0163-769X/03/$20.00/0
Printed in U.S.A.

Endocrine Reviews 24(3):357–387

doi: 10.1210/er.2001-0037

The Role of the High-Density Lipoprotein Receptor SR-BI in the Lipid Metabolism of Endocrine and Other Tissues

ATTILIO RIGOTTI, HELENA E. MIETTINEN, AND MONTY KRIEGER

Departamento de Gastroenterología (A.R.), Facultad de Medicina, Pontificia Universidad Católica, Santiago, Chile; Department of Medicine (H.E.M.), University of Helsinki, Helsinki 00290, Finland; and Biology Department (M.K.), Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

Because cholesterol is a precursor for the synthesis of steroid hormones, steroidogenic tissues have evolved multiple pathways to ensure adequate supplies of cholesterol. These include synthesis, storage as cholesteryl esters, and import from lipoproteins. In addition to endocytosis via members of the low-density lipoprotein receptor superfamily, steroidogenic cells acquire cholesterol from lipoproteins by selective lipid uptake. This pathway, which does not involve lysosomal degradation of the lipoprotein, is mediated by the scavenger receptor class B type I (SR-BI). SR-BI is highly expressed in steroidogenic cells, where its expression is regulated by various trophic hormones, as well as in the liver. Studies of genetically manipulated strains of mice have established that SR-BI plays a key role in regulating lipoprotein metabolism and cholesterol transport to steroidogenic tissues and to the liver for biliary secretion. In addition, analysis of SR-BI-deficient mice has shown that SR-BI expression is important for α-tocopherol and nitric oxide metabolism, as well as normal red blood cell maturation and female fertility. These mouse models have also revealed that SR-BI can protect against atherosclerosis. If SR-BI plays similar physiological and pathophysiological roles in humans, it may be an attractive target for therapeutic intervention in cardiovascular and reproductive diseases. (*Endocrine Reviews* 24: 357–387, 2003)

Abbreviations: ABC, ATP-binding cassette; apo, apolipoprotein; C/EBP, CCAAT/enhancer-binding protein; CETP, cholesteryl ester transfer protein; CLAMP, carboxy-terminal linking and modulating protein; CNS, central nervous system; E, embryonic development; eNOS, endothelial NO synthase; FH, familial hypercholesterolemia; FXR, farnesoid X receptor; HDL, high-density lipoprotein; HMG CoA, hydroxymethylglutaryl coenzyme A; IDL, intermediate-density lipoprotein; KO, knockout; LCAT, lecithin:cholesterol acyltransferase; LDL, low-density lipoprotein; LDLR, LDL receptor; LRH-1, liver receptor homolog 1; LIMPII, lysosomal integral membrane protein II; LPS, lipopolysaccharide(s); LXR, liver X receptor; NO, nitric oxide; PPAR, peroxisome proliferator-activated receptor; RBC, red blood cell; SF-1, steroidogenic factor-1; SR-BI, scavenger receptor class B type I; SR-BIatt, attenuated SR-BI; SRE, sterol regulatory element; SREBP, SRE-binding protein; VLDL, very LDL.

I. Introduction

CHOLESTEROL METABOLISM IS intimately associated with the proper functioning of the endocrine system. In addition to the housekeeping functions of cholesterol in all mammalian cells as a key contributor to membrane structure and function, it is the precursor for cytochrome P450 cholesterol side chain cleavage enzyme-initiated synthesis of steroid hormones. (Cholesterol can also be converted to bile acids in the liver and vitamin D in the skin and kidney.) Thus, it is not surprising that endocrine, especially steroidogenic, tissues and other cell types have evolved multiple pathways to ensure the adequate provision of this crucial lipid.

Cells can obtain cholesterol by endogenous synthesis from

mevalonate and isoprenoid precursors (1). An important rate-controlling step in biosynthesis is catalyzed by the enzyme hydroxymethylglutaryl coenzyme A (HMG CoA) reductase. Hydrolysis of cholesteryl esters stored in cytoplasmic lipid droplets can also provide cholesterol. Although most body cells have relatively small cholesteryl ester pools, cytoplasmic cholesteryl ester stores are especially abundant in steroidogenic cells, providing a ready supply of cholesterol for rapidly inducible steroidogenesis. Additionally, cells use surface receptors to extract exogenous cholesterol from the lipoprotein particles that transport this water-insoluble molecule through the aqueous circulatory system (2). In fact, circulating lipoproteins are a major physiological source of cholesterol for steroidogenic cells. Plasma lipoproteins play a critical role not only in normal cholesterol homeostasis, but also in pathophysiological states such as atherosclerotic cardiovascular disease [increased risk associated directly with the plasma concentrations of low-density lipoprotein (LDL) and inversely with those of high-density lipoprotein (HDL)] (3, 4). Here, we will review the role of the scavenger receptor class B type I (SR-BI), the first HDL receptor to be characterized, in the cellular metabolism of lipoproteins and its relevance for body lipid homeostasis and disease.

II. Lipoprotein Metabolism

Plasma lipids, *i.e.*, mainly cholesterol, triglycerides, and phospholipids along with low levels of other hydrophobic compounds such as vitamin E, are carried in the blood by water-soluble lipoproteins. Lipoproteins have a polar outer shell of protein and phospholipid and inner core of neutral lipid. The largest lipoprotein particles are chylomicrons, which are synthesized in the intestine. Dietary fat and lipid secreted via bile into the gastrointestinal lumen are absorbed and packaged into chylomicrons containing triglycerides as their major core lipid component and apolipoproteins (apo)B_{48} and apoE as key major protein constituents. Chylomicrons are secreted into lymph, and, after their entrance into the bloodstream, their core triglycerides are hydrolyzed by lipoprotein lipase (LPL), an enzyme bound to the luminal surfaces of capillary endothelial cells located in fat and muscle tissue. Hydrolysis of triglycerides reduces the volume of the lipoprotein core. Hydrolysis also results in the release of excess surface shell components, *i.e.*, phospholipids, unesterified cholesterol, and exchangeable apolipoproteins, and their transfer to other circulating lipoproteins, especially to circulating HDL. The residual chylomicron particles remaining in the circulation after lipolysis are called chylomicron remnants, which are rapidly taken up by the liver by receptor-mediated endocytosis (reviewed in Ref. 5).

Very LDL (VLDL) are triglyceride-rich lipoproteins whose major apolipoprotein components include apoB_{100} (in rodents, also apoB_{48}) and apoE. VLDL is synthesized by hepatocytes and secreted into the blood. As is the case for chylomicrons, VLDL triglycerides are hydrolyzed by LPL, giving rise to smaller intermediate-density lipoprotein (IDL) particles and excess surface components that can be transferred to other lipoproteins. IDL is either cleared from the circulation by hepatic endocytosis or, through the action of hepatic lipase and cholesteryl ester transfer protein (CETP), further converted to LDL (reviewed in Ref. 5). LDLs are the major carriers of cholesterol (as cholesteryl esters) in humans, but normally there is very little LDL in rodents that lack CETP. LDL is removed from the circulation by LDL receptor (LDLR)-mediated endocytosis, in which LDL is internalized and delivered to lysosomes for degradation (see below). Most LDLR activity, and thus clearance of plasma LDL, occurs in the liver.

HDLs are not a single macromolecular entity, but rather a group of lipoprotein particles containing nearly equal amounts of lipid and protein that has been subclassified according to physical properties and apolipoprotein composition (5–8). The major apolipoproteins of HDL are apoA-I and apoA-II (with the minor components apoA-IV, apoC, apoD, and apoE; Refs. 6–8). Both of these apolipoproteins play structural roles and serve as regulators of HDL metabolism (6–8). In some cases, the apolipoproteins are involved in the recognition of HDL by cell surface receptors. There are three major classes of HDL particles: 1) discoidal particles comprising phospholipids and apoA-I, which are present only transiently in the plasma; 2) small, very lipid-poor apoA-I/phospholipid particles, called pre-β HDL because of their electrophoretic mobilities, that are present in low concentrations in the plasma; and 3) the most abundant, α-HDLs, which are large spherical particles with neutral lipid cores and two or more apolipoproteins on their outer shells. α-HDLs are comprised of two major subpopulations differing in their relative contents of apoA-I and apoA-II; these are lipoprotein A (LpA)-I HDL, which contains apoA-I only, and LpA-I:A-II HDL, which contains both apoA-I and apoA-II.

HDL metabolism is complex, involving several HDL-remodeling enzymes, lipid transfer proteins, and cell surface receptors (reviewed in Refs. 6–18). HDL originates as discoidal particles secreted by the liver and intestine or as by-products of triglyceride-rich lipoprotein metabolism (release of surface components during lipolysis). These nascent HDL particles contain mostly apoA-I and phospholipids. They apparently mature into spherical HDL particles primarily by incorporation of unesterified cholesterol and phospholipids from cells followed by esterification of cholesterol. The transfer of cellular lipids to nascent HDL requires activity of the ATP-binding cassette (ABC) A1 transporter, and its absence results in the HDL deficiency disease called Tangier disease. The unesterified cholesterol incorporated into plasma HDL is converted to cholesteryl esters by the plasma enzyme lecithin:cholesterol acyltransferase (LCAT). Esterification creates an unesterified cholesterol concentration gradient between HDL and cell membranes and is considered critical for efficient cholesterol efflux from cells to HDL. In species that express plasma CETP, a significant fraction of HDL cholesteryl ester is transferred to other plasma lipoproteins (*e.g.*, VLDL, IDL, and LDL) for further transport, primarily to the liver (9, 10). Thus, a substantial fraction of the plasma HDL cholesterol is indirectly delivered to the liver via hepatic endocytic receptors for IDL and LDL. In rodents and rabbits, and probably in humans, there are additional pathways for

HDL lipid transport in which HDL directly delivers its cholesteryl esters to cells.

Although cellular endocytic uptake of HDL has been described (reviewed in Ref. 19), both *in vitro* and *in vivo* studies have established that a key mechanism for the direct delivery of HDL cholesterol to cells is fundamentally different from the classic receptor-mediated endocytic pathway initially described for the LDLR (Refs. 20–22; also reviewed in Ref. 23). Instead, receptor-mediated HDL binding to the cell surface results in the transfer of its cholesteryl esters to the cell and the subsequent release of the lipid-depleted HDL back into the extracellular fluid rather than the lysosomal degradation of the particle. This novel cellular mechanism, which can extract cholesteryl esters from LDL as well as HDL, is called selective lipid uptake. This pathway appears to involve temperature-dependent reversible incorporation of HDL cholesteryl ester into the plasma membrane followed by a process in which cholesteryl ester molecules are irreversibly internalized and subsequently hydrolyzed through a nonlysosomal pathway (24–32). The lipid-depleted HDL particles released from cells after selective lipid uptake have the potential for reacquiring cellular cholesterol from peripheral tissues as described above, or they can be catabolized by the kidney (33) as a consequence of glomerulofiltration and subsequent reabsorption and degradation in the proximal tubules by a cubilin-associated endocytic pathway (34, 35). In rats, the liver removes 60–70% of HDL cholesteryl esters from plasma via the selective uptake pathway (Refs. 20 and 33; also reviewed in Ref. 23), a process that appears to be efficiently coupled to biliary lipid secretion (reviewed in Ref. 36). At least in rodents, selective uptake of HDL cholesterol also plays an important role in the transport of cholesterol to steroidogenic tissues (adrenal gland, ovary, and testes; Refs. 20–22 and 37–39), providing cholesterol as substrate for steroid hormone synthesis and for storage in cytoplasmic cholesteryl ester droplets. For example, in the rodent adrenal gland, selective uptake accounts for 90% or more of the cholesterol destined for steroid hormone production (40).

The pathway by which cholesterol is removed from peripheral cells and transported via plasma lipoproteins, such as HDL, into the liver for further metabolism (*e.g.*, VLDL formation, bile acid synthesis, and biliary secretion) is essential for cholesterol homeostasis. This is because peripheral cells (apart from low levels of catabolism in steroidogenic and skin cells) are not able to degrade cholesterol. This pathway, known as reverse cholesterol transport (41), is likely to be responsible for some of the antiatherogenic activity of HDL.

III. Lipoprotein Receptors

To secure an adequate supply of cholesterol to cells, multiple mechanisms for cholesterol uptake from plasma lipoproteins have evolved. Through the work of many investigators, but especially the pioneering studies of Brown and Goldstein (42) and their colleagues, we have a detailed picture of the cellular metabolism of LDL via the LDLR endocytic pathway and the role of LDLRs in body cholesterol transport in health and disease. Other members of the LDLR family of proteins (*e.g.*, LDLR-related protein) participate in the hepatic metabolism of chylomicron and VLDL remnants, and they also appear to have functions independent of lipid metabolism (43–45). All of these receptors process lipoproteins via clathrin-coated pit-mediated endocytosis and lysosomal degradation, which releases cholesterol for subsequent cellular metabolism. The autosomal recessive hypercholesterolemia protein, a cytosolic polypeptide with a phosphotyrosine-binding domain, was recently identified by genetic analysis of patients with defects in LDL metabolism as a regulator of LDLR-mediated endocytosis (46). It presumably influences LDLR activity by binding to the NPYX endocytic motif of the cytoplasmic region of the receptor (46).

A series of metabolic regulatory responses linked to the LDLR pathway helps ensure cellular cholesterol homeostasis. For example, increase of the intracellular cholesterol pool due to the endocytosis of LDL leads to decreased cholesterol synthesis, increased cholesterol esterification for storage, and reduced LDLR levels to prevent excessive intracellular cholesterol accumulation. Substantial progress has been made in understanding the mechanisms by which these processes are regulated via membrane-bound transcription factors known as sterol regulatory element (SRE)-binding proteins (SREBPs; Ref. 47). Furthermore, knowledge of these regulatory mechanisms contributed to the development of statin drugs, which inhibit HMG CoA reductase and consequently lower plasma LDL cholesterol levels by stimulating, via the SREBP pathway, LDLR expression. The statins represent a major breakthrough in the treatment and prevention of atherosclerotic cardiovascular disease.

About 70% of the LDLR activity is concentrated in the liver, where LDLRs remove LDL and, working together with LDLR-related protein, internalize LDL, VLDL, and chylomicron remnants from the circulation. Based on both *in vitro* and *in vivo* studies, all steroidogenic tissues from human and nonhuman mammals appear to express the LDLR pathway of lipoprotein cholesterol uptake for steroid hormone synthesis (48). If the LDLR was the sole source of sufficient amounts of cholesterol for steroidogenesis, then subjects with abnormalities in LDLR-mediated endocytosis would be expected to exhibit significantly abnormal steroid hormone production. This does not appear to be the case. Abetalipoproteinemia, which is characterized by the absence of circulating LDL, is not associated with abnormal basal plasma and urinary corticosteroids, but the response of these patients to ACTH stimulation is somewhat impaired (49, 50). Post-ACTH aldosterone and androstenedione secretion is not affected in these patients. Ovarian, testicular, and placental function of abetalipoproteinemic patients has not been exhaustively studied; however, abetalipoproteinemic females, who exhibit decreased plasma progesterone during menstrual luteal phase, have normal pregnancies (51). In addition, various reports of familial hypercholesterolemia (FH), due to LDLR deficiency, have not described major adrenal, ovarian, or testicular steroidogenic dysfunction. Plasma cortisol levels in the basal state are within normal range in heterozygous FH patients; however, plasma cortisol is reduced in homozygous FH subjects relative to controls (52–54) after ACTH administration (however, see Ref. 55). In addition, LDLR-deficient Watanabe rabbits have impaired

functional adrenal (56) and ovarian (57) reserves. Although fecundity of the Watanabe rabbit is somewhat impaired (58), no apparent other major endocrine abnormalities have been reported in these rabbits, as is the case for homozygous null LDLR knockout (KO) mice. Furthermore, female homozygous FH patients can get pregnant and give birth to normal offspring. Interestingly, adverse effects on adrenal or gonadal function have not been reported in patients with FH receiving cholesterol synthesis inhibitors (53, 59, 60). Taken together, these data suggest that alternative pathways for lipoprotein cholesterol delivery to cells might be available to supply functionally adequate amounts of lipoprotein-derived cholesterol to sustain hormone synthesis in various steroidogenic tissues.

The LDLR-independent accumulation of cholesterol in macrophages in artery walls is one of the earliest steps in atherosclerosis. It is generally thought that macrophage surface receptors that are not under cholesterol-feedback regulation and that recognize and endocytose modified lipoproteins (*e.g.*, aggregated or oxidized LDL) are essential for massive cholesteryl ester lipid droplet formation in these cells. The multiligand receptors that bind and internalize modified lipoproteins are called scavenger receptors (43, 61–63). There are now many members of a superfamily of scavenger receptors that have diverse structures, expression patterns, and functions (reviewed in Refs. 12 and 61–66). *In vivo* experiments have implicated scavenger receptor class A types I and II (SR-AI/II) and the class B scavenger receptor CD36 in atherogenesis (12, 66, 67). There is strong support for the proposal that some scavenger receptors also participate in host defense as multiligand pattern recognition receptors for pathogens (65, 66).

