thematic review series

*Thematic Review Series: Lipid Transfer Proteins*

# Scavenger receptor B type 1: expression, molecular regulation, and cholesterol transport function

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**Abstract Cholesterol is required for maintenance of plasma membrane fluidity and integrity and for many cellular functions. Cellular cholesterol can be obtained from lipoproteins in a selective pathway of HDL-cholesteryl ester (CE) uptake without parallel apolipoprotein uptake. Scavenger receptor B type 1 (SR-B1) is a cell surface HDL receptor that mediates HDL-CE uptake. It is most abundantly expressed in liver, where it provides cholesterol for bile acid synthesis, and in steroidogenic tissues, where it delivers cholesterol needed for storage or steroidogenesis in rodents. SR-B1 transcription is regulated by trophic hormones in the adrenal gland, ovary, and testis; in the liver and elsewhere, SR-B1 is subject to posttranscriptional and posttranslational regulation. SR-B1 operates in several metabolic processes and contributes to pathogenesis of atherosclerosis, inflammation, hepatitis C virus infection, and other conditions. Here, we summarize characteristics of the selective uptake pathway and involvement of microvillar channels as facilitators of selective HDL-CE uptake. We also present the potential mechanisms of SR-B1-mediated selective cholesterol transport; the transcriptional, posttranscriptional, and posttranslational regulation of SR-B1; and the impact of gene variants on expression and function of human SR-B1. A better understanding of this unique pathway and SR-B1's role may yield improved therapies for a wide variety of conditions.—** Shen, W-J., S. Asthana, F. B. Kraemer, and S. Azhar. **Scavenger receptor B type 1: expression, molecular regulation, and cholesterol transport function. *J. Lipid Res.* 2018.** 59: **1114–1131.**

**Supplementary key words** adrenal • liver • bile • steroids

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Cholesterol is required for the maintenance of plasma membrane fluidity and integrity, as well as many cellular functions. Tissues such as liver, adrenal gland, and gonads have a special requirement for cholesterol, which is used as a substrate for product biosynthesis (1, 2). In many species, this cholesterol is obtained from plasma lipoproteins by a unique pathway in which circulating lipoproteins bind to the surface of the biosynthetic cells and contribute their cholesteryl esters (CEs) to the cells by a process known as the "selective" cholesterol uptake pathway (3). This pathway differs from the classic endocytic LDL receptor pathway (4) in that CEs, predominantly contained within HDL, are taken into the cell without the uptake and lysosomal degradation of the HDL particle itself (3, 5–10). As described, the selective pathway is a high-capacity physiologically regulated bulk-cholesterol delivery system operating in steroidogenic tissues of a variety of animals to selectively internalize cholesterol to produce steroid hormones (11–14), and in the liver to mediate the transfer of cholesterol into bile and provide cholesterol for bile acid production (15–18). The selective pathway also operates in isolated hepatocytes (7, 19, 20), fibroblasts (19, 20), adipocytes (21, 22), macrophages (23, 24), and adrenal (7, 11, 19, 25), ovarian (12, 13) and

Abbreviations: AcLDL, acetylated LDL; CD36, cluster determinant 36; CE, cholesteryl ester; CLA-1, cluster determinant 36 and lysosomal integral membrane protein II analogous-I; eNOS, endothelial nitric oxide synthase; 17α-E2, 17α-ethinyl estradiol; FC, free cholesterol; HDL-C, HDL cholesterol; LIMP, lysosomal integral membrane protein; LPS, lipopolysaccharide; OxLDL, oxidized LDL; PREB, prolactin regulatory element-binding protein; SF-1, steroidogenic factor-1; SIK1, salt-inducible kinase; SR-B1, scavenger receptor B type 1; TG, triglyceride; 3′ UTR, 3′ untranslated region.

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[2] For simplicity, we use the term dimerization here to include the multiple forms of the SR-B1 protein; i.e., dimers and high order oligomers.

testicular Leydig (14) cells, though its function in fibroblasts is less clear. Scavenger receptor B type 1 (SR-B1) is the physiologically relevant cell surface HDL receptor responsible for selective HDL-CE uptake (26).

## MOLECULAR AND BIOCHEMICAL CHARACTERISTICS OF SR-B1

The SR-B1 gene (*Scarb1*) was almost simultaneously cloned as a cluster determinant 36 (CD36)-related class B scavenger receptor by expression cloning using cDNA libraries from a Chinese hamster ovary (CHO) cell line, Var-261, with a mutated LDL receptor gene (27), and as CD36 and lysosomal integral membrane protein (LIMP) II analogous-I (CLA-1) from human erythroleukemia (HEL) cells based on its sequence similarity to CD36 and LIMP-2 (28). CLA-1 is a human homolog of SR-B1. Subsequently, the isolation and characterization of SR-B1 from mouse (26), rat (29), rabbit (30), pig (31), cow (32), and Northern tree shrew (33) have been described. Further studies by Monty Krieger's group revealed that SR-B1 binds HDL and mediates the selective delivery of HDL-CE (26). This led to identification of SR-B1 as the first bona fide HDL receptor (26).

SR-B1 is a member of the class B family of scavenger receptors, which is also known as the CD36 superfamily of scavenger receptors, which are plasma membrane receptors that recognize and take up macromolecules that have a negative charge. Although classified as a group, the scavenger receptor family members are structurally heterogeneous; specifically, the scavenger receptor B family members have a very different molecular structure from other scavenger receptors by having two transmembrane domains with both the N and C termini of the proteins residing intracellularly (34). Proteins in this group are cell surface-associated glycoproteins, which include SR-B1 and its splicing variant, SR-B2 (SR-BII), its human homolog, CLA-1/human SR-B1, and spliced variant, CLA-2/human SR-B2, CD36, and LIMP-2 (35–41). Full-length SR-B1 encodes a 509 amino acid protein, which, like other family members, contains a short N-terminal cytoplasmic domain of 9 amino acids (N-terminal domain), a transmembrane spanning domain of 22 amino acids, a large extracellular domain of 408 amino acids containing a cysteine-rich region and multiple sites for N-linked glycosylation, a second transmembrane domain of 23 amino acids, and a cytoplasmic C-terminal domain of 44 amino acids (37, 42). SR-B1 is posttranslationally glycosylated, and mutational analysis showed the importance of Asn-108 and Asn-173 for plasma membrane localization of SR-B1 and for the ability to transfer lipid from HDL to cells (43). The mouse SR-B1 gene is located on chromosome 5 with 13 exons and 12 introns. Due to alternative splicing, the second isoform of SR-B1, SRB2 (SR-BII), has only 12 exons and a different C terminal with 41 amino acids (36). Using a specific antibody for SR-B2 isoform, SR-B2 protein was detected in mouse liver, testis, and adrenal glands at about 5–12% of immunodetectable SR-B1 (36, 44). Recent genomic analysis revealed a third SR-B1 variant with another different alternative splicing that results in 11 exons and 520 amino acids; however, no functional significance of this variant has been reported yet. The mouse SR-B1 gene exon organization and the C termini of the three variants, as well as a cartoon of the structural features of SR-B1, are shown in **Fig. 1**. The predicted molecular mass of SR-B1 is ~57 kDa, but, because the protein is heavily glycosylated (43), it runs ~83–84 kDa on Western blot (37, 42). SR-B1 is also myristoylated and palmitoylated, but fatty acid acylation of the protein does not affect its selective HDL-CE transport function (45).

