocytic, at least from the perspective of uptake of intact lipoprotein particles, there are controversies concerning CE movement to LDs. On the one hand, it has been suggested that HDL–CEs are delivered to the cell interior during retroendocytosis of the particle, where the receptor-bound HDL particle is internalized. They traverse an intracellular pathway during which CEs are transferred to the cell interior, and the HDL particle is recycled back to the PM where the lipid-depleted HDL is now released (106). However, the documentation that an intact tunnel within the structure of SR-B1 is required for CE transfer makes this possibility unlikely (58). Alternatively, carrier-mediated mechanisms could mediate CE transport, but CE binding proteins have not been identified. HDL–CEs could also be delivered to intracellular membranes or directly to LDs. In this regard, it is noteworthy that some constituent proteins of SNARE complexes are associated with intracellular membranes and with LDs. In this context, studies have shown that treatment of steroidogenic cells with *N*-ethylmaleimide results in a total block of HDL-derived selective CE uptake (107). When considered together, these various observations strongly suggest that intracellular trafficking and transport of CEs to LDs might involve active participation of a vesicle-mediated transport process; however, experimental evidence to support this is currently absent.

SR-B1–MEDIATED REVERSE CHOLESTEROL TRANSPORT

Numerous epidemiological and clinical studies have shown that plasma levels of HDL-C correlate inversely with the risk of cardiovascular disease (108, 109). The presumptive protective effect of HDL is largely attributed to its role in RCT, the process that involves the net movement of cholesterol via HDL from peripheral tissues back to the liver for cholesterol excretion/bile acid synthesis or steroid hormone synthesis in steroidogenic organs (1, 5, 110) (**Figure 2**). The first step in RCT is the removal of excess cholesterol (by HDL or its apolipoproteins) from stores in macrophage foam cells present in atherosclerotic lesions (14). Multiple pathways contribute to cholesterol efflux, including (*a*) unidirectional efflux to lipid-free apolipoproteins, particularly apoA-1, mediated by the ATP-binding cassette A1 (ABCA1); (*b*) unidirectional efflux to mature HDL particles mediated by ABCG1; and (*c*) efflux to mature HDL particles via passive diffusion facilitated by SR-B1 (15). After transport to plasma, the next step of RCT is the SR-B1–mediated transport of macrophage-derived (HDL) cholesterol to the liver for bile acid production, with subsequent biliary secretion or transport to steroidogenic tissues, especially the adrenal gland and ovary, for steroid production and storage.

As opposed to the selective uptake of cholesterol, the binding of SR-B1 and lipoprotein particles can serve as a docking site for cholesterol efflux, presumably through the hydrophobic tunnel within the ectodomain of SR-B1, extracting free cholesterol from cells. However, measurements of the dependence of SR-B1–mediated free cholesterol efflux on HDL concentrations indicate that free cholesterol efflux and HDL binding are not completely coupled; free cholesterol effluxes differently at low and high extracellular HDL concentrations (94, 111). It appears that SR-B1