Using either direct binding or ligand blotting assays and a variety of preparations from tissues of different species, many laboratories have reported HDL binding activities (6, 7, 19, 68, 69). Serendipitously, SR-BI, originally identified by expression cloning because of its ability to bind modified LDL (70), was the first molecularly well characterized HDL receptor to be discovered (71). Its properties and functions are described below.

IV. Structure and Subcellular Distribution of SR-BI

The predicted sequences of SR-BI proteins from different mammalian species share 70–80% sequence identity over their 509-amino-acid lengths (Fig. 1). An alternatively spliced mRNA of SR-BI and its corresponding protein have been identified and designated SR-BII (72). SR-BI is a member of a family of structurally related proteins, called the CD36 superfamily (73), which includes the mammalian proteins CD36 (74) and LIMPII (a lysosomal integral membrane protein; Ref. 75); two *Drosophila melanogaster* proteins, emp (76) and croquemort (a hemocyte/macrophage receptor; Refs. 77 and 78); SnmP-1 (a silk moth olfactory neuron membrane protein; Ref. 79); a putative *Caenorhabditis elegans* protein (GenBank accession no. Z54270), and others. There are several similarities in the intron/exon organization of the SR-BI (80) and CD36 (81) genes. Human SR-BI was first cloned as a homolog of CD36 and LIMPII of unknown function that

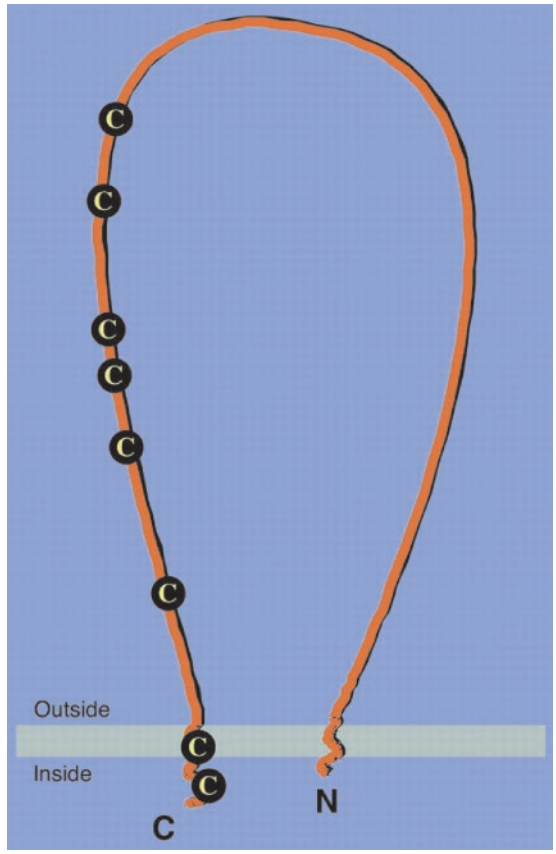

FIG. 1. Model of SR-BI. SR-BI is a 509-amino-acid glycoprotein with a large extracellular domain anchored to the plasma membrane at both the N and C termini by hydrophobic transmembrane regions that have short extensions into the cytoplasm. SR-BI is highly glycosylated on all its potential N-glycosylation sites (84, 85). SR-BI is also palmitoylated on the cysteines located at the C-terminal cytoplasmic and transmembrane domains (84, 87). SR-BI contains a well conserved set of cysteines in its carboxy-terminal half. [Reproduced with permission from M. Krieger: *J Clin Invest* 108:793–797, 2001 (372).]

mapped to chromosome 12 (73, 80) and was called CLA-1 (82). In addition, phylogenetic analysis of the CD36 gene family indicated that LIMPII, SR-BI, emp, and CD36 diverged from a common ancestor gene very early during evolution (73).

With the exception of croquemort and a potential third spliced isoform of SR-BI called SR-BIII (83), each of which has a single hydrophobic domain at the carboxy terminus (77, 83), all of the CD36 family members contain two internal hydrophobic, putative membrane-spanning domains adjacent to short cytoplasmic amino- and carboxy-terminal tails (Fig. 1). The bulk of the proteins lies between the two hydrophobic plasma membrane-anchoring domains on the extracellular side of cells and contains a set of conserved cysteines. SR-BII only differs from SR-BI in that the C-terminal 42 amino acids in the C-terminal cytoplasmic domain of SR-BI are replaced by 40 residues encoded by an alternatively spliced exon (72).

As predicted from the presence of consensus motifs for N-linked glycosylation sites in the cDNA, SR-BI is heavily N-glycosylated (84). This accounts for the difference between its mass predicted from the amino acid sequence (~57 kDa;

Ref. 81) and that observed using immunochemical methods (~82 kDa; Refs. 71 and 84). In cultured cells, SR-BI is cotranslationally modified on all of its potential N-glycosylation sites (84, 85). Some, but not all, of these N-glycosylated oligosaccharides are transformed into complex carbohydrate chains during transit through the Golgi apparatus (84). Furthermore, metabolic labeling studies have established that SR-BI is fatty acylated (84), a structural feature shared with CD36 (86). Analysis of point mutants has shown that the major sites of palmitoylation of SR-BI are cysteine residues 462 and 470 located in its carboxy-terminal transmembrane and cytoplasmic domains (87).

In cultured cells, SR-BI and SR-BII appear to be concentrated in microdomains that under certain growth conditions correspond to cholesterol and sphingolipid-enriched plasma membrane microdomains (lipid rafts) called caveolae (see below) (84, 88). For some proteins, fatty acylation can serve as a sorting signal for concentration in caveolae. However, inhibition of fatty acylation of SR-BI by simultaneous mutation of cysteines 462 and 470 has no apparent effect on SR-BI surface localization in transfected cultured cells (87). Currently, the motifs in SR-BI that determine its subcellular localization are unknown.

SR-BI is expressed in a variety of polarized epithelial cells, including hepatocytes, colangiocytes, and enterocytes. Adenovirus-mediated *in vivo* overexpression of SR-BI in murine hepatocytes results in SR-BI expression on both the apical (canalicular) and basolateral (sinusoidal) surfaces of the cells (89). Examination of normal murine liver sections for expression of endogenous SR-BI established that SR-BI is primarily located in the basolateral domain of hepatocytes (90, 91). It is also seen in the basolateral membranes of SR-BI-transfected MDCK cells (92, 93). In contrast, SR-BI is predominantly found in the apical domain of enterocytes (94, 95), the epithelial intestinal cell line CaCo2 (94), and colangiocytes (96). The marked differences in the subcellular distribution of SR-BI in polarized cells are likely to be related to important differences in sorting pathways, and possibly in the expression and function of adapter/chaperone proteins. Candidate modulators of the localization, stability, and function of SR-BI have been isolated from rat liver membrane homogenates (97). These proteins interact with the carboxy-terminal cytoplasmic domain of SR-BI. Molecular characterization of one of these proteins established that it is a soluble protein composed of multiple PDZ domains (97). This protein, called CLAMP (carboxy-terminal linking and modulating protein), recognizes SR-BI via its N-terminal PDZ domain. Coexpression of CLAMP with SR-BI in transfected cells affects the stability of SR-BI as well as the efficiency of conversion of HDL cholesteryl esters taken up via SR-BI to intracellular unesterified cholesterol (97). Furthermore, CLAMP has been proposed to be involved in determining the basolateral distribution of SR-BI in hepatocytes (97). In fact, a recent study using carboxy-terminal deletions of the SR-BI protein indicates that the CLAMP-interacting domain of SR-BI is essential for its cell surface expression in liver (98). Further studies will be required to identify the polarity and subcellular localization targeting signals in SR-BI, the role of SR-BI associating proteins such as CLAMP, and the functional consequences of the differential plasma membrane localizations of SR-BI.

V. Ligand Binding Activities of SR-BI

SR-BI is a multiligand receptor (11, 12, 14). It was initially discovered as a scavenger receptor, because of its modified (acetylated and oxidized) LDL binding activity (70, 99). SR-BI also binds hypochlorite-modified HDL (100). However, SR-BI does not bind the wide array of polyanionic molecules (*e.g.*, fucoidin, polyguanosine, carrageenan) that are all ligands of other classes of scavenger receptors (11, 12, 14, 61, 62, 64–67, 70). In addition to lipoprotein ligands (see below), cell culture ligand binding studies show that SR-BI recognizes a diverse set of ligands. SR-BI binds maleylated BSA (70), advanced glycation end product modified proteins (101), and anionic, but not zwitterionic, phospholipids in the form of liposomes (102, 103). Indeed, SR-BI and CD36 were the first molecularly well defined cell surface receptors for phosphatidylserine to be identified (102). These findings suggested that SR-BI might be able to bind senescent, damaged, and apoptotic cells with high levels of phosphatidylserine on the exofacial surface of the plasma membrane, and thus might play a role in the recognition and clearance of these cells during development, tissue remodeling, and disease (102). In fact, transfected cultured cells expressing exogenous SR-BI can bind apoptotic cells (103–107). Furthermore, SR-BI mediates binding of β-amyloid to transfected Chinese hamster ovary cells (108) and cultured microglia and brain vascular smooth muscle cells (109, 110), suggesting a potential role in Alzheimer's disease. More recently, the hepatitis C virus envelope glycoprotein E2 was reported to be a ligand for human SR-BI, suggesting its role as hepatitis C virus receptor (111). Analysis of the mechanisms by which multiple ligands with very different structures bind SR-BI indicates very complex interactions, suggesting multiple classes of binding sites (11, 12, 112).

Most of the studies of ligand binding to SR-BI have focused on native lipoproteins. The first native lipoprotein shown to bind to SR-BI with high affinity ($K_d \sim 10$ nM) was LDL (70). Before that finding, the only molecularly defined receptor for LDL was the classic LDLR (1, 2). SR-BI-mediated internalization and degradation of LDL was, however, far less efficient than that by the classic LDLR (70). Similarly, inefficient SR-BI-mediated endocytosis and degradation was observed for modified LDL (Ref. 70; however, see Ref. 99). SR-BI has also been shown to bind to VLDL (113).

Although the potential of SR-BI to function as a new "second" LDLR was intriguing, most investigations of SR-BI have been influenced by the unanticipated discovery that SR-BI was the first molecularly well defined and physiologically relevant HDL receptor to be identified (71). SR-BI binds HDL with high affinity in a calcium- and apoE-independent fashion. The ability of SR-BI to bind to several native lipoproteins suggests that it may be responsible for some of the multilipoprotein binding activities previously reported in a wide variety of cells types and tissues (6, 7, 19, 68, 69, 114). There may, however, be additional cell surface HDL receptors, and they may have diverse structures, tissue expressions, and functional activities.

As is the case for some of the other classes of scavenger receptors (43, 115), SR-BI exhibits nonreciprocal cross competition, wherein one ligand effectively blocks the binding of a second ligand, but the reverse is not the case (112). For example, HDL effectively blocks all LDL binding, whereas LDL inhibition of HDL binding is poor, relative to the K_d for LDL binding to SR-BI (71). Because of nonreciprocal cross-competition, LDL is not expected to substantially interfere with the binding of HDL to SR-BI *in vivo*. Using a method called "retroviral library-based activity dissection," Gu *et al.* (112) have identified double mutations in murine SR-BI (^{402}Glu→Arg and ^{418}Glu→Arg) that together block most of the binding of HDL to SR-BI without significantly altering LDL binding. The same method also showed that a single methionine to arginine mutation at position 158 disrupts binding to SR-BI of both HDL and LDL, but not acetylated LDL (116).

SR-BI binds spherical α-HDL. The lower the density of the α-HDL particles (larger, higher lipid content), the more tightly they bind to SR-BI (117, 118). Pre-β-HDLs are poor substrates of SR-BI (117). Several reports (117, 119) suggest that lipid-free apoA-I is also a poor substrate for SR-BI (however, see Ref. 120), whereas reconstituted discoidal complexes of phospholipid/cholesterol/apolipoprotein (*i.e.*, apoA-I, apoA-II, apoE, or apoC-III) bind more tightly to SR-BI than native spherical α-HDLs (117, 119, 121). SR-BI appears to be able to bind some lipid-free apoE, which has been reported to facilitate lipoprotein cholesterol uptake (122). The receptor binding domain is located in the amino-terminal 1–165 region of the apoE protein (121). The relative amounts of apoA-I and apoA-II in spherical HDL particles apparently influence their interactions with SR-BI, although the precise nature of the interactions is not yet clear. One report suggests that enriching plasma HDL with additional copies of apoA-II enhances its affinity for SR-BI but inhibits cholesteryl ester uptake (123). Another study reported that reconstituted apoA-I/apoA-II-containing particles exhibit decreased binding relative to particles containing apoA-I only (124). The binding of reconstituted discoidal apoA-I complexes by SR-BI requires either the amino- or carboxy-terminal amphipathic helices of apoA-I (117). These (117–119) and other (125) studies strongly suggest that the conformation/organization of apoA-I in HDL particles critically affects the nature of the interaction of the particle with SR-BI. Using phospholipid particles reconstituted with fragments of apoA-I and a model peptide, Williams *et al.* (120) have provided strong evidence that amphipathic helices play critical roles in the binding of apolipoproteins to SR-BI. This may explain the ability of SR-BI to bind to a wide variety of lipoproteins.

VI. Lipid Transfer Activity of SR-BI

A. Selective cholesterol uptake

SR-BI mediates the transfer of a variety of lipids between cells and lipoproteins. Unlike the interaction of LDL with the LDLR, the binding of HDL to SR-BI does not lead to its lysosomal degradation (71). Instead, SR-BI mediates selective lipid uptake from native lipoproteins (71). As noted above, selective lipid uptake involves the net transfer of lipids from lipoproteins to cells and the subsequent release of the lipid-depleted lipoprotein into the extracellular medium. SR-BI mediates selective uptake from HDL of cholesteryl esters (71), unesterified cholesterol (126–129), phospholipids (130), triglycerides (131), α-tocopherol (132, 133), DiI (71), BODIPY-cholesteryl ester (134), pyrene-labeled phospholipids (130), and cholesteryl ethers (often used as nonhydrolyzable analogs of cholesteryl esters; Ref. 71). The rate constant analyses of lipid transfer from reconstituted HDL to the plasma membrane of SR-BI-expressing cells have shown that the more hydrophobic lipids (*e.g.*, unesterified cholesterol, cholesteryl esters, and triglycerides) can transfer more easily than the more polar phospholipid molecules (135). The physiological relevance of SR-BI-mediated selective lipid uptake in cultured cells was first directly established using steroidogenic cells, which express high levels of SR-BI (see below), HDL binding and selective cholesterol uptake, and use HDL cholesterol for steroidogenesis. An anti-SR-BI antibody simultaneously inhibited HDL binding, selective HDL lipid uptake, and HDL cholesterol-dependent steroidogenesis in murine adrenocortical cells (136). Similar results have been reported for rat ovarian granulosa cells in primary culture (137).

Several investigators have established that selective cholesteryl ester uptake is not dependent on a single class of lipoprotein. HDL (20–31, 37–40, 138–140); reconstituted HDL-like particles prepared with apoA-I, apoC, or native or modified apoE (141); IDL (141, 142); and LDL (38, 140, 143–146) have all been shown to be sources of cholesterol for selective lipid uptake *in vitro* and/or *in vivo*. It seems likely that SR-BI is responsible for many of these activities. For example, SR-BI mediates selective uptake of cholesteryl esters from LDL (128, 146–148) and the uptake of fluorescent lipids from VLDL (113); however, the fractional transfer of surface-bound LDL-cholesteryl esters to cells via SR-BI was significantly lower compared with HDL-cholesteryl esters (149). With regard to HDL subclasses, SR-BI-mediated selective cholesteryl uptake is greater from LpA-I compared with LpA-I:A-II (150). However, it is noteworthy that recent studies provide support for the existence of additional, SR-BI-independent selective lipid uptake mechanisms, such as one facilitated by cell surface proteoglycans (151–155).