## SR-B1 LIGANDS

Scavenger receptors are cell surface membrane proteins that can bind chemically modified lipoproteins, including acetylated LDL (AcLDL), oxidized LDL (OxLDL), and often many other types of ligands (34, 46). SR-B1 was first identified in scavenger receptor expression cloning experiments using AcLDL as a ligand. Further studies have demonstrated that SR-B1 or its human homolog, CLA-1, bind an array of ligands (**Table 1**), including both native (VLDL, LDL, and HDL) (38, 47) and modified lipoproteins (OxLDL and AcLDL) (27, 47). SR-B1 can also bind maleylated BSA (38); advanced glycation end-product modified proteins, such as advanced glycation end product BSA (48); hypochlorite-modified LDL (49, 50); discoidal reconstituted phospholipid/unesterified cholesterol particles containing apoA-I, apoA-II, apoC-III, or apoE (51, 52); reconstituted HDL particles containing apoA-I or apoA-II (53); and lipid-free apoE (53). However, SR-B1 exhibits much higher affinity for native HDL (26, 37). The facts that HDL consists of particles of varying sizes and different lipid and protein compositions and densities (54), and that apoA-I is the principal component of HDL, are in accordance with observations that the physical characteristics of HDL as well as the conformation/organization of apoA-I in HDL particles are critical for optimal binding of HDL to SR-B1 (38). Indeed, it has been demonstrated that spherical α-HDL particles, which are larger in size, cholesterol rich, and lower density, bind more strongly to SR-B1 as compared with high-density lipid-poor preβ-HDL (55, 56). Interestingly, reconstituted discoidal apoA-I complexes bind SR-B1 with even much greater affinity than native α-HDL (55). Furthermore, amphipathic helices of apoA-I have been demonstrated to be critical for its binding to SR-B1 (57). The relative levels of apoA-I and apoA-II in spherical α-HDL particles also dictate the association with SR-B1 (38, 53, 58). SR-B1 can also bind anionic phospholipids (59–61), serum amyloid A (60), silica (62), oxidized phospholipids (63, 64), and bacterial cell-wall components, such as endotoxin [lipopolysaccharides (LPSs)] of gram-negative bacteria and lipoteichoic acid of gram-positive bacteria (65, 66). Additionally, SR-B1/CLA-1 can bind and internalize other bacterial and mammalian proteins containing amphipathic helices (60, 66, 67). Finally, SR-B1 has been shown to bind several types of apoptotic cells (65, 68–72). From the perspective of displaying a broad spectrum of ligand recognition, the most closely related proteins are

from the LDL receptor family (73, 74). Interestingly, the structure of the SR-B1 family is distinct from that of the LDL receptor family proteins, again by having two transmembrane domains with both the N and C termini of the protein residing intracellularly, while LDL receptor family members have a single transmembrane domain.

## CELLULAR AND TISSUE DISTRIBUTION OF SR-B1

SR-B1 is expressed in a wide variety of tissues and cell types, including adipocytes, macrophages, endothelial cells, intestine, keratinocytes, epithelial cells, smooth muscle cells, monocytes, placenta, gallbladder, and ocular tissues (37–39, 75–77). However, in rodents, SR-B1 is expressed most abundantly in the liver and steroidogenic cells of the adrenal gland, testis, and ovary (26), tissues that efficiently utilize the selective pathway in deriving CEs for use in bile acid synthesis and biliary cholesterol secretion (78–81) or steroid hormone production (12, 14, 82–86). In humans, CLA-1/human SR-B1 shows a similar tissue distribution (47, 87). Interestingly, variable expression levels of SR-B2 mRNA are also detected in mouse liver, adrenal gland, and testis, with SR-B2 transcripts ranging from 13% to 40% of total SR-B1 in mouse liver (36, 88), from 6% to 30% in adrenal (36, 88), and 80% in whole testis (36). Moreover, of the total hepatic SR-B1/SR-B2 mRNA, only 12% of SR-B1/SR-B2 protein is detected in mouse liver by Western blotting, possibly because of less efficient translation of the SR-B2 protein (36).

It is of interest that steroidogenic tissues, which express high levels of SR-B1 in vivo, are equipped with an intricate microvillar system for the trapping of lipoproteins (6, 8, 14, 83, 84, 89). This general region of steroidogenic cells is referred to as the microvillar compartment, and the specialized spaces created between adjacent microvilli are called microvillar channels. It is the microvillar channels where the various lipoproteins are trapped prior to the selective uptake of lipoprotein-CEs into cells. Use of electron microscopic immunocytochemistry techniques revealed heavy labeling of SR-B1 specifically in these regions (corresponding to microvilli and microvillar channels), and current evidence suggests that these microvillar compartments express high levels of SR-B1 to facilitate the selective uptake of HDL-CE in steroidogenic tissues. **Figure 2** displays photomicrographs demonstrating the microvillar system. In this context, we previously demonstrated that expression of SR-B1 in heterologous (Sf9 insect cells) (90) or homologous (Y1-BS1 mouse adrenocortical cells) (91) cell systems promotes microvillar channel formation and selective HDL-CE uptake. Furthermore, examination of SR-B1 knockout mice provided further evidence that SR-B1 is required for formation of microvilli and microvillar channels. Unlike their wild-type counterparts, the adrenal zona fasciculata cells from SR-B1-null mice exhibit disorganized microvilli, devoid of microvillar channels with an absence of HDL particles (92).

SR-B1 expression has also been reported in several nonmammalian vertebrates, as well as in several insect species. High expression of SR-B1 is reported in the liver, ovary, heart, and blood vessels in the turtle and in the liver of chickens, frogs, goldfish, sharks, and skates (93). SR-B1 expression is reported in the liver of Atlantic salmon (*Salmo salar L.*) (94) and in several organs of prawns (*Macrobrachium nipponense*) (95). Twelve to fourteen candidate SNMP/CD36 homologs from each of the genomes of *Drosophila melanogaster*, *Drosophila pseudoobscura*, *Anopheles gambiae*, and *Aedes aegypti* (Diptera), eight candidate homologs from *Apis mellifera* (Hymenoptera), and 15 from *Tribolium castaneum* (Coleoptera) have been identified (96, 97). The 14 *D. melanogaster* SNMP/CD36 homologs include *CG10345*, *CG1887*, *CG2736*, *CG31741*, *CG3829*, *CG40006*, *CG7227*, *CG7422*, *crq*, *emp*, *ninaD*, *pes*, *santa-maria*, and *Snmp* (98). In the silkworm, two genes, *Cameo1* and *Cameo2*, encode proteins homologous to SR-B1 (97, 99). There are 13 other genes homologous to *Cameo1* and *Cameo2*. These genes are *SCRB5*, *SCRB6*, *SCRB7*, *SCRB8*, *SCRB9*, *SCRB10*, *SCRB11*, *SCRB12*, *SCRB13*, *SCRB14*, *SCRB15*, *SNMP1*, and *SNMP2* (93).

## REGULATION OF SR-B1 EXPRESSION

### Promoter analysis

In humans, the *SCARB1* gene is located on chromosome 12, and analysis of its 5′-flanking promoter region shows that it is very guanine-cytosine rich with consensus binding sites for many nuclear transcription factors, such as SREBP-1, which regulates *SCARB1* expression in response to altered intracellular sterol levels (87, 100). In steroidogenic cells, trophic hormones stimulate *SCARB1* expression through changes of cellular cAMP levels (101), and steroidogenic factor-1 (SF-1) is one of the major transcription factors involved in this pathway through binding to its consensus sequence in the *SCARB1* promoter (101). Analysis of both the human and rat promoter 5′-flanking regions revealed the presence of many consensus sequences for binding transcription factors responsible for positive and negative regulation of the SCARB1 promoter, although the exact location of the regulatory elements varies in the human and rat promoters. **Figure 3** illustrates the presence of the binding sites for positive and negative regulatory factors in the 5′ proximal 2.2 kb region of the rat promoter. There are two binding sites for SREBP-1 that mediate positive regulation of *Scarb1* expression in steroidogenic tissue and parenchymal liver cells when cellular cholesterol is depleted (100). There is one SF-1 binding site for regulation mediated through alterations in cellular cAMP levels (101). There are three estrogen response element binding sites (ERE half-sites) through which estrogen receptor regulates *Scarb1* expression in an E2-dependent manner in coordination with mixed-lineage leukemia histone methylases (102) in human liver and placenta cells. In the adrenal, prolactin regulatory element-binding protein (PREB) can bind to the PREB-binding core element at −321 of the human *Scarb1* promoter and can induce SR-B1 protein expression under conditions that increase cellular cAMP levels (103). In both human and rodent preadipocytes and