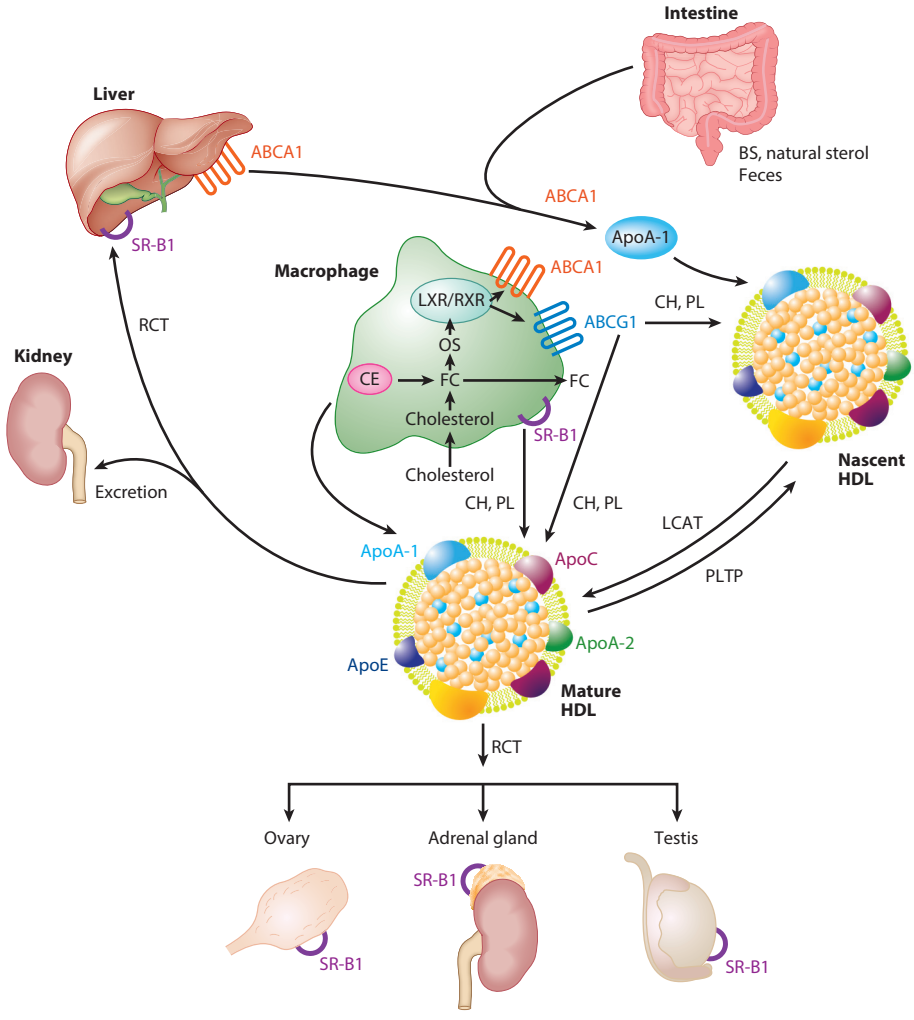

Figure 2

The role of SR-B1 in cholesterol trafficking and RCT. RCT begins with the unidirectional efflux of FC from cells to lipid-free apolipoproteins, particularly apoA-1, mediated by ABCA1. Further unidirectional efflux of FC and PLs to mature HDL particles is mediated by ABCG1, whereas SR-B1 facilitates the efflux of FC to mature HDL particles via passive diffusion. OSs, formed from FC, regulate the expression of ABCA1 and ABCG1 via binding to LXRs, which form heterodimers with RXRs. FC effluxed to HDL is esterified by the actions of LCAT, whereas the PL surface of the HDL is remodeled through the actions of PLTP. Mature HDL then delivers CEs to the liver and steroidogenic organs (ovary, adrenal, and testis) via recognition and transport via SR-B1. Abbreviations: ABCG1, ATP-binding cassette A1; BS, bile salts; CE, cholesteryl ester; CH, cholesterol; FC, free cholesterol; HDL, high-density lipoprotein; LCAT, lecithin:cholesterol acyltransferase; LXR, liver X receptor; OS, oxysterol; PL, phospholipid; PLTP, phospholipid transfer protein; RCT, reverse cholesterol transport; RXR, retinoid X receptor; SR-B1, scavenger receptor, class B type 1.

and HDL binding is important for free cholesterol transfer through the hydrophobic tunnel at low HDL concentrations. Because the CE and free cholesterol concentration gradient between the bound HDL particle and the cell PM are opposite to each other, the relatively high free cholesterol/phospholipid ratio in the cell PM results in free cholesterol being transported out of cells into HDL particles. When the phospholipid content of HDL is increased, free cholesterol efflux from cells increases accordingly (112), and because larger HDL particles bind more tightly to SR-B1 (i.e., they have a higher affinity), they will result in more free cholesterol efflux as well (94). At saturating high levels of HDL, SR-B1 induces reorganization of free cholesterol in the cell PM and creates domains of activated free cholesterol that are more susceptible to oxidation by cholesterol oxidase (111). Under these conditions, activated free cholesterol is transported to extracellular acceptors more readily through the aqueous diffusion pathway (113). Although the role of SR-B1 in mouse macrophages can be controversial, studies using cholesterol-loaded human monocyte-derived macrophages show that SR-B1 mediates cholesterol efflux together with ABCA1 (114–116).