SR-BI (71, 104, 113) and its homolog CD36 (87, 148, 156) can both bind HDL with high affinity, but of the two, only SR-BI mediates efficient selective lipid uptake (87, 148). Thus, the cell surface binding of HDL is not sufficient for selective lipid uptake. SR-BI apparently directly facilitates a lipid transfer step that follows binding (two-step mechanism of selective uptake; Ref. 87). Analysis of SR-BI/CD36 chimeras established that sequences in the extracellular domain of SR-BI are sufficient to confer efficient selective lipid uptake activity on the cytoplasmic and transmembrane domains of CD36 (87, 148). However, the carboxy-terminal cytoplasmic domain of the receptor can influence the efficiency of selective lipid uptake, because SR-BII, the isoform of SR-BI with an alternative carboxy-terminal cytoplasmic domain, facilitates selective uptake less well than SR-BI (88). Analysis of the interaction of discoidal HDL particles prepared with wild-type and mutant apoA-Is with wild-type and mutant forms of

SR-BI established that, somewhat analogously to enzyme/substrate interactions, there must be productive binding of an HDL particle to SR-BI to permit subsequent efficient lipid transport (125). Inhibition of SR-BI-mediated selective lipid uptake using small molecules identified in a chemical library screen (blockers of lipid transport) also supports a mechanistic coupling between HDL binding and lipid transport (157). Furthermore, apoA-I-deficient HDL binds with high affinity to SR-BI, but does not mediate efficient lipid uptake, indicating that the HDL features required for binding to SR-BI are distinct from those properties necessary for the selective cholesterol uptake from HDL to cells (158). The molecular details of the interactions between HDL and SR-BI that result in productive binding and lipid transport remain to be defined. Similarly, the precise mechanism of lipid transport has not been elucidated. The discovery of chemical inhibitors of the selective transfer of lipids mediated by SR-BI should provide new mechanistic insights into this lipid uptake pathway (157).

Just as specialized regions in the plasma membrane (clathrin-coated pits) are required for LDLR-mediated endocytosis (1, 25), specialized surface structures may sometimes be involved in SR-BI-dependent selective lipid uptake. Under certain culture conditions, SR-BI has been localized in cell surface caveolae (84, 88). Interestingly, SR-BI stabilizes caveolin-1 protein, independently of its transcriptional control, in cultured cells but not vice versa (159). The apparent clustering of SR-BI in caveolae in cultured cells under some culture conditions raises the possibility that these or similar lipid raft-like plasma membrane domains might be relevant for SR-BI-mediated cholesterol trafficking between lipoproteins and cells (84). Indeed, caveolae appear to be the sites where the initial steps of SR-BI-mediated selective cholesterol uptake into the plasma membrane take place before irreversible internalization of cholesterol into intracellular compartments (87, 160). Furthermore, selective uptake activity in certain cells appears to correlate with levels of caveolin-1 (161), which has cholesterol binding activity (162) and has been implicated in intracellular cholesterol transport (163, 164). One study has suggested that a caveolin-containing multiprotein complex may facilitate movement of SR-BI-derived cholesteryl esters from the cell surface to intracellular compartments (165). However, other studies have shown that: 1) caveolin-1 negatively regulates SR-BI-mediated selective uptake of HDL cholesteryl esters (166); 2) SR-BI-mediated selective uptake of HDL cholesteryl esters is not affected by caveolin-1 expression (167); and 3) localization of SR-BI in caveolae or raft-like domains is not required for selective cholesteryl ester uptake (168). In murine adrenocortical cells, SR-BI was found in numerous circular and oval structures of the cell surface that appear to represent cross-sections through previously described microvilli-rich intercellular channels (Fig. 2; and Ref. 169). HDL has been shown to accumulate in these channels (170–172), and they may play an important role in the selective lipid uptake process (134, 169–172). SR-BI has been reported to: 1) be present in microvillar channels *in vivo* (39, 137); 2) induce microvillar channel formation when overexpressed in insect cells (134); and 3) play a role in the formation of microvillar channels in murine steroidogenic cells *in vivo* (173). The important question as to whether the selective uptake of lipid from HDL occurs at the cell surface, in some internal compartment followed by retroendocytosis (secretion) of the lipid-depleted lipoprotein particle, or both has not yet been unequivocally resolved (11, 12, 14, 38, 39, 93, 137, 169–171, 174). Recent studies in which purified SR-BI was reconstituted into phosphatidylcholine/cholesterol liposomes have established that SR-BI can mediate HDL binding and selective lipid uptake without the required intervention of other proteins or specialized cellular structures or compartments (175).

The abilities of various tissue-associated lipases and plasma lipid transfer proteins to remodel HDL lipid composition might play a role in modulating the ability of SR-BI to mediate selective HDL-cholesterol uptake. Among these, hepatic lipase has been proposed to participate in HDL metabolism through several mechanisms (16, 176), including selective HDL-cholesterol uptake (11, 12, 14). It has been suggested that hepatic lipase and SR-BI might act coordinately for efficient selective transport of cholesteryl esters from HDL into cells (11, 12, 14, 16, 177–179) based on the following experimental evidence: 1) hepatic lipase activity facilitates selective HDL cholesteryl ester uptake mediated by SR-BI (180, 181); 2) SR-BI (71, 182) and hepatic lipase (183, 184) are highly expressed in tissues that exhibit the highest rates of HDL-cholesterol transport through selective lipid uptake; 3) adrenal SR-BI expression is increased in hepatic lipase KO mice (177) and in rats injected with antihepatic lipase antibodies (185); and 4) the formation of unusual vesicular lipoproteins in apoE/hepatic lipase double KO mice (179). Hepatic lipase-facilitated selective HDL-cholesterol uptake is stimulated by the presence of SR-BI and is dependent on both the lipolytic and nonlipolytic (*i.e.*, hepatic lipase-mediated HDL binding to cell surface proteoglycans) functions of hepatic lipase (180). In addition, CETP remodeling of HDL, particularly in conjunction with hepatic lipase modification, apparently stimulates SR-BI-mediated selective HDL-cholesterol uptake (181, 186). Both *in vitro* and *in vivo* SR-BI-mediated selective cholesteryl ester uptake is increased after hydrolysis of HDL phospholipids by secretory group IIa phospholipase A2 (187, 188). Consistent with the importance of enzyme-dependent lipid modification of HDL on the efficiency of cholesterol transfer activity mediated by SR-BI, a higher triglyceride content of HDL decreased the ability of SR-BI to mediate selective HDL cholesteryl ester uptake (144). Furthermore, apoA-I-dependent LCAT-mediated reorganization of HDL is also important for efficient selective HDL-cholesterol uptake by SR-BI (189). Taken together, these findings show that HDL-cholesterol metabolism through the SR-BI-mediated pathway can depend on complex metabolic interactions between different HDL remodeling enzymes and their effects on the lipid composition of HDL.

The precise mechanisms for the intracellular transport of the HDL lipids taken up by SR-BI-mediated selective uptake remain mostly unknown (31). Current evidence indicates that certain lipid transfer proteins, an intact Golgi apparatus, and some cytoskeletal elements are not required for intracellular traffic of cholesterol derived from plasma lipoproteins by selective lipid uptake. However, this process seems

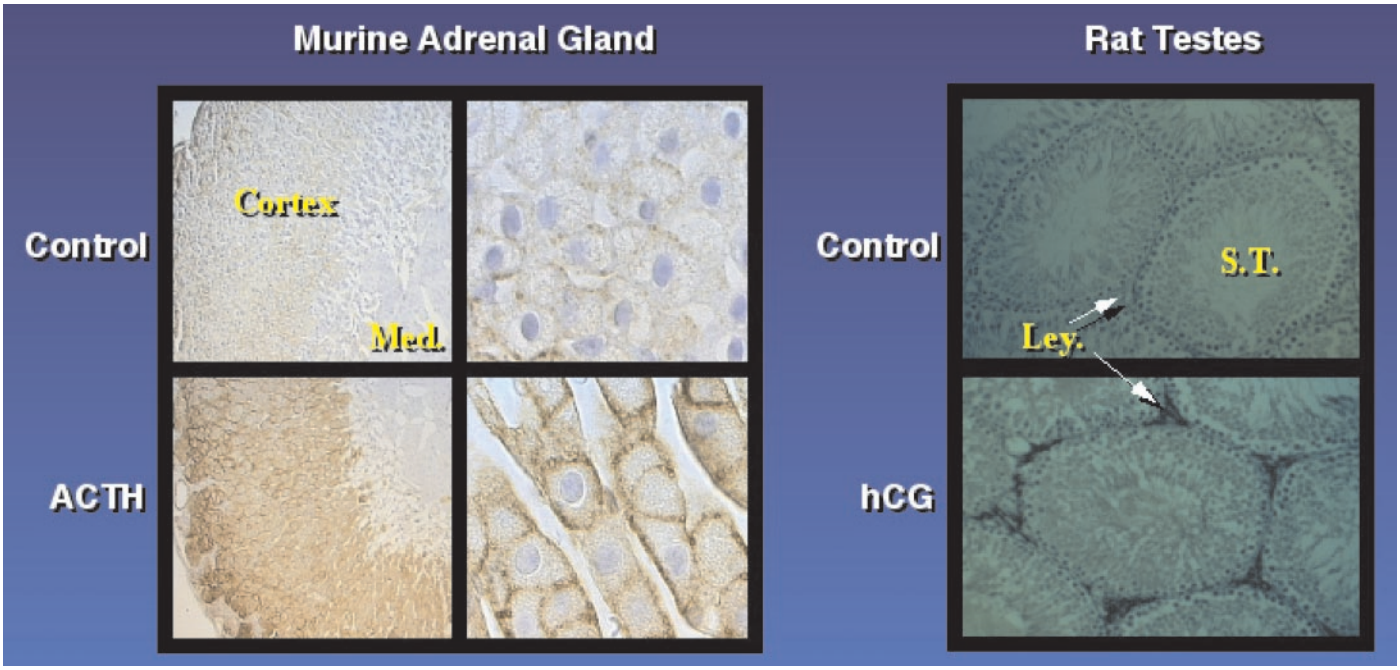

FIG. 2. Regulation of SR-BI expression in rodent steroidogenic tissues. *Left*, In murine adrenal glands, SR-BI immunostaining (*brown*) was found in the adrenal cortex but not in the medulla (Med.) of saline-treated control animals [*top panels* (169, 182)]. SR-BI staining was strongest in the outer zona fasciculata of the adrenal cortex and decreased toward the inner zona reticularis. ACTH treatment markedly increased SR-BI immunostaining in the cortex (*bottom panels*). At higher magnification, SR-BI was most abundantly detected in the plasma membrane of zona fasciculata cells, and the increased intensity of staining in the ACTH-treated mice was seen at both the sinusoidal surface and the intercellular junctions of steroidogenic cells. SR-BI was found in numerous circular and oval structures of the cell surface that appear to represent cross-sections through microvilli-rich intercellular channels (169). *Right*, In rat testes, little immunodetectable SR-BI was found in testicular steroidogenic Leydig cells of control animals [*top* (182)], but not in the seminiferous tubules (S.T.). After human chorionic gonadotropin (hCG) hormone administration, a dramatic increase in SR-BI expression was exclusively localized to Leydig cells [*bottom* (182)]. [Reproduced or derived with permission from A. Rigotti *et al.*: *J Biol Chem* 271:33545–33549, 1996 (169); and K. Landschulz *et al.*: *J Clin Invest* 98:984–995, 1996 (182).]

to be somewhat energy-dependent and mediated by *N*-ethylmaleimide-sensitive protein(s) that are yet to be identified (31). The role of the hepatic neutral cholesteryl ester hydrolase (reviewed in Ref. 190) as well as cholesterol-rich carrier vesicles or protein complexes (165) in controlling the availability and traffic of unesterified cholesterol derived from the uptake of HDL cholesteryl esters by SR-BI deserves to be explored. Indeed, the generation of unesterified cholesterol after delivery of cholesteryl esters from HDL to cells via SR-BI involves cell type-specific neutral cholesteryl ester hydrolases (32). In addition, CLAMP modulates the efficiency of conversion of HDL cholesteryl esters taken up via SR-BI to intracellular unesterified cholesterol (97). A caveolin and annexin II-containing complex may in some cases be involved in the movement of SR-BI-derived cholesteryl esters from the plasma membrane to intracellular sites (165). Further studies of the detailed molecular mechanism(s) of intracellular cholesterol traffic linked to selective cholesterol uptake will provide new insights to the understanding of this pathway for lipoprotein metabolism.

B. Cholesterol efflux

The discovery of SR-BI-mediated selective lipid uptake (influx) raised the possibility that SR-BI might be able to mediate another step in the reverse transport process, cholesterol efflux from cells to appropriate acceptors in the extracellular fluid (11, 89). Consistent with this proposal were the observations that: 1) caveolae, the plasma membrane domains in which SR-BI appears, at least under some conditions, to be concentrated in cultured cells, have been proposed to be major sites of cholesterol efflux from cells (191); and 2) SR-BI expression levels in different cell lines correlate with rates of unesterified (free) cholesterol efflux to HDL in those cells (126). The ability of SR-BI to mediate cholesterol efflux from cells was directly established by studies in which SR-BI-transfected cultured cell lines were shown to exhibit increased radiolabeled unesterified cholesterol efflux to HDL and phosphatidylcholine liposomes, but not lipid-free apoA-I (127). SR-BI has also been reported to influence cholesterol efflux from cells to exogenously added apoE (192). SR-BI-mediated transfer of unesterified cholesterol between cells and HDL is bidirectional (188). Because SR-BI-mediated transport does not appear to be dependent on ATP, net flux of lipids is likely driven by the concentration gradient between cells and extracellular donor/acceptor particles. Although it mediates efflux to lipid-poor HDL from macrophages loaded with nonmetabolizable cholesterol, SR-BI apparently facilitates selective cholesterol uptake from cholesterol-rich particles to the plasma membrane of hepatocytes and steroidogenic cells down a gradient determined by further intracellular cholesterol metabolism.

In all studies performed to date, SR-BI-mediated cholesterol efflux has been correlated with the ability of this receptor to mediate selective uptake (116, 193), suggesting that

the mechanisms of influx and efflux may be linked. Analysis of mutant forms of SR-BI that have lost the ability to bind and mediate selective uptake from either HDL alone or HDL and LDL (but not acetylated LDL), combined with the analysis of the effect of antibodies that block lipoprotein binding to SR-BI, strongly suggests that lipoprotein binding is required for SR-BI-dependent cholesterol efflux (116). Furthermore, decreased SR-BI-mediated cholesterol efflux to HDL particles reconstituted with mutant apoA-I forms suggests that the formation of a productive complex between HDL and SR-BI is required for efficient cholesterol transport activity (125). However, an alternative view that cholesterol-acceptor binding to SR-BI is not required for SR-BI-dependent cholesterol efflux has been proposed (194, 195). Interestingly, it has been shown that SR-BI expression in cultured cells alters the accessibility of cellular cholesterol to modification by cholesterol oxidase added to the culture medium (194, 195). The relationship between this change in surface cholesterol accessibility and efflux is not yet certain, but this important observation is likely to lead to new insights into the mechanisms underlying SR-BI-mediated lipid transport.

SR-BI-dependent cholesterol efflux activity is modulated by enzymatic and nonenzymatic changes in HDL lipid composition (188). Both phosphatidylcholine and sphingomyelin enrichment of HDL increase net cholesterol efflux from SR-BI-expressing cultured cells. Cholesterol efflux mediated by SR-BI is significantly correlated with HDL phosphatidylcholine content, suggesting that the relative phospholipid/cholesteryl ester composition of HDL influences the efficiency of cholesterol efflux. This may be due to a dependence on the cholesterol gradient between HDL particles and cell plasma membrane (reviewed in Refs. 68 and 196).

Tangier disease, characterized by impaired cholesterol efflux from cells to lipid-free or lipid-poor apoA-I and dramatically reduced plasma HDL levels, is a consequence of mutations in the gene encoding the ABCA1 transporter (197–200). This discovery has had a major impact on the study of cellular cholesterol efflux. The potential structural and/or functional interaction between ABCA1 and SR-BI in regulating cellular cholesterol efflux has only just begun to be explored (201). It is also interesting to note that although ABCA1 facilitates efflux of cholesterol, it may be a primary transporter for phospholipid efflux that secondarily drives cholesterol transport out of cells (202–204). It is conceivable that SR-BI and ABCA1 might act coordinately in cellular cholesterol efflux because nascent HDL particles formed from lipid-free apoA-I by ABCA1-mediated phospholipid efflux (202–204) could serve as an acceptor for further cholesterol efflux mediated by SR-BI. In this regard, it is interesting that ABCA1 binds lipid-free apoA-I in preference to spherical HDL particles (203–206), and the opposite is true for SR-BI (117–119). A study involving coexpression of high levels of SR-BI and ABCA1 suggested that SR-BI and ABCA1 may have distinct and, under some circumstances, opposite effects on unesterified cholesterol flux between HDL and cells (201).

The SR-BI-mediated transfer of unesterified cholesterol between cells and the extracellular fluid need not always involve lipoproteins or phospholipid carriers. SR-BI can facilitate the cellular uptake of unesterified cholesterol added directly to culture medium in the absence of lipoproteins (147, 207). This lipoprotein-independent activity of SR-BI may be related to the recent report that SR-BI is indeed a cholesterol binding protein (206).