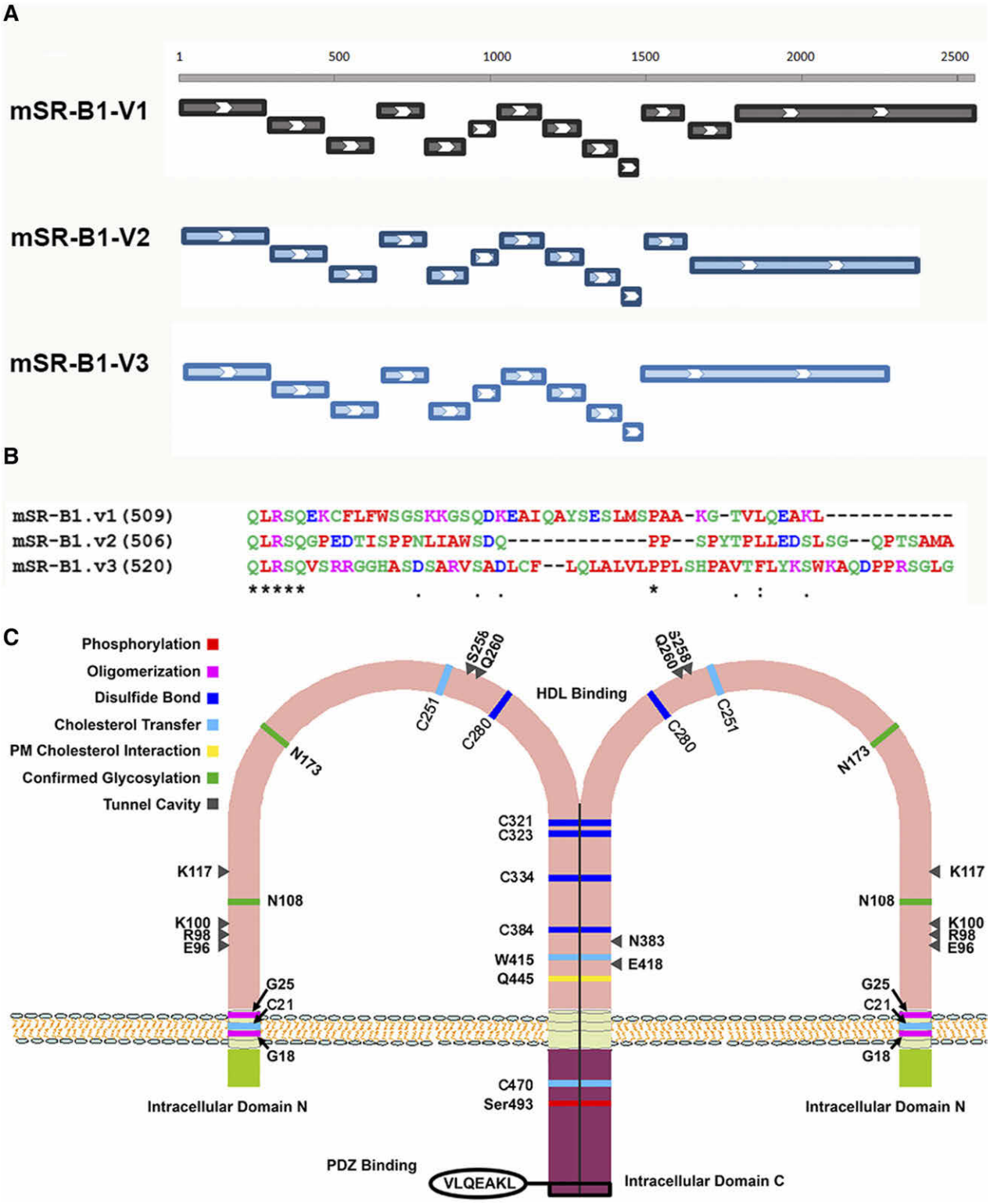


**Fig. 1.** Gene exon organization (A) and C-termini sequences (B) of mouse SR-B1 variants and structural features of SR-B1 (C). A: Exon organization. Mouse SR-B1 variant 1 has 13 exons and 509 amino acids. Variant 2 arises from alternative splicing at the C-terminal end resulting in 12 exons and 506 amino acids. Genomic analysis shows that variant 3 has 11 exons and 520 amino acids. B: C-terminal sequences of mouse SR-B1 variants. C: Structural features of SR-B1. SR-B1 has an N-terminal and a C-terminal intracellular domain and an extended extracellular ectodomain. Several structural features are important for the function of SR-B1. An N-terminal transmembrane glycine motif (G15_G18_G25) was shown to be required for oligomerization and lipid transport. The C terminal of SR-B1 also contains sequences important for oligomerization. Six conserved cysteine residues (C251, C280, C321, C323, C334, and C384) found in the ectodomain of SR-B1 were also demonstrated to be involved in dimer/oligomer formation. Analysis of human SR-B1 revealed 11 putative N-linked glycosylation sites. Mutational analysis showed the importance of Asn-108 and Asn-173 for plasma membrane localization and for the ability to transfer lipid from HDL to cells. Structural analysis of SR-B1 homolog, LIMP-2, showed that there are eight amino acids that work coordinately to form a tunnel cavity that spans the entire length of the ectodomain allowing facilitated lipid transfer. E96, R98, K100, K117, W258, Q260, N383, and

TABLE 1. SR-B1 ligands

| Ligands |
|---|
| Native VLDL, LDL, and HDL |
| OxLDL and AcLDL |
| Maleylated BSA |
| Liposomes containing anionic phospholipids |
| Hypochlorite-modified LDL |
| Lipoprotein (a) |
| Discoidal POPC-apoE particles |
| Discoidal reconstituted phospholipid/unesterified cholesterol particles containing apoA-I, apoA-II, or apoC-III |
| Advanced glycation end product BSA |
| Lipid free apoE |
| Oxidized phosphatidylcholine CD36 and other oxidized phospholipids |
| Myeloperoxidase-$H_2O_2$-$NO_2$-modified LDL |
| Serum amyloid A |
| Silica |
| Endotoxin (LPSs of gram-negative bacteria and lipoteichoic acid of gram-positive bacteria) |
| Amphipathic helices containing bacterial and mammalian proteins |
| Apoptotic cells |

liver cells, LXRα/RXR and LXRβ/RXR were shown to bind the *Scarb1* promoter and induce *Scarb1* transcription (104). In the rat *Scarb1* promoter, there is a PPRE motif located at −1622, and PPARα and RXRα were shown to bind to the SR-B1 PPRE motif and result in increased expression of *Scarb1* in hepatic and macrophage cell lines (105). Estrogen receptors α and β bind to the three estrogen-responsive elements in the rat SR-B1 promoter and liver receptor homolog 1 binds to an LRH binding site in the promoter, both upregulating *Scarb1* (106). There are two binding sites for Yin Yang 1 transcription factor in the rat *Scarb1* promoter at −1329 and −1211, through which YY1 binds and represses *Scarb1* promoter activity under basal conditions (107). Using two-hybrid studies, Shea-Eaton and colleagues also confirmed that YY1 can bind to SREBP-1a, therefore inhibiting the interaction of SREBP-1a binding to the SRE and negatively regulating the expression of *Scarb1* (107). Other negative regulators for the *Scarb1* promoter include the nuclear receptor, NR0B1 (DAX-1), a protein that plays an important role in adrenal development. DAX-1 was shown to repress the expression of the *Scarb1* promoter through interaction with SREBP-1a and SF-1 (108). In addition, pregnane X receptor, which is a regulator of detoxification processes, was shown to repress the expression of human *SCARB1* in response to the pregnane X receptor agonists, rifampicin and lithocholic acid (109).

**The 3′ untranslated region**

Recently, small noncoding RNAs, including microRNAs, were demonstrated to regulate expression of many genes. These microRNAs are about 22 nucleotides and can bind to specific motifs, mostly at the 3′ untranslated region (3′ UTR) of a gene, silencing gene expression via mRNA degradation or preventing mRNA from being translated. Analysis of the sequence of the SR-B1 3′ UTR revealed potential binding sites for several miRNAs. Further analysis demonstrated negative regulation of SR-B1 in liver and macrophages by miR-185, miR-96, and miR-223 (110). The 3′ UTR of SR-B1 also possesses binding sites for miR-125a and miR-455. Studies show that both miR-125a and miR-455 are present in steroidogenic cells and their expression was suppressed by ACTH and cAMP treatment. Mutational analysis of their binding sites in the 3′ UTR of SR-B1 revealed that both miRNA-125a and miRNA-455 bind to those specific sites in the 3′ UTR of SR-B1 mRNA and negatively regulate SR-B1 expression and inhibit steroidogenesis (111).