With its capacity for forming a hydrophobic tunnel, binding lipoproteins at its extracellular domain, and interacting with cellular proteins at its C-terminal intracellular domain, SR-B1 is uniquely positioned at the PM for modulating the influx and efflux of CE, free cholesterol, and related lipids into and out of the cell. Depending on the gradient concentration and the interacting intracellular proteins, SR-B1 would be expected to function differently in different cells.

SR-B1, SELECTIVE UPTAKE, AND STEROIDOGENESIS

As previously mentioned, SR-B1 expression is high in steroidogenic tissues (adrenal glands, placenta, ovary, and testis) and is regulated by trophic hormones. Unlike polypeptide hormones, which can be stored as mature hormones in large amounts for rapid release, steroid hormones are synthesized acutely in steroidogenic cells upon stimulation. Therefore, when steroid production is stimulated, there is a surge of demand for cholesterol as a precursor for conversion to steroid hormones. The cholesterol utilized for steroidogenesis is derived from a combination of sources: (*a*) de novo cellular cholesterol synthesis, (*b*) the mobilization of CEs stored in LDs, and (*c*) lipoprotein-derived CEs obtained by either LDL receptor–mediated endocytic uptake or selective cellular uptake via SR-B1. The observation that steroidogenic cells of both *SR-B1*$^{-/-}$ and *apoA-1*$^{-/-}$ null mice (apoA-1 is the major HDL protein that binds SR-B1) have almost no CE accumulation suggests that SR-B1-mediated selective uptake provides the bulk of cholesterol needed for steroidogenesis (117), at least in rodents. However, SR-B1 also appears to be important in humans as individuals with mutations in *SR-B1* have been shown to have diminished adrenal steroid production (75, 76).

It is of interest that steroidogenic tissues, particularly adrenal glands and ovary, which express high levels of SR-B1 in vivo, are endowed with an intricate microvillar system for the trapping of cholesterol-rich lipoproteins. This general region of steroidogenic cells is called the microvillar compartment, and the specialized spaces created between adjacent microvilli are termed microvillar channels (74, 99, 118, 119). Studies using electron microscopy and immunolocalization show that in rat ovarian luteal cells, testicular Leydig cells, and adrenocortical cells, SR-B1 is preferentially localized on the microvillar domains that form channels in which various lipoproteins, including HDL, get trapped (99, 118). Interestingly, overexpression of rodent SR-B1 in steroidogenic-cultured cells, such as in the Y1 adrenal cell line, or infection of insect cells with baculovirus rSR-B1 cDNA leads to the induction of SR-B1–enriched intracellular channels that morphologically resemble steroidogenic cell microvillar channels. These studies suggest that the expression of SR-B1 protein in cells is intimately linked to channel formation. In addition, SR-B1

was also shown to increase the flux of free cholesterol, alter PM properties, and enhance formation of specific lipid rafts necessary for forming microvillar channels (119). In essence, these combined effects of SR-B1 serve to boost the efficiency of the selective HDL–CE transport process.

Thus, the SR-B1–mediated formation of microvilli/microvillar channels appears to be another mechanism through which both acute and chronic trophic hormone stimulation of SR-B1 enhances steroidogenesis via the increased delivery of cholesterol by altering its own functional expression and/or phosphorylation status, dimerization, and interaction with other cellular protein partners (for a detailed review, please see 6).