VII. Tissue Expression, Regulation, and Function of SR-BI

Immunochemical methods have shown that SR-BI is most highly expressed in adult mammal tissues that are the principal sites of selective lipid uptake *in vivo*, *i.e.*, the liver and steroidogenic tissues (71, 182). In addition, SR-BI has been observed at lower levels in intestine (94, 95, 182, 207), mammary glands of pregnant rats (71, 182), trophoblast, yolk sac and placenta during intrauterine development (208, 209), and uterine endometrium (210). The presence of SR-BI has also been reported in lung (211), biliary tree (96), macrophages (104, 126, 212–214), endothelial cells (132, 208, 215–217), smooth muscle cells (217), neuroglia (109, 110, 218), retinal pigmental epithelial cells (219), and keratinocytes (220). Substantial amounts of SR-BI mRNA have been detected in 3T3-L1 adipocytes and murine adipose tissue (70); however, the relationship between the mRNA and protein levels of SR-BI in fat is not yet resolved (71, 182). In addition, regulation of SR-BI protein expression is not always correlated with variations in mRNA levels (91, 211, 221–223). Thus, evaluation of the absolute levels and changes in SR-BI mRNA levels may not necessarily reflect the levels of SR-BI protein and SR-BI activity in tissues or cells.

A. Liver

The liver expresses the highest levels of total tissue SR-BI protein, a finding consistent with the major role of the liver in selective HDL-cholesterol uptake. The liver accounts for 90% of selective HDL cholesteryl ester uptake as well as 50% of total HDL cholesteryl ester clearance in non-CETP-expressing rodents (rats and mice; Refs. 20–23), and it mediates approximately 20% of total HDL cholesteryl ester clearance in CETP-expressing animals (224). SR-BI may account for much of the previously described hepatic lipoprotein binding site activity (225), because both SR-BI (70, 71, 113, 128, 146) and lipoprotein binding site (114, 140, 142, 143, 226) exhibit multilipoprotein binding as well as selective cholesterol uptake activities for different classes of lipoproteins.

Under basal conditions, most hepatic SR-BI expression is in parenchymal cells (90, 91, 212). Although SR-BI can be detected in the canalicular domains of hepatocytes in mice overexpressing hepatic SR-BI (89) and in cultured hepatocyte couplets (93), immunofluorescence analysis indicates that SR-BI is almost exclusively expressed on the sinusoidal surface of hepatocytes in wild-type animals (90, 91). In addition to its expression in liver parenchymal cells, SR-BI protein expression has been reported in Kupffer (212, 227) and liver endothelial cells (227).

Hepatic SR-BI expression can be regulated by a series of dietary, hormonal, and pharmacological manipulations. In the hamster, dietary plant-derived polyunsaturated fatty acids have been shown to stimulate hepatic SR-BI expression

and HDL cholesteryl ester uptake (228). In contrast, dietary myristic acid decreased liver SR-BI levels in association with increased plasma HDL levels in hamsters (229). SR-BI expression is inversely regulated by cellular α-tocopherol concentrations in the HepG2 human hepatocyte cell line and by dietary vitamin E supply in the mouse liver (223). In hamsters, a novel acyl-coenzyme A:cholesterol acyltransferase inhibitor has been reported to increase hepatic SR-BI, but not LDLR, expression (230). In contrast, lipopolysaccharide (LPS), TNF, and IL-1 decreased hepatic SR-BI mRNA and protein levels in the Syrian hamster (231). Streptozotocin administration in genetically hypercholesterolemic RICO rats increased SR-BI protein levels, which correlated with lower plasma HDL (232). On the other hand, insulin-treated diabetic hamsters exhibited lower levels of SR-BI compared with similar hamsters injected with saline only (233). In rats, estrogen administration at pharmacological levels suppresses total hepatic SR-BI expression (182, 212, 234, 235), which also correlates with decreased hepatic selective cholesterol uptake (236). Interestingly, estrogens increase hepatic SR-BII expression (235). The decrease in hepatic SR-BI expression was an indirect effect that was abolished by hypophysectomy and dependent on the estrogen-induced increase in LDLR activity (90). Other studies established that administration of high levels of estrogen increases hepatic Kupffer cell (macrophage) expression while lowering parenchymal cell expression (212). This study also demonstrated similar reciprocal changes in parenchymal and Kupffer cell expression after cholesterol feeding (212). However, studies with hamsters and mice did not find that hepatic SR-BI levels and/or HDL cholesteryl ester transport were regulated by changes in dietary cholesterol (237–239). In addition, a deficiency of plasma HDL in apoA-I KO mice does not increase hepatic SR-BI expression (240). Taken together, these studies indicate that, at least in some species, *in vivo* hepatic levels of SR-BI are not under sensitive feedback control by hepatic cholesterol content and/or plasma HDL-cholesterol concentration.

A recent study has shown that prolonged adrenal stimulation by ACTH in rats and mice decreased hepatic SR-BI protein expression associated with increased plasma HDL-cholesterol levels (241). This effect was not reproduced by exogenous corticosteroid administration and was abolished by adrenalectomy (241). These findings suggest that under chronic ACTH stimulation, adrenals release a factor that represses hepatic SR-BI levels as a potential mechanism for preferential channeling of plasma lipoprotein cholesterol to the adrenal tissue during stress.

In addition, the effects of pregnancy and lactation on hepatic SR-BI expression in female rats has been described (242). Hepatic levels of SR-BI increase in late gestation, are maintained at those levels early after birth, return to nonpregnant levels by 3 d postpartum, drop under control levels in late lactation, and revert to basal levels in postlactating females. Interestingly, the regulation of SR-BI and LDLR expression was not the same, suggesting that the roles of these receptors during pregnancy and lactation differ substantially.

The regulation of hepatic SR-BI expression by nuclear receptors (91, 243–245) and the roles of hepatic SR-BI expression in lipoprotein metabolism and associated diseases are considered below.

B. Adrenal gland

The highest expression levels of SR-BI per gram of tissue have been found in rodent adrenal glands (71, 182). High levels of SR-BI expression also have been detected in the human adrenal gland (80). Immunofluorescence and immunohistochemical methods have established that SR-BI is expressed primarily on the surfaces of steroidogenic parenchymal cells, such as in the zona fasciculata and zona reticularis cells of the adrenal cortex (Refs. 169 and 182; Fig. 2). High resolution immunohistochemistry established that in murine adrenocortical cells, SR-BI was found in numerous circular and oval structures on the cell surface that appear to represent cross-sections through previously described structures rich in microvillar channels (Ref. 182 and Fig. 2). These channels accumulate HDL, and they seem to play an important role in the selective lipid uptake process (38, 170, 172). The formation of similar cell surface double-membrane channels has been observed in insect cells expressing high levels of recombinant SR-BI (134). In addition, hormonal regulation of adrenal SR-BI expression is closely associated *in vivo* with changes in microvillar mass and microvillar channel formation in this rat steroidogenic tissue (246). By ultrastructural analysis of adrenal glands obtained from SR-BI-deficient mice, it has been established that SR-BI expression is essential for microvillar channel formation and the localization of HDL particles on the plasma membrane of adrenocortical cells (173). This finding indicates that expression of SR-BI can induce channel formation, probably directly as a consequence of the high-density expression of the receptor on the surfaces of cells.

ACTH treatment of mice, which induces adrenal steroidogenesis in concert with enhanced selective uptake of HDL cholesterol (reviewed in Ref. 247), increases SR-BI protein expression in adrenocortical cells (Ref. 169; Fig. 2). It seems likely that ACTH acts directly on the adrenocortical cells, rather than indirectly, because it also dramatically stimulates SR-BI protein and mRNA levels in cultured murine adrenal cells (169, 177, 248). The effect of ACTH on SR-BI expression is likely mediated by the second messenger cAMP (80, 249, 250). SR-BI expression in cultured human adrenal cells and its regulation by ACTH (249, 250) are similar to those observed in murine cells (169, 177, 248). The ACTH-mediated regulation of human SR-BI *in vivo* is probably similar to that of the mouse, because levels of SR-BI mRNA in normal adrenal tissue adjacent to Cushing adenoma are low, likely due to the reduced plasma ACTH levels found in these patients (249).

In vivo administration of the glucocorticoid dexamethasone, which suppresses ACTH secretion and thus adrenocortical steroidogenesis, dramatically suppresses SR-BI protein expression in the murine adrenal gland, suggesting that the relatively high basal levels of SR-BI in this tissue may be due to endogenous basal ACTH production (169). Taken together, these studies of hormonal regulation of adrenal SR-BI expression strongly support the hypothesis that in this tissue SR-BI mediates physiologically relevant selective up-

take of cholesteryl esters to supply substrate for steroid hormone synthesis.

In addition to the activity of the hypothalamic-hypophyseal-adrenal axis, the adrenal cholesterol content can independently regulate adrenal SR-BI levels, although this cholesterol-dependent effect is overridden by ACTH regulation *in vivo* and *in vitro* (80, 248). Increased adrenal SR-BI expression has also been reported in apoA-I-deficient (177), hepatic lipase-deficient (177), and LCAT-deficient (251) mice, suggesting that the expression of these lipoprotein metabolism-related genes directly or indirectly influences the levels of SR-BI in the adrenal gland. However, another study of apoA-I KO mice detected no changes in SR-BI mRNA or protein in the adrenal gland when compared with apoA-I-expressing animals (240). Further studies are required to established the basis for these divergent results.

In vivo estrogen treatment of rats: 1) induces adrenocortical expression of SR-BI (182); 2) enhances binding of HDL (apoA-I) to the surface of adrenal cells (182); 3) stimulates uptake of a fluorescent lipophilic dye surrogate for cholesteryl esters, DiI (71), from circulating DiI-labeled HDL (182); and 4) increases adrenocortical selective uptake of HDL cholesteryl ester (252). The relationship in the rat between estrogen's stimulation of adrenocortical expression and suppression of hepatic expression of SR-BI is not established. Hypophysectomy dramatically decreases adrenal SR-BI expression (182), and chronic estrogen therapy affects ACTH secretion (253), strongly suggesting that trophic hormones play a key role in the estrogen-induced regulation of this receptor. In fact, dexamethasone administration, which inhibits endogenous ACTH production, blocked the increase in SR-BI expression in the adrenals of estrogen-treated hypophysectomized rats, demonstrating that ACTH is a critical factor involved in the estrogen-associated increase in adrenal SR-BI expression (90).

The functional significance of adrenocortical SR-BI expression has been established *in vitro* and *in vivo*. Anti-SR-BI antibodies that block HDL binding inhibit HDL-dependent steroidogenesis in cultured murine adrenocortical cells (136). Furthermore, SR-BI can provide HDL cholesteryl esters for steroidogenesis in cultured human adrenocortical cells, suggesting a potential role for SR-BI in human adrenals (254). Under normal physiological conditions, however, cultured human adrenocortical cells may derive more cholesterol from the LDLR pathway than the HDL pathway (250), suggesting that in humans LDL may be the primary lipoprotein delivering cholesterol to the adrenals via LDLRs. Nevertheless, in FH patients or patients with abetalipoproteinemia, plasma cortisol responses to ACTH are normal except under prolonged maximal stimulation (see above), indicating the existence of LDLR-independent pathways for adrenal lipoprotein cholesterol uptake. Furthermore, treatment of FH patients with mevinolin, a statin that inhibits cholesterol synthesis, did not result in impairment in adrenal function (53, 59). These results suggest that normal LDL uptake via LDLRs is not required for essentially normal adrenal function and that SR-BI might be able to supply cholesterol for steroidogenesis in human adrenals, at least when the LDLR pathway is impaired.

Analysis of mice with targeted null mutations in the SR-BI gene has established that SR-BI plays a role in murine adrenocortical cholesterol metabolism. Biochemical and histochemical studies established that these mice exhibit depleted adrenal cholesterol stores (cytoplasmic cholesteryl ester storage droplets) in a gene-dose-dependent manner with reductions of 42% in heterozygotes and 72% in homozygote null SR-BI mutants (SR-BI KO mice; Ref. 255; Fig. 3). Similar lipid depletion is also observed in the ovaries (see below). Comparable adrenal cholesterol depletion has been observed in other murine mutants with disturbances in HDL metabolism, including apoA-I-deficient (172) and LCAT-deficient (251) mice, both of which exhibit abnormally high adrenal SR-BI mRNA levels (177, 251) that presumably represent regulatory responses made to compensate for reduced uptake of HDL-derived cholesterol. Furthermore, apoA-I KO mice also had blunted adrenal steroidogenic response to ACTH stimulation (172). Although SR-BI KO mice show no gross phenotypic indications of adrenal insufficiency, additional studies will be required to determine whether there are more subtle alterations in adrenal steroidogenesis in these mice. It is important to note that, except under conditions of very high demand, endogenous cholesterol synthesis via the HMG CoA reductase pathway would be expected to provide adequate amounts of substrate cholesterol for steroidogenesis in the adrenal glands, ovaries, and testes, even when LDLR- or SR-BI-mediated cholesterol import was not available.

It has long been known that plasma lipoproteins, in particular HDL, are able to neutralize bacterial LPS (endotoxin) and thus are protective against endotoxemia and bacterial sepsis (256–258). This is believed to be due, in part, to the binding of LPS by HDL (259), thus preventing LPS from stimulating the production of cytokines (TNFα, IL-1, and IL-6) by monocyte/macrophages (257). In rats, HDL-bound LPS accumulates in the adrenal gland, ovary, and liver (260, 261), precisely those tissues that express high levels of SR-BI. Furthermore, the accumulation of HDL-bound LPS in the adrenal gland is increased by ACTH and decreased by dexamethasone (260, 261) in a manner similar to HDL binding and SR-BI expression (169). In the case of the adrenal gland, the SR-BI-dependent removal of LPS from HDL may contribute to the occurrence of acute adrenocortical insufficiency or hemorrhage observed in severe gram-negative sepsis, particularly fulminant meningococcemia (reviewed in Ref. 262). Therefore, SR-BI may influence the tissue distribution of LPS, and thus the body responses to septic shock.

C. Ovary

The distribution and regulation of SR-BI in ovaries has been investigated both *in vitro* and *in vivo* (106, 137, 182, 263–269). In the preovulatory rodent and bovine ovary, SR-BI mRNA and protein are found in the theca interna cells, which actively synthesize androgens from cholesterol, but not in the granulosa cells, which convert androgens into estrogens. SR-BI expression appears in granulosa cells during formation of the corpus luteum in rodents and cows (106, 137, 182, 263–268) and correlates with increased serum progesterone levels *in vivo* (137, 267). Analysis of *in vitro* and *in vivo* luteinized rat ovarian cells reveals SR-BI expression on the cell

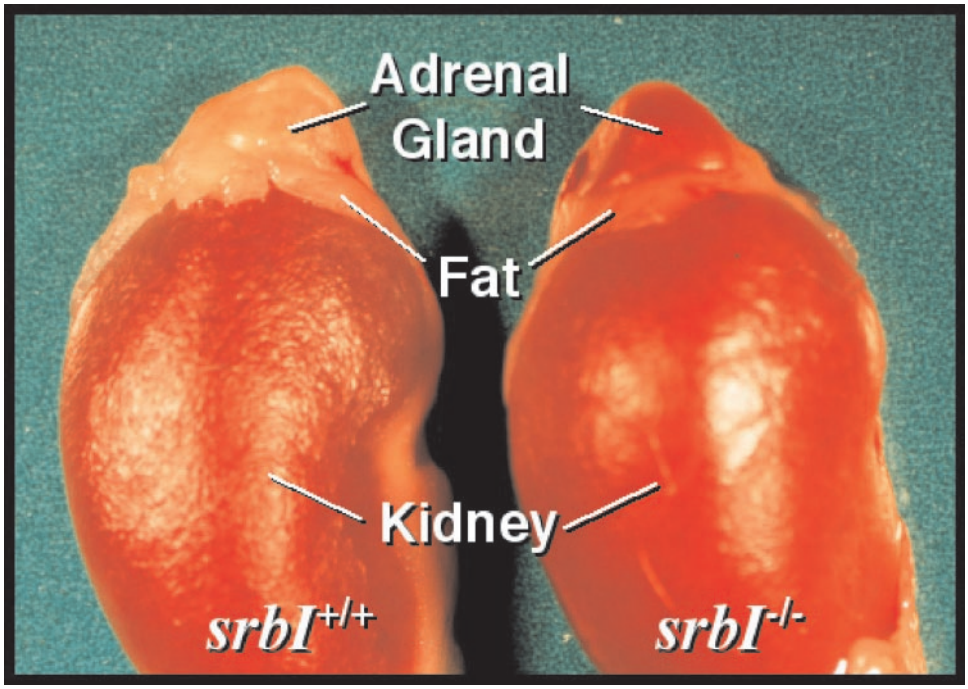

FIG. 3. Adrenal lipid depletion in SR-BI-deficient mice. In normal animals (*srbI*+/+, *left*), the adrenal gland is *light yellow* due to the massive accumulation of cholesterol in lipid droplets in the cytosol of steroidogenic cells. In SR-BI KO animals (*srbI*$^{-/-}$, *right*), the adrenals are *brownish-red* because of a substantial reduction in the cellular cholesterol pool (255). [Photograph by Bernardo Trigatti, Massachusetts Institute of Technology and McMaster University.]

surface in microvilli and microvillar channels, which bind HDL and show selective HDL fluorescent cholesteryl ester uptake (137, 267). Consistent with the coordinate regulation of SR-BI expression with selective HDL-cholesterol uptake and progesterone production during luteinization, prostaglandin F2α-induced luteolysis in the rat is associated with a decrease in both SR-BI expression and serum progesterone concentration (266).