## STRUCTURAL FEATURES OF SR-B1

Various approaches, including site-directed mutagenesis, "domain swap," and chemical cross-linking, have been utilized and have identified several structural features to be important for the function of SR-B1 (Fig. 1C). The C-terminal intracellular domain contains an interacting domain (VLQEAKL) for binding with PDZ domain-containing protein, through which the function of SR-B1 is regulated in a tissue-specific manner (for detail see below). SR-B1 was shown to form oligomers, which display improved function (84, 112–116), with several portions involved in oligomerization. An N-terminal transmembrane glycine motif (G15_G18_G25) was shown to be required for oligomerization and lipid transport (114), whereas studies using fluorescence resonance energy transfer techniques to visualize SR-B1 homo-oligomerization revealed that the C termini of SR-B1 appeared to be involved in its homo-dimerization (113). Meanwhile, using a sulfhydryl-reactive reagent, the six conserved cysteine residues (C251, C280, C321, C323, C334, and C384) found in the ectodomain of SR-B1 were also demonstrated to be involved in dimer/oligomer formation (117). Experiments using chimeric SR-B1 and CD36 revealed that the N terminal of the extracellular domain is important for unesterified cholesterol efflux to HDL (118, 119).

Several recent studies have also examined the impact of cysteine residues on cellular trafficking and selective HDL-CE transport function (117, 120–123). These studies were achieved primarily by mutating cysteine residues in mouse, rat, or human SR-B1 individually or in certain combinations to either Ser or Gly, and subsequent expression of individual constructs in cultured cells followed by determination of receptor activity, subcellular distribution of receptor protein, or selective lipid transport function. Two reports demonstrated that four cysteine residues, C280, C321, C323, and C334, may be involved in disulfide bond formation and critically involved in the expression and function of SR-B1 (117, 122). In addition, Yu et al. (123), using a mass spectrometry technique, have reported the identification of two disulfide bonds in SR-B1 that connect cysteine residues within the conserved C321-P322-C323

E418 are the amino acids that comprise the tunnel cavity to facilitate lipid transfer of SR-B1. The C-terminal intracellular domain contains an interacting domain (VLQEAKL) for binding with PDZ domain-containing proteins, through which the function of SR-B1 is regulated in a tissue-specific manner.

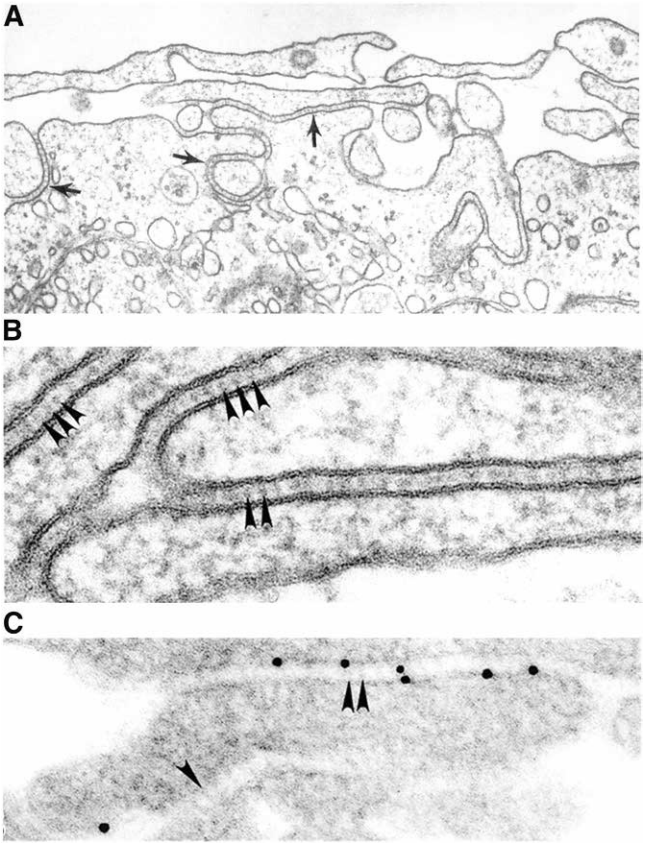


**Fig. 2.** Microvillar channels in murine adrenocortical cells. A: Ultrastructure appearance of microvilli (denoted by arrows). B: High magnification of microvillar channels containing HDL (denoted by arrowheads). C: Localization of immunogold-labeled HDL in microvillar channels. This research was originally published in the *Journal of Lipid Research* (84). © The American Society for Biochemistry and Molecular Biology.

(CPC) motif and connect C280 to C334 and a reduced cysteine side chain that contribute to the functional expression of SR-B1. Using a C323G mutant, a blocking antibody against C323 region, and a C323G mutant transgenic mouse model, Guo et al. (121) demonstrated that C323 plays a critical role in HDL binding to cell surface SR-B1 and SR-B1-mediated selective HDL-CE uptake. An exoplasmic cysteine, C384, of SR-B1 has also been implicated in SR-B1-mediated selective HDL-CE transport activity (120).

The crystal structure of LIMP-2 was obtained recently and showed that the main ectodomain of the protein contains an antiparallel β-barrel core with many short α-helical segments (124). Two disulphide bridges stabilize the fold. The disulphide bridge pattern for LIMP-2 (C274-C329 and C312-C318) is similar to that predicted for SR-B1 (C321-C323, C274-C329) and for CD36 (C313-C322, C272-C333), and is consistent with experimental data (123, 125, 126). Most of the proteins in this family have lipid transport activity, and the crystal structure of LIMP-2 showed that eight amino acids work coordinately to form a tunnel cavity that spans the entire length of the ectodomain, allowing facilitated lipid transfer. These eight acidic and basic amino acids form a network of hydrogen and ionic bonds and contribute to the lining of the cavity, which is predominately hydrophobic to accommodate lipid moieties. **Figure 4** displays the structure of SR-B1, both as a monomer and as a dimer, modeled on the crystal structure of LIMP-2, with the eight amino acids comprising the tunnel cavity highlighted. As illustrated, there are conformational changes in the tunnel cavity that are predicted to occur during the transition between monomer and dimer. Further experimental studies will be needed to explore the functional significance of the structural transition between monomer to dimer.

Recently, a fragment of SR-B1 (residues 405-475), which includes the C-terminal transmembrane domain, was purified and reconstituted in detergent micelles (123). Analysis of this fragment using NMR has generated high-resolution structural information of the C-terminal transmembrane domain of SR-B1 (127), which revealed that there are two short α-helices (residues 409-419 and 427-436) and a long α-helix spanning the entire transmembrane domain (residues 438-469). There is a potential GXXXG glycine dimerization motif starting at G420 together with a putative leucine zipper motif spanning from amino acid 413 to amino acid 455. Mutational analysis showed that mutants L413A and L448A resulted in decreased receptor efflux of unesterified cholesterol to HDL. G420 was previously shown to be important for SR-B1 to function for CE delivery (128).When a smaller SR-B1 fragment containing residues 405-445, which lacks the hydrophobic transmembrane domain, was purified and examined by NMR, this fragment was shown to require a hydrophobic environment to fold properly, suggesting the existence of a potential membrane-interacting juxtamembrane domain.