SR-B1, REVERSE CHOLESTEROL TRANSPORT, AND ATHEROSCLEROSIS

Both gain-of-function and loss-of-function strategies in mice have established that SR-B1 is a key player in RCT by determining the levels of HDL-C by promoting selective transport of HDL–CE to the liver for the conversion into bile acids or biliary cholesterol secretion (30, 31, 34, 120). Consistent with its importance in RCT, several mouse models have shown that SR-B1 overexpression in the liver decreases atherosclerosis (121, 122), whereas partial or total loss of SR-B1 increases atherosclerosis (32, 123). Recently, Zanoni et al. (124) reported the identification of a homozygote subject harboring a P376L missense mutation in the *SCARB1* gene that is associated with increased coronary heart disease despite increased plasma HDL-C. Thus, SR-B1 is atheroprotective by impacting HDL metabolism and promoting RCT (116). The hepatic uptake of cholesterol by SR-B1 through the RCT pathway depletes CE from HDL, and in turn, allows HDL to accept more CE that is effluxed from peripheral cells. When binding to its ligand HDL, SR-B1 regulates macrophage inflammation through activation of Akt and reduces activation of NF-κB, leading to increased anti-inflammatory cytokines such as interleukin (IL)-10 and transforming growth factor-beta (TGF-β). Acting through the Src/PI3K/Akt/Rac1 signaling pathway, macrophage SR-B1 can also mediate the efferocytosis or removal of apoptotic cells, resulting in increased survival of phagocytes and an anti-inflammatory response. In endothelial cells, SR-B1 has been shown to be involved in transcytosis of HDL from the apical to basolateral side of the cell to promote cholesterol efflux from intimal macrophages as well as lymphatic vessels (125).

Recent results have demonstrated the direct binding of Src to SR-B1. Similar to interactions with NHERF family members, Src interacts with the PDZK1 domain in SR-B1 when Src is phosphorylated. This SR-B1/Src interaction functionally promotes endothelial nitric oxide synthase (eNOS) signaling, protects endothelial cells from apoptosis, enhances endothelial cell growth and migration (126), and leads to less foam cell formation. Trafficking of CE to lysosomes for hydrolysis is one of the major pathways for the clearance of cytoplasmic CE; this process involves autophagosomes, with macrophage autophagy considered to be beneficial at reducing atherosclerosis (127, 128). Recent studies show that autophagy is defective in SR-B1–deficient macrophages (129). In addition, SR-B1 can traffic to lysosomes together with Rab7, a protein critical for autophagosome and lysosome fusion (130, 131), thus potentially facilitating the clearance of cytoplasmic CE in foam cells of atherosclerotic lesions.

SR-B1 FUNCTION IN OTHER PATHOPHYSIOLOGICAL CONDITIONS

Human *SCARB1* gene variants have been shown to be associated with abnormal lipids in women with coronary artery disease (132), and analysis of common genetic variations near the *SCARB1* locus shows significant association with plasma HDL-C levels (133), as well as with combined high HDL-C and high lipoprotein (a) (134). Intestinal SR-B1 is upregulated in the insulin-resistant state and is associated with overproduction of intestinal apoB48-containing lipoproteins (135).

SR-B1 also appears to play an important role in HCV entry into host cells. HCV initially binds directly to the extracellular domain of SR-B1 through recognition of the hypervariable region 1 of the E2 glycoprotein of HCV, which facilitates the binding of viral particles to CD81 and enhances the entry of virus particles into the host cell. SR-B1 can also interact with virus-associated lipoproteins. ITX5061, a small-molecule SR-B1 antagonist (136, 137), is under development as a promising inhibitor for HCV infection (138). SR-B1 has also been implicated in dengue virus infection (139).

Carcinogenesis and tumor development have a drastic impact on cholesterol metabolism of cells. Abnormal SR-B1 expression has been associated with increased risk, progression, and poor survival in prostate and breast cancers (140). High SR-B1 expression was shown to be associated with prostate cancer, and the disease-free survival time was reduced in patients with high intratumor levels of SR-B1 (141). Analysis of breast cancer cases showed that high SR-B1 expression was associated with an increased risk of breast cancer and related to more aggressive tumor type, larger tumor size, lymph node metastasis, and the absence of estrogen receptors (142, 143). Quantitative real-time polymerase chain reaction analysis comparing cancer samples with those of normal tissues have demonstrated considerable increased expression of SR-B1 in most tumor samples of breast, ovarian, colorectal, and pancreatic cancer (144), raising the potential for using SR-B1 as a biomarker for diagnosis and the development of inhibitors for use in specific cancer conditions (145).

DELIVERY OF THERAPEUTIC AND DIAGNOSTIC AGENTS THROUGH THE SELECTIVE SR-B1–HIGH-DENSITY LIPOPROTEIN UPTAKE PATHWAY

With its capacity for forming a hydrophobic tunnel within the PM and for mediating the selective uptake of hydrophobic molecules that would bypass lysosomal processing, SR-B1 has great potential to serve as a gateway for delivery of therapeutic agents reconstituted within HDL (rHDL) particles. Indeed, anticancer agents within rHDL can be taken up by cancer cells (146). When paclitaxel was packaged within rHDL nanoparticles and exposed to SR-B1–overexpressing prostate cancer cells, SR-B1–mediated entry of the drug was significant, representing 82% of the total paclitaxel incorporated by these cells (147). In another study, HDL–gold nanoparticles were shown to target SR-B1 receptors on lymphoma cells, inducing apoptosis in those cells (148).