Estrogen administration concomitantly induces SR-BI expression, steroidogenesis, and selective uptake in the rat ovary (182). In rat ovaries, high-dose estrogen treatment decreases SR-BI expression in theca cells and increases it in luteal cells (182). The overall estrogen-induced increase in SR-BI in the luteinized ovary correlates with higher uptake of DiI from DiI-labeled HDL (182).

Gonadotropin treatment of immature female rats induces a rapid increase in SR-BI mRNA expression in the theca interna cells during folliculogenesis followed by the appearance of SR-BI protein expression in luteal cells during luteinization (264). These gonadotropin-induced changes in rat ovarian SR-BI expression correlate with concomitant changes in selective HDL-cholesterol uptake (137, 267). Similar findings have been reported in SR-BI expression during endogenous ovarian cycling in cows (265).

The role of cholesterol in the modulation of physiological SR-BI expression in the ovary is unclear. Cholesterol loading apparently does not affect SR-BI levels in luteinized granulosa cells of the rat (267), whereas cholesterol depletion only modestly stimulates SR-BI expression (137). However, ovary desensitization by multiple gonadotropin administrations in rats, which decreases ovarian cholesterol content and progestin synthesis, induces selective HDL cholesteryl ester uptake and SR-BI expression compared with that in the luteinized ovary (137). These data suggest that under some conditions SR-BI might be regulated by the cholesterol content of the luteal cell independently of gonadotropic stimulation. There is a striking defect in ovarian function in SR-BI KO mice that will be discussed below.

D. Testis

In the testis, SR-BI is most abundantly expressed in steroidogenic Leydig cells (182), with lesser amounts in Sertoli cells (105). SR-BI expression in Sertoli cells has been suggested to have a role in phagocytosis of apoptotic spermatogenic cells (105); however, additional studies will be required to test this proposal. In the testis of the normal mature rat, SR-BI is barely detectable by Western blot analyses or immunohistochemical techniques (Fig. 2), which correlates with very low selective HDL-cholesterol uptake and steroidogenesis from HDL-derived cholesterol (39), suggesting that Leydig cells are not dependent on exogenous lipoprotein-cholesterol during normal steroid hormone production. In contrast, SR-BI expression in Leydig cells is dramatically stimulated after gonadotropin treatment (182) that also induces HDL binding, cholesteryl ester uptake, and testosterone synthesis (137, 182). SR-BI expression is also stimulated by testicular desensitization *in vivo* (39). These data suggest that SR-BI may be important for cholesterol metabolism in Leydig cells *in vivo* (182). Under gonadotropin-mediated desensitization, some Leydig cells show SR-BI localized to surface microvilli, as is the case in steroidogenic cells of the adrenal and ovary, but most receptors are found in a complex membrane channel system deep within the cytoplasm of these cells (39). Although it is possible that there may be subtle functional defects in the testes in SR-BI KO mice, there are no overt defects in male fertility in these SR-BI-deficient animals (255). Thus, SR-BI expression is not required for adequate testosterone synthesis and any other function necessary for functional sperm production.

E. Gut

Although the liver and steroidogenic tissues are the sites of greatest SR-BI expression, SR-BI is expressed in other sites throughout the body. SR-BI is expressed in the intestines (71, 182, 208, 270), primarily on the apical surfaces of epithelial cells (94, 95, 207). There is a gradient of expression along the gastrocolic axis of the small intestine with the highest expression levels of SR-BI found in the proximal (duodenal) region (94, 95, 270). SR-BI is also expressed in the CaCo-2 human colonic adenocarcinoma cell line (94, 207). Intestinal SR-BI expression is regulated by treatments that alter biliary lipid composition. In rodents, expression is suppressed coordinately with decreased intestinal cholesterol absorption when biliary lipid delivery into the intestinal lumen is impaired as a consequence of bile duct ligation, bile diversion, or null mutations in the genes encoding either the multidrug resistance-2 glycoprotein or cholesterol 7α-hydroxylase (95). These *in vitro* and *in vivo* data supported the suggestion that SR-BI might play a critical role in intestinal cholesterol absorption (207). This suggestion was especially attractive in light of the observation of SR-BI-mediated cell uptake of unesterified cholesterol in the absence of lipoproteins (147) and that the cholesterol absorption inhibitors ezetimibe and its derivatives bind to and block the activity of SR-BI (271). However, SR-BI is not essential for absorption of cholesterol by the intestine (see *Section X.D*). At least some of the long-sought cholesterol transporters for controlling net absorption of cholesterol from the intestine appear to include members of the ABC transporter family (see below).

As would be expected from its common embryological origin with the intestine, the gallbladder also expresses SR-BI. Both murine and human gallbladders have SR-BI in the apical domains of their epithelial cells (96, 272). Furthermore, diet-induced biliary lipid hypersecretion in mice is associated with decreased gallbladder SR-BI expression (96, 272). These findings suggest that SR-BI might be involved in lipid transport across the gallbladder epithelium and, as appears to be the case for the small intestine, its expression is regulated by biliary lipid content.

F. Lung

Within the lung, type II pneumocytes are involved in significant lipid uptake from lipoproteins for alveolar surfactant production. In particular, vitamin E supply from plasma HDL is important for protecting surfactant from oxidative damage in the alveolar space. Interestingly, SR-BI, which can mediate selective vitamin E (α-tocopherol) uptake (132, 133, 273), is expressed in the embryonic lung from 1 d before birth, increasing thereafter in type II pneumocytes (211, 273). Its expression in these cells is inversely regulated with dietary vitamin E supply, apparently by posttranscriptional mechanisms (273). These findings strongly suggest that the expression of SR-BI on alveolar type II cells may help determine the cellular supply of vitamin E. The relevance of SR-BI for pneumocyte metabolism of nonvitamin E lipids remains to be established.

G. Nervous system

Apolipoproteins, lipoprotein-remodeling enzymes, and lipoprotein receptors are present in peripheral nerves and brain, including the cerebrospinal fluid (274). Furthermore, it is interesting to note that very large plasma lipoproteins cannot cross the blood-brain barrier by simple diffusion, indicating the presence of a distinct receptor-mediated lipid transport system between plasma and the central nervous system (CNS). SR-BI is found in endothelial cells derived from the blood-brain barrier, suggesting an important function in supplying lipids and vitamins from plasma lipoproteins to the CNS (132). In addition, SR-BI expression has been reported in glial, but not neuronal, cells of the CNS (109, 110, 218). SR-BI has been detected in cultured human fetal and murine newborn, but not adult, microglia (109, 110, 218). In contrast, it is found in astrocytes and vascular smooth muscle cells in normal adult mouse and human brains (109, 110, 218). SR-BI expression in cultured human glia appears to be regulated by lipoprotein availability (218). SR-BI mRNA has been localized by RT-PCR in the parietal cortex as well as in the cerebellum of the human brain (275). Interestingly, SR-BI has been found in brains from Alzheimer's disease patients (110, 275), which together with its β-amyloid binding activity (108, 109), suggests a potential role for this receptor in the pathogenesis of Alzheimer's disease. On the other hand, rat peripheral sympathetic neurons, which internalize lipids from both LDL and HDL, do not express SR-BI (276).

H. Mammary gland

SR-BI is expressed in pregnant rat mammary gland (182) and a human breast carcinoma cell line (277). In the latter, cholesterol acquisition from HDL is dependent on SR-BI-mediated selective cholesterol uptake (277). The transfer by a LDLR-independent pathway of a lipid-depleted lipoprotein particle from plasma across the mammary epithelium into the milk of lactating mice has been reported (278). The relevance of SR-BI expression in this latter process, as well as mammary gland physiology in general, remains to be established. The absence of SR-BI in gene-targeted mice does not appear to significantly impede the ability of mothers to nurse their young (279).

I. Endothelium

Endothelial SR-BI expression was initially reported in the decidual tissue surrounding the embryo during early mouse development (208). SR-BI has also been found in caveolar fractions of human microvascular endothelial cells in culture (215). In this latter system, SR-BI appears to mediate the protective effect of HDL on oxidized LDL-induced cholesterol depletion of caveolar cholesterol and subcellular redistribution of endothelial nitric oxide (NO) synthase (eNOS; Ref. 215). More recently, SR-BI was detected in ovine fetal pulmonary arterial endothelial cells (280) and endothelial cells derived from the blood-brain barrier (132), suggesting a role in lipid transfer from plasma lipoprotein into the CNS (216). Functional studies also indicate that SR-BI is expressed in murine aortic endothelial cells and participates in the regulation of NO synthase (Ref. 280; also see below).

J. Macrophages

SR-BI mRNA and protein levels are low in human monocytes, but increase upon differentiation into macrophages (Refs. 126 and 213; however, see Ref. 104). Agonists of the nuclear receptors peroxisome proliferator-activated receptor (PPAR)-α and PPAR-γ (214), 15-deoxy-δ-12,4-prostaglandin J2 (281), testosterone (282), and advanced glycation end products (283) increase macrophage SR-BI expression; whereas it is decreased by LPS (221), interferon-γ (Ref. 221; however, see Ref. 281), TNF-α (221), and TGF-β (284). The suppression of SR-BI by LPS in macrophages is dependent on the modulation of SR-BI gene promoter activity by p21- activated protein kinase-1 (285). The LPS-activated p21-activated protein kinase-1 pathway decreases the binding of a novel transcription factor to a myeloid zinc finger protein-1-like element present in the human SR-BI promoter (285). Reduced mRNA SR-BI levels in LPS-treated macrophages also appear to involve nuclear factor-κB activation (286). Oxidized LDL also seems to reduce macrophage SR-BI mRNA and protein levels (Ref. 287; however, see Ref. 213). The ability of oxidized LDL to decrease SR-BI expression is dependent on the degree of LDL oxidation and can be mimicked by 7-ketocholesterol, but not unoxidized cholesterol (287). Interestingly, SR-BI has been found in macrophage-derived lipid-loaded cells of apoE KO mice (126), human atherosclerotic lesions (213, 214), and cholesterolotic gallbladders (96), raising the possibility that it may play a role in lipid deposition in these disease conditions.

K. Skin

SR-BI has been found in cultured human and murine epidermis (220). Calcium-induced keratinocyte differentiation is associated with decreases in both SR-BI expression and uptake of HDL cholesterol (220). Although keratinocyte SR-BI mRNA levels were higher after inhibiting cholesterol synthesis, they were decreased by 25-hydroxycholesterol (220). In both human and murine epidermis, SR-BI mRNA content was higher after skin barrier disruption (220), suggesting that SR-BI may facilitate cholesterol uptake required for barrier restoration, which includes the deposition of lipids to form a water impermeant seal.

L. Embryonic and extraembryonic tissues

Placenta and yolk sac are considered to function as active interfaces between maternal circulation and the embryo and, thus, play major roles in the maternal-fetal lipoprotein transport system (reviewed in Ref. 288). The exact mechanisms of this transplacental cholesterol transport are not clear (208, 289–292). In humans, the placenta expresses several lipoprotein receptors, including LDLR (293) and VLDL receptor (294), LDLR-related protein (295), and SR-BI (80). The placental syncytiotrophoblast cell is proposed to play a key role in the exchange of nutrients between the mother and the developing fetus. Interestingly, the presence of SR-BI protein and HDL binding has been observed in the syncytiotrophoblast on the brush border membrane (*i.e.*, the side facing the mother; Refs. 296 and 297) as well as in basal plasma membrane (*i.e.*, the side facing the developing fetus; Ref. 297). Although the physiological significance of this is unknown, it is possible that maternal HDL may have a role in providing cholesterol and other lipids, conceivably via SR-BI, for the needs of the growing fetus.

The expression pattern of SR-BI during embryogenesis was first described for the mouse (208). On d 7.5 of murine embryonic development (E7.5), there are newly formed maternal blood vessels within the endometrium-derived decidua providing nutrients to the developing embryo. At this time, SR-BI is significantly expressed in endothelial cells of the decidua, but little expression is seen in intraembryonic and extraembryonic tissues. On d E8.5, when embryonic vascular structures develop, there is a significant increase in SR-BI expression in the trophoblast cells that surround the developing embryo. On d E10, when the placenta becomes a main site for transport of nutrients, SR-BI is expressed in both the placenta and yolk sac. High expression of SR-BI is also found during hamster embryonic development (209) in the yolk sac apical surface (d E10.5 and E14.5). Analysis of HDL clearance, however, showed that the yolk sac appeared to remove substantial amounts of the entire HDL particles from the maternal circulation, suggesting that selective uptake may not be the only mechanism involved in yolk sac clearance of maternal HDL in the hamster (209).

Within the murine embryo itself, *in situ* hybridization signal of SR-BI mRNA was detected on d E11.5 in the urogenital ridge of both male and female embryos, but on d E12.5, high levels of SR-BI mRNA were detected only in testes, which are active in steroidogenesis at this stage, but not in the ovaries, in which steroidogenesis takes place later in gestation (298). *In situ* hybridization also revealed SR-BI expression in the liver at d E12.5 and E14.5, with declining expression by d E16.5 (298), but immunofluorescence methods did not detect SR-BI expression in the murine embryonic liver up to d E17.5 (208). SR-BI expression is detectable in fetal adrenal gland by d E14.5 (208, 298) and in the hindgut (d E17) outlining the folds of the gut epithelium (208). High levels of SR-BI expression have also been detected in the human fetal adrenal (80, 182).

VIII. Mechanisms Underlying the Regulation of SR-BI Expression

The mechanisms involved in the control of SR-BI expression have only just begun to be deciphered. The promoter of the human SR-BI gene contains consensus-DNA sequences that bind several transcription factors including steroidogenic factor-1 (SF-1), CCAAT/enhancer-binding protein (C/EBP), SREBP-1 (80, 299), liver X receptor (LXR; Ref. 243), and liver receptor homolog 1 (LRH-1; Ref. 244). The regulation of SR-BI expression by trophic hormones, cholesterol, and polyunsaturated fatty acids *in vivo* (106, 137, 169, 177, 212, 225, 228, 248, 263–269, 298) is likely to be controlled by transcriptional regulation through these and other as yet unidentified factors.

SR-BI regulation by trophic hormones in steroidogenic cells may depend on cAMP/protein kinase A signal transduction that stimulates the transcriptional function of SF-1 (300) and C/EBPs (301). The SF-1-sensitive site is required for

the basal and cAMP-stimulated transcriptional activity of the SR-BI promoter in adrenocortical cells *in vitro* (80, 299), and SF-1 is also critical for the expression of SR-BI during the development of murine steroidogenic tissues *in vivo* (298). Because C/EBPs are intracellular mediators of various trophic factors (301), they may also be involved in the regulation of SR-BI by cAMP-dependent trophic hormones in non-SF-1-expressing tissues. On the other hand, vitamin E-dependent regulation of SR-BI in hepatic cells might be mediated by protein kinase C activity (223). Taken together, these data indicate that activation of multiple signaling pathways may participate in modulating SR-BI expression.

The expression of SR-BI in some steroidogenic cells in culture and *in vivo* can be regulated by cholesterol (177, 248, 298). Furthermore, SREs reside within the 2.2-kb promoter region upstream of the transcriptional start site of the SR-BI gene (299). The ability of SREBP-1a to stimulate the expression of a reporter gene linked to the SR-BI promoter depends on the presence of these elements (299). SREPB-1a expression is induced by gonadotropin treatment and precedes the increased expression of SR-BI in the ovarian tissue (302). Estrogens appear to stimulate ovarian SR-BI expression through dual activation of estrogen receptors and SREPB-1a, both of which may interact with response elements on the SR-BI gene promoter *in vitro* (303). Furthermore, SERBP-1a-dependent regulation of SR-BI expression appears to be synergistic with the increased expression mediated by SF-1 (299). Additional studies have shown that SR-BI expression in macrophages is regulated by activators of PPARs (214) and that estrogen and dietary cholesterol induce activation of SR-BI expression in hepatic macrophages while suppressing parenchymal cell expression (212). Therefore, it is likely that the regulation of SR-BI expression involves complex and interrelated activation of various transcription factors in different tissues.