As mentioned above, oligomerization of SR-B1 improves its function. Recently a crystal structure of LIMP-2 dimer bound with cholesterol and phosphatidylcholine was obtained. Further analysis revealed that LIMP-2 switches from a monomeric form to a dimeric form when binding to different ligands. When a monomer, it binds glucocerebrosidase; whereas as a dimer, it preferentially binds anionic phosphatidylserine (126). This shifting of ligand specificity

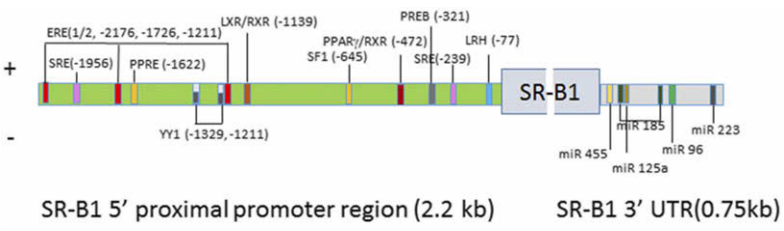


**Fig. 3.** Regulation of SR-B1 expression. The 5′ proximal 2.2 kb region of the rat *Scarb1* promoter contains binding sites for various regulatory factors for positive and negative regulation of *Scarb1* expression. The 3′ UTR of the rat *Scarb1* gene contains binding sites for miR-185, miR-96, and miR-223 for negative regulation of SR-B1 expression in liver and macrophages, as well as binding sites for miR-125a and miR-455 for negative regulation of SR-B1expression in steroidogenic tissues.

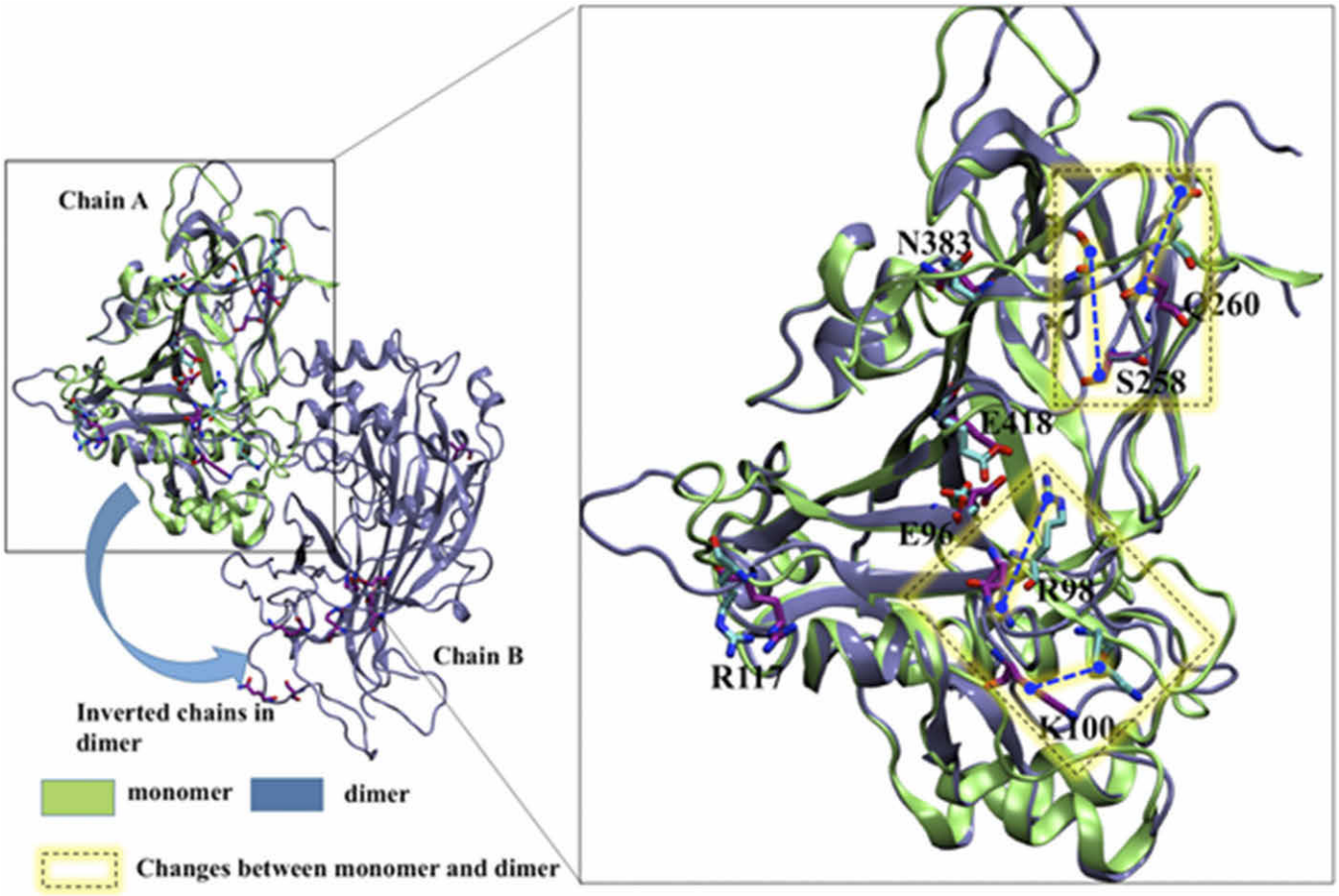


**Fig. 4.** Structure of human SR-B1, both as a monomer and as a dimer. The monomer and dimer forms of human SR-B1 were built separately through homology modeling using MODELLER (246). From 200 generated models, the top ranked models were chosen for energy minimization through Amber molecular dynamics simulation (247). The energy-minimized structures were used for the structural analysis. The residues comprising the tunnel cavity are labeled, and the regions where conformational differences are observed between monomers and dimers are highlighted in yellow squares.

through oligomerization could be a mechanism of regulation shared with other proteins in the family, such as SR-B1 and CD36, but awaits experimental evidence.

## LIPID UPTAKE FUNCTION OF SR-B1

A major function of SR-B1 is to facilitate the transport of CEs from HDL or other lipoproteins to cells by a nonendocytic mechanism referred to as selective uptake (37–39, 75, 76, 129–131). Numerous studies have demonstrated that SR-B1-mediated selective uptake of CE does not show a specificity toward a single class of lipoproteins. It can utilize a number of lipoproteins, including human and rat HDL, reconstituted synthetic HDL particles containing apoA-I, apoC, or native or modified apoE, IDL, and LDL as donors of CE for SR-B1-mediated selective CE uptake in vitro and/or in vivo (38, 76). However, because these donor lipoproteins differ in characteristics, such as apolipoprotein conformation and apolipoprotein and lipid composition, as well as the fact that some of these lipoproteins may serve as ligands for other important pathways (e.g., human LDL and apoE-rich rodent HDL are potent ligands for the LDL receptor endocytic pathway), these lipoproteins do not deliver CEs to cells with similar efficacies. Based on the evidence obtained using CD36/SR-B1 chimeras (132, 133), SR-B1 mutant (N173Q) (43), apoA-I mutants (134), apoA-I$^{-/-}$ HDL particles (135, 136), and a chemical inhibitor of selective CE transport (137), it appears that initial binding of HDL to cell surface-associated SR-B1 and subsequent selective CE transport to cells are independent processes (39). The selective uptake process itself can be broadly divided into three steps: *1*) binding of cholesterol-rich donor lipoprotein particles to the loop domain of SR-B1; *2*) SR-B1-mediated transfer of CEs from the lipoprotein particles to the plasma membrane; and *3*) the release of the cholesterol-poor lipoprotein particles back into the circulation (37, 39, 138). Among these steps, the mechanism by which SR-B1 facilitates the transfer of CEs to the plasma membrane is not fully understood. Rodrigueza et al. (139) provided evidence in favor of a model in which SR-B1 forms a nonaqueous channel between lipoprotein particles and the cell membrane through which CEs move down in a concentration gradient manner. The validity of this model is supported by the recent report of the high-resolution crystal structure of the extracellular domain of the lysosomal

LIMP-2, and by modeling the structure of SR-B1 and its other family member, CD36 (124, 140). Importantly, the crystal structure shows the existence of a large cavity or tunnel that traverses the entire length of the molecule. The dimensions (with 5 × 5 Å opening and 22 × 11 × 8 Å cavity) of this hydrophobic tunnel are sufficient to accommodate CE and free cholesterol (FC) molecules, and SR-B1 mutagenesis studies provided direct support for the involvement of this hydrophobic tunnel as a facilitator of cholesterol ester transfer from bound donor HDL particles to the cell surface plasma membrane (124, 140, 141). This is further supported by the observation that an inhibitor of selective HDL-CE uptake binds covalently to Cys384, which is located in the lumen of the tunnel. It is predicted that binding of the inhibitor to this site would block cholesterol (ester) transport (120, 141). Once selectively delivered to the cell, the intact CEs are either transported to lipid droplets for storage (12) or hydrolyzed extra-lysosomally by neutral cholesteryl esterase (39, 80) (142–145) to provide cholesterol substrate for product formation or reesterification. Previously, we provided evidence that hormone-sensitive lipase serves as the neutral cholesterol esterase in adrenal cells and participates in CE turnover and steroidogenesis (131, 146).