The use of rHDL-targeting SR-B1 to target cancer chemotherapeutic drugs overcomes several issues typically associated with more conventional delivery systems, including solubility, biodistribution, and tissue nonspecificity (149). The rHDL particles offer many potential advantages because they are small, biocompatible, and nonimmunogenic, and importantly, they have a long circulating half-life and exhibit selective delivery via the SR-B1 channel. This use of the rHDL-targeting SR-B1 strategy was first proposed in 1982 by Counsell & Pohland (150), and the first reported use was a systematic study carried out in 2002 using anticancer drugs trapped in HDL or LDL (151). Reconstitution had minimal effect on the properties of the complexes, whereas the encapsulated drugs showed enhanced cytotoxicity toward human carcinoma cells. Further studies showed that tumor tissues are characterized by a leaky vasculature and low lymphatic drainage, leading to unequal interstitial pressure between different parts of the tumor (152). This pressure difference leads to uneven retention of particles between the center of the tumor and its periphery. HDL and HDL-like particles are delivered via SR-B1 instead of by passive targeting through the enhanced permeability and retention effect (153). The therapeutic index of drug delivery also improves with the preferential accumulation in malignant cells using this approach (154). Other examples include the antineoplastic drug, aclacinomycin, which showed a preferential cytotoxicity

toward malignant cells when encased in rHDL (155). Valrubicin, when encapsulated into rHDL nanoparticles, was effective with 1.8- and 2.6-times lower minimum inhibitory concentrations than the free drug against prostate and ovarian cells, respectively (156). These experiments demonstrate the selective tumor delivery capabilities of rHDL nanoparticles that utilize the SR-B1 pathway.

This pathway can also be used to deliver agents for diagnostic imaging. When apo E knockout mice were injected with rHDL that was coupled with gadolinium-chelate, which is visible in magnetic resonance imaging (MRI), and with a green-emitting amphiphilic fluorophore, 7-nitro-2-1,3-benzoxadiazol-4-yl, an MRI scan of the mouse abdominal aorta showed significant accumulation of rHDL in the aortic wall (157). Other developments include a synthetic HDL/apoA-1 mimicking nanoparticle composed of lipids and an apoA-1–derived, amphiphatic α-helical peptide, 37pA (158). Using this method, a variety of diagnostic agents has been delivered to susceptible atherosclerotic plaques in a mouse model and successfully imaged using MRI, computerized tomography, or optical means (159).

SUMMARY POINTS

1. SR-B1 is a multiligand membrane receptor that functions as a physiologically relevant HDL receptor to mediate the selective delivery of HDL-C to cells.
2. SR-B1 can potentially form a hydrophobic tunnel within the PM, which appears to facilitate the selective cellular influx and efflux of lipid molecules.
3. The SR-B1 selective pathway provides the bulk of the cholesterol needed for steroidogenesis in rodents.
4. SR-B1 mediates the first step of RCT by facilitating cholesterol efflux from peripheral tissues and mediates the last step of RCT by facilitating the selective delivery of HDL-C to hepatocytes.
5. SR-B1 can also facilitate the uptake of other molecules, including vitamins, viruses, and apoptotic cells.
6. SR-B1 can serve as a potential biomarker for cancer diagnosis and prognosis.
7. The SR-B1–linked selective HDL–CE uptake pathway has the potential for the delivery of therapeutic and diagnostic agents.

FUTURE ISSUES

1. Future efforts should use genetic or pharmacological approaches to increase the functional efficiency of SR-B1, including SR-B1–mediated cholesterol efflux from macrophages, selective HDL–CE uptake (liver, adrenal glands, and gonads), elimination of excess cholesterol via biliary cholesterol secretion, catabolism of cholesterol to products (bile acids and steroids), and consequently, attenuation of atherosclerosis.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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