Hepatic SR-BI expression is regulated and, thus can influence the last step of reverse cholesterol transport and whole body cholesterol homeostasis. Studies with hypophysectomized rats have suggested that the dramatic reduction of hepatic SR-BI expression after high-dose estrogen treatment is a consequence of changes in circulating levels of hypophyseal trophic hormones (90, 182). As noted above, under chronic ACTH stimulation, adrenal glands release a factor that represses hepatic SR-BI levels (241).

Recent *in vivo* and *in vitro* data have emphasized the importance in regulating hepatic SR-BI expression of the nuclear receptors farnesoid X receptor (FXR), LXR, LHR-1, and PPAR-α (91, 243–245). The administration to mice of cholic acid, an activator of the FXR, significantly increases hepatic SR-BI mRNA and protein levels (245). The FXR-dependent regulation of SR-BI in the murine liver was further demonstrated by low SR-BI expression in FXR KO mice as well as the lack of cholic acid-induced up-regulation of SR-BI in FXR-deficient animals (245). It is not known whether FXR regulates SR-BI expression by direct interaction with the SR-BI gene promoter or whether regulation is indirect. LXRα, LXRβ, and LHR-1 induce SR-BI transcription in human and murine hepatoma cells by binding to the corresponding nuclear receptor response element located in the promoter region of the SR-BI gene (243, 244); however, the *in vivo* relevance of these activities remains to be established. It is noteworthy that SR-BI mRNA levels are reduced in LRH-1-deficient mice (244), but not in LXR-α KO mice (304).

Stimulation of PPAR-α by fibrates increases SR-BI mRNA levels and protein in macrophages (214). Mardones *et al.* (91) have shown that fibrates do not significantly alter SR-BI mRNA levels in the murine liver, yet they substantially lower hepatic SR-BI protein expression (and correspondingly increase HDL particle size), apparently via a posttranscriptional regulatory mechanism. Posttranscriptional control of SR-BI expression was originally suggested by the initial characterization of its expression pattern in different tissues (70, 71) and subsequently was reported in a variety of experimental models (95, 222, 223). PPAR-α mediates the effects of fibrates on hepatic SR-BI expression, because these effects are abolished in PPAR-α deficient mice (91). The identification of endogenous or exogenous factors and pathways that modulate the expression and/or activity of SR-BI in the liver may provide new insights in developing novel approaches to manipulate HDL metabolism, reverse cholesterol transport, and atherosclerosis in humans (255, 305–307).

IX. SR-BI and Lipoprotein Metabolism

A. HDL metabolism

The expression pattern of SR-BI (*i.e.*, most abundantly expressed in the liver and steroidogenic tissues, the principal sites involved in selective HDL-cholesterol uptake), as well as the regulation of SR-BI expression in these tissues (see above) strongly indicated that SR-BI is a physiologically relevant HDL receptor (reviewed in Ref. 12). Direct evidence for the role of SR-BI in HDL metabolism *in vivo* (Fig. 4) has come from studies in which the levels of SR-BI in mice have been manipulated either by overexpressing the SR-BI gene in the liver using adenovirus-mediated gene transfer or transgenic approaches (89, 129, 308, 309) or by introducing targeted mutations into the SR-BI gene (255, 310).

In the first *in vivo* experiments, recombinant adenovirus-mediated gene transfer was used to induce hepatic SR-BI overexpression in mice (89). The resulting transient increase in SR-BI on both sinusoidal and canalicular surfaces of hepatocytes was accompanied by a dramatic transient reduction in the levels of plasma HDL cholesterol and apoA-I and a concurrent increase in the cholesterol concentration in hepatic bile (89). The increased SR-BI-mediated hepatic HDL selective uptake was also associated with increased catabolism of apoA-I (89). In fact, SR-BI overexpression in apoA-I-deficient mice leads to accumulation of small dense HDL remnants and increased HDL apolipoprotein uptake in liver and kidney (311), which are the main sites apoA-I degradation *in vivo*. The reciprocal relationship between plasma HDL-cholesterol and biliary cholesterol levels in SR-BI-overexpressing mice suggested that increased biliary cholesterol secretion originated from plasma HDL cholesterol taken up by the liver. Consistent with this hypothesis, there was a dramatic increase in the excretion of DiI into the bile of hepatic SR-BI overexpressing mice after iv administration of DiI-HDL (89). These conclusions were subsequently confirmed in studies using transgenic mice overexpressing SR-BI

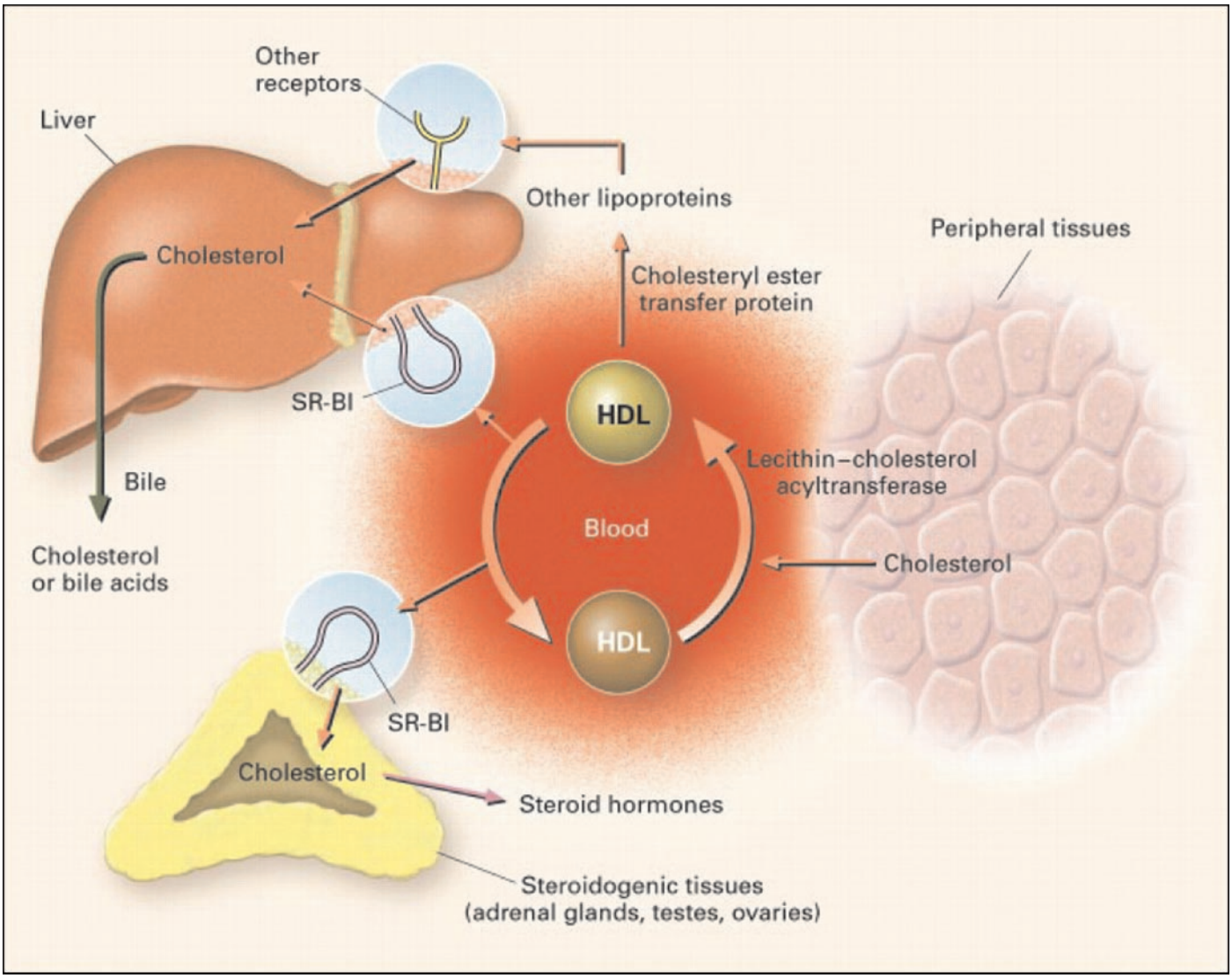

FIG. 4. Role of SR-BI in HDL metabolism *in vivo*. HDL can efficiently remove cellular cholesterol from peripheral tissues by an ATP-dependent mechanism involving the ABC transporter ABCA1 (not shown). Although SR-BI can also mediate cholesterol efflux from cultured cells to HDL, the relevance of this activity *in vivo* remains to be determined. After HDL cholesterol is esterified to cholesteryl esters by the enzyme LCAT (not shown), it is transported to the liver by either direct or indirect pathways. In the indirect pathway, CETP transfers cholesteryl esters from HDL to non-HDL lipoproteins, which then deliver this cholesteryl ester to the liver by receptor-mediated endocytosis. The direct pathway involves SR-BI-mediated selective cholesterol uptake. HDL cholesterol taken up by the liver can be ultimately destined for bile secretion, either as cholesterol or as bile acids, products of hepatic cholesterol metabolism. The delivery of cholesterol from peripheral tissues via plasma HDL to the liver and bile is called reverse cholesterol transport. SR-BI also mediates HDL-cholesterol uptake by steroidogenic tissues for steroid hormone synthesis or cholesterol storage. [Reproduced with permission from A. Rigotti and M. Krieger: *N Engl J Med* 341:2011–2013, 1999 (373). © Massachusetts Medical Society.]

specifically in the liver (129, 308, 309, 312, 313). Furthermore, metabolic kinetic analyses of radiolabeled HDL cholesterol have suggested that SR-BI expression in the liver is correlated with hepatic HDL cholesterol (both esterified and free cholesterol) uptake and secretion into bile (129). However, it has not been formally established that SR-BI overexpression in the liver increases overall reverse cholesterol transport (net movement of cholesterol from nonhepatic tissues to the liver and then secretion into the bile, *e.g.*, see Ref. 313).

Analysis of SR-BI KO mice definitively established a role for SR-BI in HDL metabolism in this species (255). SR-BI KO mice have, relative to wild-type control animals, a 2- to 2.5-fold increase in total plasma cholesterol levels, mostly due to increased cholesterol in HDL particles (255). These HDL particles are larger and more heterogeneous in size than those in wild-type animals, and they are enriched with apoE. Despite increased plasma HDL-cholesterol levels, no difference is observed in the plasma apoA-I levels between SR-BI null and wild-type mice, suggesting that the increase in HDL cholesterol was due to impaired selective uptake of cholesterol from HDL (255). An independently derived mutant mouse strain with attenuated SR-BI expression due to a serendipitous promoter mutation (SR-BIatt mice) (310) has a 50% reduction in hepatic SR-BI expression (similar to that of

heterozygous SR-BI KO mice; Ref. 255) and more moderate increases in plasma total cholesterol levels as well as in HDL size and cholesterol content, similar to the heterozygous null SR-BI mouse. The reduced hepatic levels of SR-BI in SR-BIatt mice are associated with reductions in hepatic selective HDL-cholesterol uptake and plasma clearance of HDL-cholesteryl esters *in vivo* (310). Together, these studies demonstrate that SR-BI is important for the maintenance of normal plasma HDL-cholesterol levels and HDL structure, and they support the proposal that the increased cholesterol content and size of HDL in SR-BI KO mice are due to impaired selective HDL-cholesterol uptake in the liver (255). Consistent with this, SR-BI KO mice also exhibit reduced biliary cholesterol secretion and gallbladder bile cholesterol content (238, 305) without concomitant changes in either biliary bile acid or phospholipid secretion, bile acid pool size, or fecal bile excretion. Thus, SR-BI deficiency appears to specifically affect biliary cholesterol secretion. Taken together, these studies indicate that SR-BI is important for normal hepatic selective HDL-cholesterol uptake and biliary cholesterol secretion in mice, thus supporting the idea that SR-BI plays a key role in the late stages of reverse cholesterol transport (Fig. 4).

B. Metabolism of other lipoproteins

In addition to binding HDL and selectively taking up HDL cholesterol, SR-BI can also bind non-HDL lipoproteins such as LDL and VLDL (70, 113) and mediate selective cholesterol uptake from LDL (128, 146), suggesting that SR-BI may also participate in the metabolism of non-HDL lipoproteins. This has been supported by several *in vivo* studies. Under standard chow (low-fat) diet conditions, hepatic SR-BI overexpression slightly, but consistently, decreases plasma LDL/IDL cholesterol levels (89, 308, 309), and SR-BI deficiency subtly increases the amounts of LDL/IDL-sized lipoproteins (255). Furthermore, hepatic overexpression of SR-BI increases the clearance of labeled LDL from the plasma (309).

Mice, but not humans, normally transport the majority of their plasma cholesterol in HDL particles and have only very small amounts of non-HDL particles (*i.e.*, apoB-containing particles) in their circulatory systems. Plasma levels of non-HDL lipoproteins (*e.g.*, apoB-containing lipoproteins) can be stimulated in mice by dietary (high-fat/cholesterol; Ref. 314) or genetic (*e.g.*, LDLR deficiency, Ref. 315; and apoE deficiency, Refs. 316 and 317) manipulations.

Overexpression of SR-BI in mice fed high-fat/high cholesterol diets or in heterozygous and homozygous LDLR-deficient mice results in reduced plasma levels of VLDL and IDL/LDL cholesterol compared with non-SR-BI transgenic controls (308, 309, 318). Conversely, SR-BI deficiency in apoE KO mice (SR-BI/apoE double KO mice) increases the levels of cholesterol in VLDL-size lipoproteins when compared with SR-BI-expressing apoE KO mice, suggesting that SR-BI may directly or indirectly contribute to the clearance of the cholesterol in VLDL-sized particles in single apoE KO mice (305). Reduced expression of SR-BI in LDLR KO mice (*i.e.*, SR-BIatt/LDLR KO mice) results in significantly increased levels of plasma LDL cholesterol when these mice are fed a Western type high-fat/cholesterol diet, but not when they are fed a low-fat chow diet (319). In metabolic kinetic analysis, no differences were observed in hepatic clearance and uptake of LDL protein or cholesterol in SR-BIatt/LDLR double KO mice compared with single LDLR KO control mice. The authors concluded that SR-BI does not appear to have a direct role in LDL cholesterol catabolism *in vivo* (319), but rather acts indirectly on LDL metabolism (*e.g.*, by inducing LDL production). Similar kinetic studies in SR-BI-overexpressing apoB transgenic mice showed a slight increase in LDL cholesteryl ester clearance, but no change in LDL apolipoprotein turnover (149). Taken together, most, but not all (319), studies suggest that in addition to HDL, SR-BI may, at least in rodents, also function as a receptor for apoB-containing lipoproteins *in vivo*. The influence of SR-BI on murine LDL metabolism appears to be substantially less than that of LDLRs, and its influence on HDL metabolism appears to be much greater than its effects on non-HDL lipoprotein metabolism.

X. Role of SR-BI in Physiology and Pathophysiology

A. Reproductive biology: female fertility

Studies showing coordinate regulation of SR-BI expression, steroid hormone production, and HDL-cholesterol uptake in the ovaries in both mice and humans (see above) have all indicated that SR-BI may play an important role in normal ovarian function. Further support for this suggestion has come from the observation that female SR-BI KO mice are infertile (305). Despite the dramatic reduction in ovarian lipid stores in the corpora lutea (see above), SR-BI KO mice are able to produce normal amounts of plasma progesterone during pseudopregnancy (305), suggesting that normal ovarian lipid stores are not required for production of adequate amounts of progesterone, a phenomena also seen in apoAI-deficient and LCAT-deficient (251, 320) mice. Furthermore, several ovarian functions requiring adequate steroid hormone production and proper interaction within the hypothalamic-hypophyseal-ovarian axes apparently seem to be normal in SR-BI KO females. For example, they exhibit no obvious defects in their gross ovarian morphology, estrus cycles, or numbers of ovulated oocytes (305). These findings suggest that SR-BI-independent sources of cholesterol (endogenous cholesterol synthesis, endogenous cholesterol stores, SR-BI-independent pathways of cholesterol uptake) are sufficient to meet most of the steroid biosynthetic precursor requirements of steroidogenic cells.