Besides CEs, SR-B1 also mediates the selective uptake of other lipid components of receptor bound HDL particles, including FC, triglycerides (TGs), phospholipids, and α-tocopherol (38, 39, 147). Nonpolar FC, CE, and TG are transported five to ten times more efficiently than more polar phospholipid molecules. The relative selective uptake rate constants for CE, FC, TG, and phospholipid (phosphatidylcholine) have been calculated to be 1.0, 1.6, 0.7, and 0.2, respectively (147). SR-B1 also promotes the bidirectional flux of FC between cells and lipoproteins (39, 141, 147–149). In addition, in the liver, SR-B1 functions in reverse cholesterol transport (130, 141, 150), including selective uptake of CEs from HDL into the liver (one of the later steps in reverse cholesterol transport) and biliary cholesterol secretion (the last step in reverse cholesterol transport), thus promoting conversion of hepatic HDL cholesterol (HDL-C) to bile acids (16, 79, 81). SR-B1 also alters the composition of lipid domains of plasma membranes, which then leads to changes in FC flux, changes in membrane cholesterol content, or altered physical/chemical properties of membranes (151, 152).

## OTHER MAJOR FUNCTIONS OF SR-B1

In addition to mediating the selective transport of HDL-CEs and other lipids, SR-B1 also performs many other essential functions. Besides facilitating selective cholesterol influx into cells, SR-B1 enhances the efflux of cellular cholesterol to HDL (149, 153–155). This property of SR-B1 in mediating the bidirectional flux of FC between cells and HDL is different from two other proteins involved in cellular cholesterol efflux, ABCA1 and ABCG1; ABCA1 mediates unidirectional efflux of cholesterol and phospholipids to apolipoprotein acceptors, such apoA-I and apoE (156), whereas ABCG1 facilitates unidirectional efflux of cholesterol to nascent HDL particles (157). Both gain-of-function and loss-of-function strategies in mice have established that SR-B1 determines the level of plasma-HDL-C by promoting selective transport of HDL-CE to the liver for transfer to bile and that SR-B1 is a key component of reverse cholesterol transport (158–161). Consistent with its importance in reverse cholesterol transport, several mouse models have shown that SR-B1 overexpression in the liver decreases atherosclerosis (162–165), whereas partial or total loss of SR-B1 increases atherosclerosis (166–170). Thus, SR-B1 can exert atheroprotective actions by impacting HDL metabolism and reverse cholesterol transport, mediating removal of cholesterol from macrophages via cholesterol efflux, and minimizing inflammation and oxidation (138, 150, 171). In addition, macrophage and endothelial cell SR-B1 could interfere with the development of atherosclerosis by altering cholesterol trafficking to suppress atherosclerotic lesion formation (171). Likewise, platelet SR-B1 has been implicated as a negative regulator in the development of thrombosis (138). SR-B1 signaling also helps to minimize inflammation and apoptosis, and promotes efferocytosis of apoptotic cells in atherosclerotic lesions, thus minimizing vulnerable plaque formation (171). In contrast, endothelial cell SR-B1 plays a more complex role, perhaps through involvement in LDL transcytosis, and may contribute to the development of early atherosclerotic lesions (172). SR-B1 has also been shown to regulate fertility (161, 166, 173), modulate erythrocyte development (174) and platelet function (138, 175), contribute to the pathogenesis of inflammation (175), regulate immunity (175), protect against nitric-oxide-induced cytotoxicity, mediate inducible glucocorticoid production and LPS clearance, protect against sepsis, and play a role in lymphocyte homeostasis and autoimmunity (175). SR-B1 has been implicated in some pathological processes as well. For instance, SR-B1, in concert with several viral and cellular factors, mediates hepatitis C virus entry into hepatocytes (33, 176), enhances dengue virus infection (177), mediates bacterial adhesion and bacterial invasion in cells (65), potentiates LPS-induced inflammation and acute liver and kidney injury in mice (178), and contributes to the pathogenesis of cancer and tumor progression.

## SR-B1 SIGNALING

In view of the large variety of ligands reported to bind SR-B1 and the large number of functions attributed to SR-B1 in addition to lipid uptake and efflux, the observation that SR-B1 mediated the ability of HDL to stimulate endothelial nitric oxide synthase (eNOS) in cultured endothelial cells suggested that SR-B1 might possess signaling properties (179). Although neither cytoplasmic tail of SR-B1 possesses intrinsic signaling properties, experiments identified the interaction of c-Src with SR-B1 following HDL binding (180) with downstream activation of PI3 kinase, Akt, and MAPK, resulting in phosphorylation and activation of eNOS (181). The adaptor protein, PDZK1, which interacts with SR-B1

(see below), was reported to be required for SR-B1 signaling (180); however, a mutation in the C-terminal transmembrane domain that disrupts the ability of SR-B1 to bind plasma membrane cholesterol eliminated SR-B1 signaling to eNOS without altering HDL binding, cholesterol uptake or efflux, or interaction with PDZK1 (182), suggesting that the processes are separate. Recent work suggests that the localization of SR-B1 in lipid rafts and its ability to sense plasma membrane cholesterol link it to signal transduction (183). Whether all signaling via SR-B1 is due to its function as a lipid sensor is currently unclear. In favor of functioning as a lipid sensor, cell signaling that is induced by cellular cholesterol depletion with methyl-β-cyclodextrin is dependent on SR-B1 and, specifically, its ability to bind plasma membrane cholesterol (182). Moreover, serum amyloid A binding to SR-B1 induces activation of ERK1/2 and p38 MAPKs leading to increased cytokine production (184), while serum amyloid A also promotes SR-B1-mediated cholesterol efflux (185). In addition, SR-B1 can mediate the uptake or efflux of sphingosine-1-phosphate, along with interaction of sphingosine-1-phosphate receptors with SR-B1, leading to activation of signaling via sphingosine-1-phosphate receptors (186, 187). Likewise, SR-B1-mediated efferocytosis occurs through the binding of phosphatidylserine with induction of Src phosphorylation and activation of PI3 kinase and Rac1 leading to clearance of apoptotic cells (188). Other downstream signaling pathways have also been suggested to be involved in SR-B1 signaling because apoA-I binding to SR-B1 has been reported to stimulate AMP-activated protein kinase (189). On the other hand, CpG binds to SR-B1 and promotes pro-inflammatory cytokine production by triggering calcium entry via phospholipase C-mediated activation of TRPC3 channels in a Toll-like receptor-independent process (190) without evidence for cellular lipid changes, though it is possible that alterations in membrane lipids occur.

## REGULATION OF HEPATIC SR-B1

SR-B1 mRNA and protein are primarily expressed within the liver in hepatocytes (138, 191). Hepatic SR-B1 is subject to both transcriptional and posttranscriptional regulation. Several different transcription factors, including nuclear receptors (PPARγ, HNF4α, PPARα, LXRα, LRH-1, and FXR) (191, 192), estrogen receptor (192, 193), and SREBPs, control SR-B1 transcription (see above). A variety of dietary components, hormones, metabolites, and pharmacological agents also modulate gene transcription of hepatic SR-B1 (192).

Though under transcriptional control, hepatic SR-B1 is primarily regulated posttranscriptionally by a key scaffolding protein termed PDZK1 or NHERF3. PDZK1/NHERF3 belongs to the NHERF family, which consists of three additional proteins, namely, NHERF1, NHERF2, and NHERF4 (194). All four NHERFs contain multiple "PDZ" domains [postsynaptic density (PSD-95/SAP90), the *Drosophila* septate junction protein disc-large (Dlg), and the tight junction protein, zona occludense-1 (ZO-1)] (193). NHERF1 (*SLC9A3R1* gene, also called EBP50) and NHERF2 (*SLC9A3R2* gene, also called E3KARP) consist of two tandem PDZ domains and a C-terminal MERM (merlin-ezrin-radixin-moesin) domain, which binds to the actin-associated proteins, ezrin, radixin, moesin, and merlin (194), whereas NHERF3 (*PDZK1* gene, also called PDZK1, CLAMP) and NHERF4 (*PDZD3* gene, also called IKEPP) contain four tandem PDZ domains (193). PDZ domains are protein-protein interaction modules that generally consist of ∼90 amino acid residues and usually bind to a specific peptide sequence located at the extreme C terminus of a target; although in some cases, the target peptide sequence has an internal location. NHERF proteins bind a variety of membrane transporters and receptors, and modulate membrane localization, interaction with other proteins, formation of signaling complexes, and maintenance of microvilli on the apical surface of endothelial cells (193, 194).

Ikemoto et al. (195) and Silver (196) initially demonstrated that the extreme C terminus of SR-B1 interacts with the first N-terminal PDZ domain of PDZK1/NHERF3/CLAMP. Gene deletion studies demonstrated that the level of hepatic SR-B1 was reduced by >95% in PDZK1-null mice and plasma HDL-C was significantly elevated (197) to a value similar to that observed in SR-B1 knockout mice (158). Further studies demonstrated that PDZK1 regulates hepatic SR-B1 stability and steady state levels, but does not directly affect the ability of SR-B1 to transport HDL-CE (197–201). Furthermore, it was demonstrated that overexpression of the first PDZ domain of PDZK1 increases hepatic SR-B1 abundance and affects localization in both wild-type and PDZK1 knockout mice, but was not completely effective in restoring normal SR-B1 function in PDZK1-null mice (199). Likewise, overexpression of the first three PDZ domains of PDZK1 in PDZK1-deficient mice partially restored cell surface localization of hepatic SR-B1 and selective HDL-CE uptake, but failed to fully restore hepatic SR-B1 abundance and cell surface localization, as compared with the control (200, 201). Only full-length native PDZK1 or a mutant missing the C-terminal PDZ domain-binding motif of PDZK1 in PDZK1-null mice fully restored normal SR-B1 abundance and selective HDL-CE transport function (199). Interestingly, steroidogenic tissues express very low levels of PDZK1 (197, 202), and its deficiency has no apparent effect on SR-B1 levels or its selective HDL-CE transport function in steroidogenic tissues (see below) (197). A small PDZK1-associated protein, SPAP/DD96/MAP17, is also involved in the regulation of PDZK1 (203), and hepatic DD96 overexpression can alter plasma HDL-C levels (204). One recent report suggests that microRNAs 185, 96, and 223 negatively regulate the expression of hepatic SR-B1 at a posttranscriptional level (110).

## REGULATION OF STEROIDOGENIC SR-B1

The selective uptake pathway was shown to be the major supplier of exogenous cholesterol for storage or steroidogenesis in steroidogenic cells of the adrenal gland (3, 7, 9, 11, 142, 205–207), ovary (3, 6–8, 205, 208–210), and, under certain conditions, testicular Leydig cells (211–214) in rodents, prior to the discovery of SR-B1. SR-B1 was then

cloned and identified as the receptor responsible for selective cholesterol uptake (26–28). Given this, it is not surprising that, in addition to liver (115), SR-B1 is abundantly expressed in the steroidogenic cells of the adrenal gland (84, 115), ovary (83, 115), and hormone-stimulated testis (14, 115). SR-B1 in steroidogenic tissues is regulated transcriptionally, posttranscriptionally, and posttranslationally. Trophic hormone-stimulated cAMP and activation of PKA are the key pathways responsible for regulating SR-B1 gene transcription in the adrenal gland (84, 115, 202, 215–218), ovary (12, 32, 83, 219–221), and testis (14, 86, 216, 217).

In the rodent adrenal gland, SR-B1 is localized on the cell surface of fasciculata-reticularis cells (84, 115, 215). Adrenal SR-B1 mRNA and protein expression is increased by treatment of mice or rats with ACTH and suppressed by treatment of animals with the synthetic corticosteroid, dexamethasone (which inhibits the hypothalamic pituitary axis and decreases ACTH secretion) (84, 98, 202, 215). Likewise, cAMP treatment of mouse adrenocortical cells (Y1-BS1) (217) and primary human adrenocortical cells (217) upregulates SR-B1. Besides ACTH, adrenal glomerulosa cell lines respond to angiotensin II stimulation with increased expression of SR-B1 mRNA and protein levels (222). Adrenal SR-B1 mRNA and protein levels are upregulated in apoA-I knockout mice, but not in mice deficient in apoA-II, LDL receptor, or apoE, or in CE transfer protein transgenic mice (223). Likewise, adrenal SR-B1 mRNA and protein levels are also increased and the content of stored CEs decreased in female hepatic lipase knockout mice (223). Depletion of adrenal cholesterol ester stores is associated with increased expression of SR-B1 in an ACTH-independent manner in vivo and in cultured Y1-BS1 adrenocortical cells (218). As additional evidence for non-ACTH regulation of adrenal SR-B1 expression, SR-B1 mRNA levels are increased in adrenals from corticosterone-insufficient Crh (−/−) mice, whereas corticosterone replacement by oral administration inhibited SR-B1 gene expression in these mice (224). Adrenals from mice deficient in lecithin:cholesterol acyltransferase exhibit elevated levels of SR-B1 mRNA and protein (225). A previous study (84) from our laboratory reported that treatment of rats with ACTH or 17α-ethinyl estradiol (17α-E2) leads to increased expression of SR-B1 in the adrenal gland (especially in the microvillar compartment of adrenocortical cells), whereas dexamethasone treatment results in decreased levels of SR-B1. These changes in SR-B1 levels are also accompanied by striking ultrastructural changes in the adrenocortical cell microvillar compartment, i.e., microvillar area and microvillar channel formation and complexity are dramatically increased in response to ACTH or 17α-E2 treatment, whereas these structures are decreased significantly following dexamethasone treatment.

Granulosa cells, isolated from mouse (226), rat (12), pig (221), and cow (32) and cultured under basal conditions, exhibit very little or no expression of SR-B1 mRNA and protein, but expression is increased many fold following luteinization of the cells with gonadotropins or cAMP. In the rat ovary, insulin and trophic hormone LH/hCG stimulate the expression of SR-B1 in theca-interstitial cells and increase intracellular cholesterol, which is subsequently mobilized for androgen production (220, 227). Similarly, treatment of immature rats with PMSG/eCG or PMSG/eCG + hCG also results in the induction of SR-B1 mRNA by several fold, especially in theca interna cells (29, 219), whereas prostaglandin F2α treatment downregulates SR-B1 mRNA expression (219). Estrogen treatment of normal cycling rats also induces SR-B1 protein expression in luteal cells of the ovary (115). Using a novel hormone-desensitized rat ovarian model, it was demonstrated that HDL binding, SR-B1, and selective HDL-CE uptake are tightly linked (83). Moreover, immunostaining at the light microscope level indicated strong expression of SR-B1 specifically on the surface of luteal cells in the luteinized and desensitized ovary. Immunoelectron microscopy further demonstrated that SR-B1 protein was associated with microvilli and microvillar channels of the luteal surface (83), further confirming that these structures represent a cell surface compartment that is specialized for the selective uptake of lipoprotein-derived cholesterol into steroidogenic cells for hormone production or storage. Normal rat Leydig cells under basal conditions (14, 115) show only negligible expression of SR-B1. However, both mRNA and protein levels of SR-B1 in rodent Leydig cells are dramatically induced following chronic treatment of animals with hCG (14, 115). Interestingly, in contrast to the adrenal gland and ovary, hormone-induced SR-B1 is not localized in surface microvilli, but is present in an elaborate and complex channel system within the cytoplasm of the Leydig cells (14). Leydig tumor cell lines, such as MA-10 and MLTC-1, express significant levels of basal SR-B1 and hormonal/cAMP treatment further upregulates its expression (86, 111, 228). R2C Leydig tumor cells, which constitutively secrete large amounts of steroids, also show extremely high basal levels of SR-B1 protein and mRNA levels, and cAMP treatment modestly increases their levels further (86).