The ovulated oocytes in SR-BI KO mice, however, are dysfunctional, and preimplantation embryos isolated from SR-BI KO females the morning after mating either are dead or die soon afterward (Ref. 305; Fig. 5). This suggests that SR-BI may either directly (*e.g.*, disturbed cholesterol influx or efflux in the absence of SR-BI) or indirectly (*e.g.*, abnormal plasma lipoproteins due to the lack of SR-BI expression) influence oocyte maturation and development (305). The exact mechanism leading to the defect in oocyte development is currently under study. Genetic, surgical, and pharmacological studies suggest that abnormal lipoprotein metabolism plays a key role in female SR-BI KO infertility (279). Indeed, reduction in the plasma HDL-cholesterol levels by treatment with the cholesterol-lowering drug

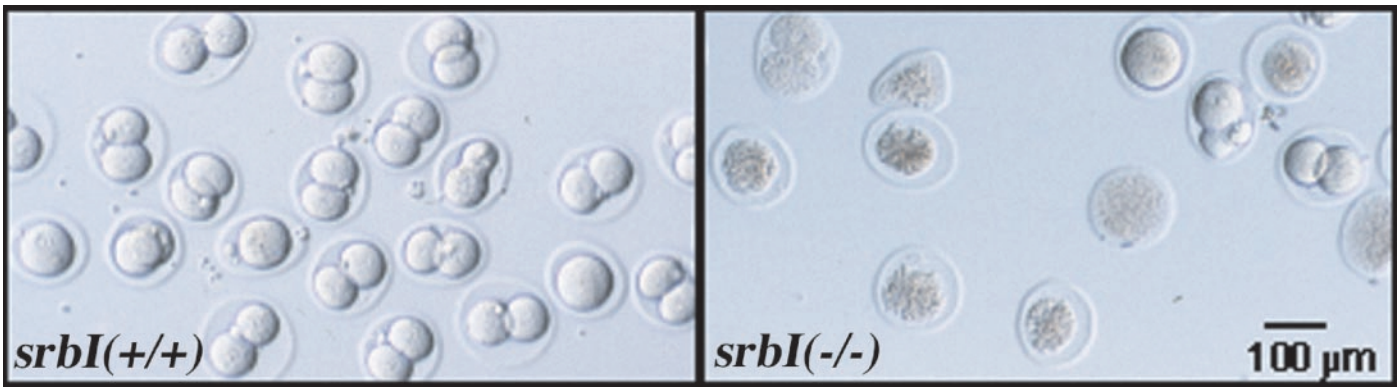

FIG. 5. Infertile SR-BI KO female mice produce abnormal preimplantation embryos. When preimplantation embryos from wild-type females (*srbI*+/+) are maintained in culture for 1 d, they divide and exhibit normal morphologies (*left*). In contrast, the majority of embryos from $srbI^{-/-}$ females do not divide and exhibit abnormal nonrefractile morphologies (*right*). [Reproduced with permission from B. Trigatti *et al.*: *Proc Natl Acad Sci USA* 96:9322–9327, 1999 (305). © National Academy of Sciences, U.S.A.]

probucol fully restores fertility to SR-BI KO female mice (279).

It is of interest that in many species, including humans, HDL is the only lipoprotein detected in substantial amounts in the follicular fluid surrounding the developing oocyte in the ovary (321–324). The exact function of follicular fluid HDL is unknown, but it may deliver lipid nutrients to the oocytes and/or the surrounding cumulus cells (*e.g.*, for local steroid hormone production or membrane synthesis required for normal oocyte maturation). HDL may also be involved in cholesterol efflux (reviewed in Refs. 12, 196, and 325) from the oocyte/cumulus cells, thus contributing to maintenance of normal cellular cholesterol balance. In this regard, it is interesting that homozygous ABCA1 transporter KO females have impaired female fertility, presumably due to placental malformation (326). These mice lack spherical plasma HDL particles due to impaired cholesterol efflux from cells to nascent discoidal HDL particles (327, 328). Furthermore, an inactivating mutation in the gene coding for oocyte vitellogenesis receptor, a VLDL receptor-like protein that binds VLDL and vitellogenin (reviewed in Refs. 329 and 330) causes hyperlipidemia in the restricted ovulator strain of chickens. Interestingly, these chickens also exhibit oocyte growth defects and female sterility (331). Although the relationship between the infertility of SR-BI KO and ABCA1 KO mice, as well as restricted ovulatory chickens, remains to be determined, it is conceivable that changes in HDL (structure/composition/abundance) and/or SR-BI structure and function may disturb normal human oocyte development and thus contribute to some forms of human female infertility. The potential influence of dyslipidemia in female infertility of unknown etiology may warrant further exploration (279).

B. Atherosclerosis

Epidemiological studies have shown that low serum HDL-cholesterol (*i.e.*, the "good" cholesterol) concentration is an independent risk factor for coronary artery disease (reviewed in Ref. 332). Indeed, low HDL cholesterol is the most common dyslipidemia found among patients with premature coronary artery disease, although it is usually combined with other lipid disorders (333). Although the association between low HDL cholesterol and increased risk of coronary artery disease was first described several decades ago, the underlying mechanism(s) by which HDL protects against coronary artery disease are still uncertain. The most popular proposed mechanism is reverse cholesterol transport (41) in which HDL removes excess cholesterol from peripheral cells, including those in arterial wall, and transports it to the liver where cholesterol can be excreted into bile (reviewed in Ref. 334). In addition, HDL has been suggested to exhibit additional properties that could potentially contribute to its antiatherogenic capacity, including its capacity to inhibit LDL oxidation and protect endothelial cells from the cytotoxic effects of oxidized LDL (reviewed in Ref. 335) as well as having a variety of beneficial effects on coagulation/fibrinolysis, inflammation, and blood cell and endothelial cell biology (280, 336, 337). It has also been suggested that low HDL cholesterol itself may not be atherogenic, but rather a secondary marker of some related atherogenic primary event, such as abnormal metabolism of the triglyceride-rich lipoproteins (338, 339).

SR-BI could influence atherosclerosis and coronary artery disease because of its involvement in the initial step of reverse cholesterol transport (*i.e.*, cholesterol efflux from peripheral cells to HDL), as well as the later steps (*i.e.*, hepatic cholesterol uptake from HDL and subsequent excretion into bile). The role of SR-BI in the development/prevention of atherosclerosis (reviewed in Ref. 306) has been addressed by manipulating the levels of SR-BI in different mice models particularly vulnerable to atherosclerosis [*i.e.*, the LDLR KO mouse (315, 340), the apoB transgenic mouse (341) fed a high-fat/high-cholesterol diet (342), and the apoE KO mouse (316, 317)]. These mice have increased plasma total cholesterol levels, primarily due to increased levels of atherogenic, apoB-containing lipoproteins (LDL-like in LDLR KO and apoB transgenic mice, and VLDL- and IDL/LDL-like in the apoE KO mice). LDLR KO and apoB transgenic mice develop atherosclerotic lesions in the aorta when fed a high-fat/high-cholesterol diet (340–342), whereas 3- to 5-month-old mice deficient in apoE spontaneously develop atherosclerosis in their aortic sinus when fed a normal chow diet (316, 317).

When SR-BI/apoE double KO mice are maintained on a

normal chow diet, they exhibit, compared with the apoE single KO mice, increased plasma cholesterol levels, mainly in VLDL-sized particles (305). Also, they have no normal-sized HDL, but rather very large HDL-like lipoproteins indicative of impaired selective uptake of HDL cholesterol by the liver (305). Consistent with this, biliary cholesterol levels are decreased, suggesting a substantial reduction in reverse cholesterol transport (305). Atherosclerosis is dramatically accelerated in SR-BI/apoE double KO mice. They exhibit massive atherosclerosis in the aortic sinus and coronary arteries (305) at a surprisingly young age, 4–7 wk. The mechanism(s) by which SR-BI deficiency lead to accelerated atherosclerosis are currently under study and may include changes in plasma lipoprotein levels and/or structures, disturbed cholesterol flux into or out of the arterial wall (*e.g.*, macrophages; Refs. 213 and 214) and impaired reverse cholesterol transport due to loss of selective uptake by the liver (305). The influence of SR-BI on vitamin E transport (Ref. 132; also see below) and on endothelial cell NO metabolism (Ref. 280; also see below) may also contribute to the accelerated atherosclerosis. Remarkably, all of the double KO mice die by approximately 8 wk of age (305, 343). Further examination of these mice has shown extensive coronary artery occlusions and spontaneously developed multiple myocardial infarctions and cardiac dysfunction. Their coronary arterial lesions are strikingly similar to human complex atherosclerotic plaques with the presence of cholesterol clefts and extensive fibrin deposition, indicating hemorrhage and clotting. Thus, SR-BI/apoE double KO mice provide a novel murine model for coronary heart disease and may provide novel insights on the role of lipoprotein metabolism and atherosclerosis in the pathogenesis of myocardial infarction and cardiac dysfunction (343).

SR-BIatt/LDLR KO mice fed a Western-type high-fat/cholesterol diet also exhibit increased plasma total cholesterol levels (primarily due to increases in LDL cholesterol; Ref. 319) and significantly more aortic root atherosclerosis than the SR-BI-positive LDLR KO controls (319).

Unlike SR-BI deficiency, hepatic overexpression of SR-BI can suppress murine atherosclerosis. For example, a single administration of SR-BI recombinant adenovirus results in transient hepatic overexpression of SR-BI in LDLR-deficient mice fed a Western-type high-fat/high-cholesterol diet and significantly reduced HDL cholesterol, but not non-HDL cholesterol, levels (344). When analyzed 4 wk after virus administration, at a time at which the plasma lipoproteins had returned to pretreatment levels, the SR-BI-overexpressing mice had significantly reduced areas of atherosclerotic lesions relative to controls. The sizes of the lesions in individual mice correlated with their mean HDL-cholesterol levels and in some, but not all, experiments atherosclerotic lesion size also correlated with the mean non-HDL-cholesterol level. These data suggest that the antiatherosclerotic effect of SR-BI overexpression in this model is mediated, at least partly, by changes in HDL-cholesterol flux, and in some cases potentially also by reductions in non-HDL-cholesterol levels. In heterozygous null LDLR KO mice, stable transgenic hepatic expression of SR-BI, significantly reduced atherosclerosis if the animals were fed an atherosclerosis-inducing high-fat/high-cholesterol/cholic acid diet (318). There was no antiatherosclerotic effect of the SR-BI transgene when mice were fed a more modest, Western-type diet lacking cholic acid. In contrast to the conclusions drawn from the adenovirus experiments, the authors of this latter study concluded that the transgene-mediated decrease in atherosclerosis was primarily due to the decrease in non-HDL cholesterol rather than the HDL cholesterol. These SR-BI overexpression studies clearly demonstrate that hepatic overexpression of SR-BI can be antiatherogenic. This may be due to changes in structures and quantities of circulating lipoproteins or increases in HDL-cholesterol flux to the liver, *i.e.*, increased reverse cholesterol transport.

The complexity of the role of SR-BI on atherosclerosis is highlighted by a study of the effects of hepatic SR-BI overexpression on atherosclerosis in a different murine model, mice expressing the human apoB transgene (345). The effects on lipoprotein metabolism and atherosclerosis of varying levels of stable hepatic SR-BI expression were examined. Surprisingly, only mice with moderately elevated hepatic SR-BI expression were found to be protected against diet-induced atherosclerosis. The reason why high levels of hepatic SR-BI overexpression failed to protect against atherosclerosis is not clear, but may be due to structural/compositional changes introduced to HDL or non-HDL particles in these animals or changes in reverse cholesterol transport. Thus, the consequences of SR-BI overexpression in the liver on atherosclerosis and lipoprotein metabolism are complex and may depend on levels of SR-BI expression as well as the mouse model of atherosclerosis. However, this study suggests that very high unphysiological levels of SR-BI expression may not always be beneficial.

In most circumstances in the mouse, expression of SR-BI appears to be cardioprotective and conversely, absence of SR-BI is atherogenic. Whether SR-BI has similar functions in humans, remains yet to be seen. If so, the selective modulation of SR-BI-mediated lipoprotein metabolism by dietary, pharmacological, and gene therapy approaches to reduce the risk of atherosclerotic cardiovascular disease would be an appealing subject for basic and clinical research. It is noteworthy that in the murine studies performed to date, low HDL-cholesterol levels may actually reflect accelerated reverse cholesterol transport rather than increased risk for coronary artery disease, and conversely, very high plasma HDL-cholesterol levels may be a sign of impaired reverse cholesterol transport. These observations raise the question of whether, in addition to assessing coronary artery disease risk in humans solely by concentration of plasma HDL cholesterol, more emphasis should be directed to the evaluation of functionality of HDL particles and flux of cholesterol through the plasma HDL pool.

C. Cholesterol gallstone disease

Because SR-BI controls biliary cholesterol secretion and gallbladder bile cholesterol content (89, 129, 238, 305, 312), it is a candidate gene to be involved in pathogenesis of cholesterol gallstone disease. There has been one report of increased expression of hepatic SR-BI associated with biliary cholesterol hypersecretion and gallstone formation in a gallstone-susceptible mouse strain (346). However, a similar,

independent study did not reproduce this finding (347). SR-BIatt mice with a partial deficiency of hepatic SR-BI expression do not exhibit a significant decrease in gallstone susceptibility when fed with a lithogenic diet (348). This latter finding indicates that SR-BI is much less relevant for controlling biliary cholesterol hypersecretion derived from intestinal chylomicrons during murine cholesterol gallstone formation. SR-BI is still likely to be a prolithogenic gene when the underlying pathogenic event is an increased HDL-mediated reverse cholesterol transport. If so, SR-BI may provide another target for pharmacological prevention and treatment of this common disease.

D. Intestinal cholesterol absorption

The expression of SR-BI in the intestines on the apical surface of epithelial cells (94, 95, 207), the regulation of intestinal SR-BI expression (95), and *in vitro* cholesterol transport assays in brush border membranes and cultured epithelial cells all suggested that SR-BI might have a role in cholesterol absorption (207). For instance, SR-BI ligands and anti-SR-BI antibodies were reported to inhibit unesterified and esterified cholesterol uptake from bile salt mixed micelles and phospholipid vesicles into intestinal brush border membrane preparations and CaCo-2 cells (207). Furthermore, in cultured cells, the intestinal cholesterol absorption inhibitor ezetimibe binds with high affinity to SR-BI, blocking cholesterol uptake by SR-BI (271). However, intestinal dietary cholesterol absorption *in vivo* is either slightly higher or not changed in SR-BI-deficient mice (238, 271), clearly demonstrating that SR-BI expression is not essential for murine intestinal cholesterol absorption. Moreover, ezetimibe inhibits cholesterol absorption in SR-BI-deficient mice fed chow and cholesterol-rich diets (271). Thus, if SR-BI normally participates in intestinal cholesterol absorption, SR-BI KO mice must have compensatory, SR-BI-independent mechanisms for cholesterol absorption.

A recent discovery revealed that human sitosterolemia, a condition characterized by extensive accumulation of plant sterols and cholesterol in plasma and tissues and accelerated development of atherosclerosis, is caused by mutations in the two adjacent genes encoding the ABC transporter family members ABCG5 and ABCG8 (349–352). These proteins were suggested to normally have an important role in limiting intestinal cholesterol absorption by promoting cholesterol excretion (349–352). We do not yet know whether SR-BI, which also mediates cholesterol efflux in cultured cells (see above), has a similar role in the intestine, potentially interacting with ABC proteins.

E. Embryogenesis and fetal development

SR-BI apparently contributes to the later stages of embryonic development and pregnancy. Developing embryos require substantial amounts of cholesterol for membrane synthesis and for steroid hormone production (reviewed in Ref. 288). This cholesterol is acquired by endogenous synthesis and from exogenous sources, *i.e.*, maternal lipoproteins. SR-BI has been shown to be expressed during murine embryonic development in a variety of extraembryonic and maternal tissues (*see above*), including decidual cells adjacent to the embryo, trophoblast cells, yolk sac, and placenta (208).

Interestingly, SR-BI expression in the trophoblast coincides with increased expression of the trophoblast cell P450 cholesterol side chain cleavage enzyme, which converts cholesterol to pregnenolone, indicative of active local progesterone production (353). The exact function of this progesterone production is unclear but it has been suggested to be involved in preventing rejection of the implanted fetus (354, 355). These studies suggested that SR-BI might provide cholesterol for embryonic membrane production and/or steroid hormone synthesis and that lack of SR-BI in either extraembryonic or maternal tissues may impair these processes. The expression of SR-BI in extraembryonic tissues is correlated with uptake of the lipophilic fluorescent dye DiI from DiI-labeled HDL injected into pregnant mice (208). This pattern of SR-BI expression during embryogenesis, as well as its localization on the apical sides of cells facing the maternal circulation, is consistent with a potential role in cholesterol uptake from maternal lipoproteins into extraembryonic tissues and/or within the developing embryo itself for growth and/or steroidogenesis. In addition, the expression pattern of SR-BI in the murine embryo (see above) resembles that of steroidogenic acute regulatory protein and cholesterol side chain cleavage enzyme, both key proteins in the steroidogenic pathway (356). These studies suggest that SR-BI may deliver cholesterol for steroid hormone synthesis within the embryo itself. Because SR-BI can also mediate the delivery of LDL cholesterol to cells, it is possible that, at least under some conditions (*e.g.*, FH due to LDLR deficiency), SR-BI might deliver cholesterol from LDL as well as HDL to embryonic and extraembryonic tissues (302). Whatever its normal role in embryogenesis, in an appropriate genetic or pharmacological background (279), SR-BI is not absolutely essential for fertilization, pregnancy, or delivery of healthy pups.