It is becoming clear that the physical form of SR-B1 also plays a key role in the expression and function of SR-B1. It is well-known that hormonal changes in tissues (which alter the expression of SR-B1, alter selective CE uptake in the same tissues, and correspondingly produce architectural changes in the cell surface of affected cells) also show changes in dimerization[2] of SR-B1 in cell or tissue samples. In one of the earliest demonstrations of protein-protein interaction involving SR-B1, we showed (by Western blotting) that SR-B1 exists as homodimers in 17α-E2-primed and microvilli-enriched rat adrenal plasma membranes (84). In subsequent studies, it was demonstrated that SR-B1 exists in dimeric and higher order oligomeric forms in all cells and tissues that are active in "selective" uptake of HDL-CEs [e.g., hormone-activated steroidogenic tissues (such as mouse and rat adrenals, testis, and ovary), steroidogenic-derived cells (such as rat ovarian luteal cells, mouse adrenal Y1-BS1 cells, rat Leydig R2C tumor cells, and MLTC-1 Leydig tumor cells), liver from SR-B1 transgenic mice, SR-B1-transfected nonsteroidogenic and steroidogenic cells (such as HEK-293, Y1-BS1, CHO, and COS cells), or primitive Sf9 insect cells programmed to express SR-B1] (116). Early functional evidence for SR-B1 dimerization came from the observation that, in normal rat adrenal

tissue, SR-B1 exits primarily in a monomeric form with some dimer formation. ACTH stimulation increased the dimerization of SR-B1 in the adrenal along with increased selective HDL-CE uptake, and dexamethasone-induced suppression of ACTH led dramatically to the loss of SR-B1, SR-B1 dimers, and selective HDL-CE uptake (84). These results are coupled with striking architectural changes of the microvillar compartment at the adrenocortical cell surface, and suggest that SR-B1 dimers may, in a very basic way, be associated with SR-B1 sites of action and function.

As noted above, PDZK1/NHERF3 regulates hepatic SR-B1 stability and steady-state levels, but does not directly affect the ability of expressed SR-B1 to mediate HDL-CE transport. However, steroidogenic tissues express very low levels of PDZK1, and its deficiency has no apparent effect on SR-B1 levels or HDL-CE transport function in steroidogenic tissues. In contrast, NHERF1 and NHERF2 mRNA and protein are expressed at varying levels in model steroidogenic cell lines and the adrenal gland, with only low expression of NHERF4 (202). Using several different mechanistic approaches, our laboratory recently established that NHERF1 and NHERF2 specifically interact with SR-B1 in liver and steroidogenic tissues/cells and reduce SR-B1 levels via novel translational/posttranslational mechanisms and, consequently, negatively impact SR-B1-mediated selective HDL-CE uptake and HDL-supported steroidogenesis (202). Recently, a mouse line carrying a 507Ala/STOP mutation of the SR-B1 gene that produces a truncated receptor (SR-B1ΔCT) was generated (88). Results show a significant decrease in the level of SR-B1 in steroidogenic cells (adrenal cortical cells, ovarian cells, and Leydig cells), providing additional evidence for the function of non-NHERF3 adaptors for SR-B1 in steroidogenic tissues.

Salt-inducible kinase (SIK1) is a serine/threonine kinase that is a member of the stress- and energy-sensing AMPK family of kinases (229). Its expression is rapidly induced in Y1 adrenal cells in response to ACTH and was presumed to act as a repressor of adrenal steroidogenesis. Recently, it was demonstrated that SIK1 in fact stimulates adrenal steroidogenesis by modulating the selective HDL-CE transport activity of SR-B1. Evidence showed that overexpression of SIK1 increased cAMP-stimulated and SR-B1-mediated selective CE uptake in steroidogenic cell lines without impacting SR-B1 protein levels. Conversely, knockdown of SIK1 resulted in attenuation of cAMP-stimulated selective HDL-CE uptake. It was further observed that SIK1 forms a complex with SR-B1 by interacting with its cytoplasmic C-terminal domain and catalyzes the phosphorylation of this domain at Ser493. Finally, loss-of-function and gain-of-function strategies demonstrated that SIK1 increased SR-B1-mediated selective delivery of HDL-derived cholesterol. This was the first report demonstrating that SIK1 functions as a positive modulator of selective cholesterol transport function of SR-B1.

## *SCARB1* GENE POLYMORPHISM

Studies in animal models have established a role for SR-B1 in lipid homeostasis, specifically involving HDL-C and apoB-containing lipoprotein metabolism. However, the plasma lipoprotein profiles of rodents and humans are different in that the bulk of plasma cholesterol in adult humans is in LDL and VLDL particles, whereas mice utilize HDL as the major cholesterol-carrying lipoprotein in plasma (230). The involvement of SR-B1 in regulating lipoprotein metabolism in humans has begun to be clarified by examining the association of gene polymorphisms in *SCARB1* with lipoprotein levels. In an early study in Spanish Caucasians, single-strand conformation polymorphism analysis together with direct sequencing following PCR amplification of interested regions identified five variants, one each at introns 3 and 5 and three each at exons 1, 8, and 11. Further analysis showed that the variants at exon 1 were significantly associated with increased HDL-C and lower LDL cholesterol values, as well as TGs and BMI, in men (231), consistent with the involvement of SR-B1 in the metabolism of both lipoprotein classes in humans. Subsequent population-based genetic studies of SR-B1 gene polymorphisms, including the Framingham Study (232) and the Rancho Bernardo Study (233), not only confirmed the association of common *SCARB1* variations with plasma lipid profiles (234, 235), but also expanded the populations to include women (234), multi-ethnics (236–239), diabetics (232), and subjects with heterozygous familial hypercholesterolemia (240), as well as populations with subclinical atherosclerosis (241). Recently, a patient with a missense mutation for *SCARB1* S129L was shown to have high levels of both HDL-C and lipoprotein (a) (242). Subsequent analysis of two cohorts identified rare or uncommon missense or splice site mutations in *SCARB1*. Further analysis of four *SCARB1* variants in functional studies in vitro (c.386C>T, c.631-14T>G, c.4G>A, and c.631-53$^{m}$C>T and c.726+55$^{m}$CG>CA) demonstrated decreased receptor function, providing a functional mechanism for the association of *SCARB1* gene variants with the high HDL-C and high lipoprotein (a) phenotype (242).

In humans, four more mutations in *SCARB1* have now been reported. A family with a single loss-of-function mutation in P297 to S was identified in 2011 (243), and the mutant carrier had increased HDL-C and reduced cholesterol efflux from macrophages. The carriers also displayed decreased adrenal steroidogenesis and changes in platelet function; however, they did not have evidence for significant atherosclerosis. Almost at the same time, a separate study identified two novel mutations in the *SCARB1* gene, S112F and T175A, and showed that these mutations are associated with high HDL-C (244). Most recently, through targeted sequencing of the coding region of lipid-modifying genes in a population with extremely high HDL-C levels, a homozygote subject harboring a P376L missense mutation in the *SCARB1* gene was identified (245). Carriers of this P376L mutation have increased risk of coronary heart disease, even though they have very high plasma HDL-C levels.

## CONCLUSIONS

In conclusion, SR-B1 is a multiligand membrane receptor that functions as a physiologically relevant HDL receptor to selectively deliver HDL-C to cells, but it has a number of other functions. SR-B1 is primarily expressed in liver

and steroidogenic cells, where the SR-B1/selective pathway provides the bulk of the cholesterol needed for steroidogenesis in rodents. The expression of SR-B1 is regulated by hormones, and its function is regulated by many posttranslational interactions and modifications. Structurally, SR-B1 forms a hydrophobic tunnel within the plasma membrane, which appears to facilitate the selective cellular influx and efflux of lipid molecules, as well as other molecules, including vitamins, viruses, and apoptotic cells. SR-B1 polymorphism analysis and identification of mutations in human SR-B1 have confirmed the involvement of SR-B1 in regulating lipoprotein metabolism in humans.

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