The lower than expected yield (50% reduction) of homozygous SR-BI KO mice born to heterozygous parents suggests that SR-BI-deficiency in the tissues of embryonic origin may result in partial embryonic lethality (255). The influence of the absence of SR-BI in maternal tissues on embryogenesis may in part be indirect, *e.g.*, through the changes introduced in maternal lipoproteins, the structure/abundance of which may potentially influence fetal development (357). It is not known whether SR-BI KO fetuses suffer from impaired cholesterol delivery.

F. Red blood cell (RBC) maturation

RBCs are derived from multipotential hematopoietic progenitor cells in the bone marrow. A key step in RBC maturation is the formation of reticulocytes by the expulsion of nuclei from erythroblasts in the bone marrow. Early reticulocytes have irregular shapes and contain cytoplasmic RNA and organelles (*e.g.*, polyribosomes, mitochondria; Ref. 358). As reticulocytes mature, they destroy or expel their RNA, surface transferrin receptors, cytoplasmic organelles, and ribosomes. They also remodel their cytoskeletons as they transform into flexible, biconcave, oxygen-carrying erythrocytes. Analysis of SR-BI KO mice (359) has established that specific alterations in plasma lipoprotein metabolism can

profoundly influence erythroid differentiation. SR-BI KO mice are mildly anemic, and their RBCs exhibit mild developmental abnormalities that are exacerbated by either feeding the animals a high-cholesterol diet or by inactivating the apoE gene (SR-BI/apoE double KO mice). In the most extreme case—the double KO mice—the cells resemble proposed intermediates in reticulocyte differentiation. They are anucleate, hemoglobin- and RNA-rich; they express surface transferrin receptors, are macrocytic, irregularly shaped, and contain large, membrane-enclosed, intracellular autophagolysosomes. These unusual RBCs contain abnormally high levels of cholesterol, and the severity of their developmental defects is correlated with their cholesterol content. The apparent block in maturation is reversible, because transfusion of RBCs from SR-BI/apoE double KO mice into wild-type recipients results in their apparently normal maturation into erythrocytes. At least some of the maturation process (extrusion of autophagolysosomes, loss of RNA) can be recapitulated *in vitro*, where extraction of excess cholesterol by addition of the cholesterol sequestering agent methyl cyclodextrin accelerates autophagolysosome expulsion. Thus, autophagocytosis and SR-BI- and cholesterol-sensitive phagolysosome expulsion are probably key steps in normal erythropoiesis. Further analysis of SR-BI KO mice should provide additional insights into the cellular mechanisms of RBC maturation. The severe reticulocytosis in SR-BI/apoE double KO mice may contribute to the accelerated atherosclerosis, cardiac dysfunction, myocardial infarction, and early death of these animals (343).

G. NO metabolism

Endothelium-derived NO plays a key role in vascular physiology and pathophysiology, including atherosclerosis (360). NO is generated by eNOS, and its decreased availability facilitates atherosclerotic plaque formation induced by hypercholesterolemia. Interestingly, eNOS activity, which is localized in caveolae, and NO production are stimulated by HDL, and this HDL-dependent effect is impaired by anti-SR-BI blocking antibodies in cultured endothelial cells (215). This finding suggested that endothelial SR-BI expression might be the molecular link between the protective effect of HDL with respect to eNOS function and NO synthesis. Using SR-BI and eNOS transfected Chinese hamster ovary cells, Yuhanna *et al*. (280) have shown that SR-BI mediates the activation of eNOS by HDL. The SR-BI-mediated stimulation of eNOS is dependent on the presence of native HDL particles, but not lipid-free HDL apolipoproteins (280). The mechanism by which HDL binding to SR-BI stimulates eNOS activation appears to be mediated by an increase in intracellular ceramide levels (361). Both eNOS activation and vascular relaxation induced by HDL in murine aortic ring preparations are significantly reduced in samples isolated from SR-BI KO compared with SR-BI-positive control mice (280). These studies indicate that SR-BI-associated atheroprotection may be related not only to its role in reverse cholesterol transport but also to its influence on the modulation of intracellular signal transduction that controls NO production.

H. Vitamin E transport

Recent studies have shown that selective lipid uptake, rather than endocytosis, is important for α-tocopherol delivery to cells (362, 363). Consistent with this, SR-BI can mediate the cellular uptake of α-tocopherol from HDL (132, 133). Overexpression of SR-BI in cultured cells by either DNA-mediated transfection or recombinant adenovirus-mediated transduction increases net selective uptake of α-tocopherol from the HDL (133, 363). Thus, in addition to the previously suggested pathways involving LPL, phospholipid transfer protein, and the LDLR (364, 365), SR-BI-mediated selective uptake can supply physiologically relevant levels of α-tocopherol to cells. In fact, relative to wild-type control animals, SR-BI-deficient mutant mice exhibit a substantial increase in plasma α-tocopherol levels due primarily to the elevated α-tocopherol content of their abnormally large plasma HDL-like particles (133). This increase in plasma α-tocopherol in SR-BI KO mice is correlated with a decrease in the α-tocopherol content of both the bile and several tissues, including ovaries, testes, lung, and brain. SR-BI deficiency did not significantly alter the α-tocopherol contents of the liver, spleen, kidney, or white fat. These data show that SR-BI plays an important role in transferring α-tocopherol from plasma lipoproteins to specific tissues. Also, SR-BI-mediated uptake of α-tocopherol in the liver is primarily coupled to biliary excretion rather than to accumulation in hepatic tissue. Similar findings have been reported for SR-BI-dependent hepatic cholesterol transport (238). As a consequence of its role in regulating cellular α-tocopherol content, SR-BI expression may confer protection against oxidative stress in cells. Thus, defective tissue uptake of α-tocopherol carried in lipoproteins in SR-BI-deficient mice might be one of the pathogenic mechanisms underlying the reproductive and cardiovascular disorders exhibited by these animals. Interestingly, a *Drosophila* class B scavenger receptor mediates cellular vitamin A uptake, and its loss of function is associated with a carotenoid-deficient phenotype characterized by abnormal visual chromophore and blindness in the fruit fly (366).

XI. SR-BI in Humans

Although the role of SR-BI in rodent lipoprotein metabolism as a physiologically relevant HDL receptor is well established, its role in human lipoprotein metabolism is not well defined experimentally. Both the selective HDL-cholesterol uptake activity of human SR-BI and the similar patterns of SR-BI gene expression [*i.e.*, most abundant expression in liver and steroidogenic tissues, in human and rodent tissues (71, 80, 182) and regulation in human steroidogenic cells (104, 234, 249, 250, 254)] suggest that SR-BI is likely to be involved in human HDL metabolism.

There have not yet been any reports of naturally occurring functionally significant mutations in the human SR-BI gene, although polymorphisms, some weakly associated with plasma LDL cholesterol levels and body mass index, have been described (367). In addition, a small-scale intervention study in human subjects has shown that plant stanol ester consumption changed plasma lipoprotein cholesterol irre-

spective of the SR-BI gene polymorphisms (368). A Japanese large-scale study also found no association between SR-BI gene variants and increased risk for myocardial infarction (369). However, another study has reported an association between an *SR-BI* gene *Hae*III polymorphism with coronary artery disease and lower body mass index in Korean subjects (370). A recent association study also reported a relationship between a SR-BI gene polymorphism and morbid obesity (371). Additional studies of the relationships of SR-BI polymorphisms and human phenotypes will be required to assess the importance of SR-BI in humans.

XII. Concluding Remarks

The discovery and analysis of the HDL receptor SR-BI has contributed to our understanding of cellular lipoprotein cholesterol metabolism, especially that which occurs through selective lipid uptake. This receptor is not only relevant for general body cholesterol homeostasis, but also for physiological cholesterol uptake and metabolism in steroidogenic tissues. Furthermore, experimental evidence from various animal models has established that alterations in the levels of SR-BI expression can significantly cause or influence pathology in a number of key physiological systems, *e.g.*, atherosclerosis/cardiovascular disease, female fertility, and RBC maturation. Thus, SR-BI represents a novel target which, after additional basic and clinical research, may prove valuable for the development of new pharmacological or genetic therapies to prevent or treat a variety of human diseases.

Acknowledgments

We acknowledge the invaluable contributions of our many colleagues and collaborators in our studies of SR-BI.

Address all correspondence and requests for reprints to: Monty Krieger, Department of Biology, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Room 68-483, Cambridge, Massachusetts 02139. E-mail: krieger@mit.edu

H.M. was a Postdoctoral Fellow supported by the Academy of Finland, Finnish Cultural Foundation, and Yrjo Jahnsson Foundation. A.R. is supported by Grant FONDECYT 8990006, and M.K. is supported by grants from the National Institutes of Health–National Heart, Lung and Blood Institute.

References

1. **Goldstein JL, Brown MS** 1990 Regulation of the mevalonate pathway. Nature 343:425–430
2. **Goldstein JL, Brown MS, Anderson RG, Russell DW, Schneider WJ** 1985 Receptor-mediated endocytosis: concepts emerging from the LDL receptor system. Annu Rev Cell Biol 1:1–39
3. **Kannel WB, Castelli WP, Gordon T, McNamara PM** 1971 Serum cholesterol, lipoproteins, and the risk of coronary heart disease. The Framingham study. Ann Intern Med 74:1–12
4. **Gordon T, Castelli WP, Hjortland MC, Kannel WB, Dawber TR** 1977 High density lipoprotein as a protective factor against coronary heart disease. Am J Med 62:707–714
5. **Havel RJ, Kane JP** 1995 Introduction: structure and metabolism of plasma lipoproteins. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic and molecular basis of inherited disease. 7th ed. New York: McGraw-Hill; 1841–1851
6. **Eisenberg S** 1984 High density lipoprotein metabolism. J Lipid Res 25:1017–1058
7. **Pieters MN, Schouten D, Van Berkel TJ** 1994 *In vitro* and *in vivo* evidence for the role of HDL in reverse cholesterol transport. Biochim Biophys Acta 1225:125–134
8. **Breslow JL** 1995 Familial disorders of high density lipoprotein metabolism. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. The metabolic and molecular basis of inherited disease. 7th ed. New York: McGraw-Hill; 2031–2052
9. **Tall AR** 1990 Plasma high density lipoproteins: metabolism and relationship to atherosclerosis. J Clin Invest 86:379–384
10. **Bruce C, Chouinard Jr RA, Tall AR** 1998 Plasma lipid transfer proteins, high-density lipoproteins, and reverse cholesterol transport. Annu Rev Nutr 18:297–330
11. **Rigotti A, Trigatti B, Babitt J, Penman M, Xu S, Krieger M** 1997 Scavenger receptor BI: a cell surface receptor for high density lipoprotein. Curr Opin Lipidol 8:181–188
12. **Krieger M** 1999 Charting the fate of the "good cholesterol": identification and characterization of the HDL receptor SR-BI. Annu Rev Biochem 68:523–588
13. **Krieger M** 1998 The "best" of cholesterols, the "worst" of cholesterols: a tale of two receptors. Proc Natl Acad Sci USA 95:4077–4080
14. **Trigatti B, Rigotti A, Krieger M** 2000 The role of the high-density lipoprotein receptor SR-BI in cholesterol metabolism. Curr Opin Lipidol 11:123–131
15. **Santamarina-Fojo S, Lambert G, Hoeg JM, Brewer HBJ** 2000 Lecithin-cholesterol acyltransferase: role in lipoprotein metabolism, reverse cholesterol transport and atherosclerosis. Curr Opin Lipidol 11:267–275
16. **Thuren T** 2000 Hepatic lipase and HDL metabolism. Curr Opin Lipidol 11:277–283
17. **Hayden MR, Clee SM, Brooks-Wilson A, Genest Jr J, Attie A, Kastelein JJ** 2000 Cholesterol efflux regulatory protein, Tangier disease and familial high-density lipoprotein deficiency. Curr Opin Lipidol 11:117–122
18. **Huuskonen J, Olkkonen VM, Jauhiainen M, Ehnholm C** 2001 The impact of phospholipid transfer protein (PLTP) on HDL metabolism. Atherosclerosis 155:269–281
19. **Fidge NH** 1999 High density lipoprotein receptors, binding proteins, and ligands. J Lipid Res 40:187–201
20. **Glass C, Pittman RC, Weinstein DB, Steinberg D** 1983 Dissociation of tissue uptake of cholesterol ester from that of apoprotein A-I of rat plasma high density lipoprotein: selective delivery of cholesterol ester to liver, adrenal, and gonad. Proc Natl Acad Sci USA 80:5435–5439
21. **Stein Y, Dabach Y, Hollander G, Halperin G, Stein O** 1983 Metabolism of HDL-cholesteryl ester in the rat, studied with a non-hydrolyzable analog, cholesteryl linoleyl ether. Biochim Biophys Acta 752:98–105
22. **Glass C, Pittman RC, Civen M, Steinberg D** 1985 Uptake of high-density lipoprotein-associated apoprotein A-I and cholesterol esters by 16 tissues of the rat *in vivo* and by adrenal cells and hepatocytes *in vitro*. J Biol Chem 260:744–750
23. **Pittman RC, Steinberg D** 1984 Sites and mechanisms of uptake and degradation of high density and low density lipoproteins. J Lipid Res 25:1577–1585
24. **Knecht TP, Pittman RC** 1989 A plasma membrane pool of cholesteryl esters that may mediate the selective uptake of cholesteryl esters from high-density lipoproteins. Biochim Biophys Acta 1002:365–375
25. **Rinninger F, Jaeckle S, Pittman RC** 1993 A pool of reversibly cell-associated cholesteryl esters involved in the selective uptake of cholesteryl esters from high-density lipoproteins by Hep G2 hepatoma cells. Biochim Biophys Acta 1166:275–283
26. **Pittman RC, Knecht TP, Rosenbaum MS, Taylor CAJ** 1987 A nonendocytotic mechanism for the selective uptake of high density lipoprotein-associated cholesterol esters. J Biol Chem 262:2443–2450
27. **Sparrow CP, Pittman RC** 1990 Cholesterol esters selectively taken up from high-density lipoproteins are hydrolyzed extralysosomally. Biochim Biophys Acta 1043:203–210
28. **DeLamatre JG, Carter RM, Hornick CA** 1991 Evidence for extralysosomal hydrolysis of high-density lipoprotein cholesteryl esters in rat hepatoma cells (Fu5AH): a model for delivery of high-density lipoprotein cholesterol. J Cell Physiol 146:18–24
29. **DeLamatre JG, Carter RM, Hornick CA** 1993 Evidence that a neutral cholesteryl ester hydrolase is responsible for the extraly-

sosomal hydrolysis of high-density lipoprotein cholesteryl ester in rat hepatoma cells (Fu5AH). J Cell Physiol 157:164–168
30. **Shimada A, Tamai T, Oida K, Takahashi S, Suzuki J, Nakai T, Miyabo S** 1994 Increase in neutral cholesteryl ester hydrolase activity produced by extralysosomal hydrolysis of high-density lipoprotein cholesteryl esters in rat hepatoma cells (H-35). Biochim Biophys Acta 1215:126–132
31. **Reaven E, Tsai L, Azhar S** 1996 Intracellular events in the "selective" transport of lipoprotein-derived cholesteryl esters. J Biol Chem 271:16208–16217
32. **Connelly MA, Kellner-Weibel G, Rothbla GH, Williams DL** 2003 SR-BI-directed HDL-cholesteryl ester hydrolysis. J Lipid Res 44: 331–341
33. **Glass C, Pittman RC, Keller GA, Steinberg D** 1983 Tissue sites of degradation of apoprotein A-I in the rat. J Biol Chem 258:7161–7167
34. **Kozyraki R, Fyfe J, Kristiansen M, Gerdes C, Jacobsen C, Cui S, Christensen EI, Aminoff M, de la Chapelle A, Krahe R, Verroust PJ, Moestrup SK** 1999 The intrinsic factor-vitamin B12 receptor, cubilin, is a high-affinity apolipoprotein A-I receptor facilitating endocytosis of high-density lipoprotein. Nat Med 5:656–661
35. **Hammad SM, Stefansson S, Twal WO, Drake CJ, Fleming P, Remaley A, Brewer Jr HB, Argraves WS** 1999 Cubilin, the endocytic receptor for intrinsic factor-vitamin B(12) complex, mediates high-density lipoprotein holoparticle endocytosis. Proc Natl Acad Sci USA 96:10158–10163
36. **Bothman KM, Bravo E** 1995 The role of lipoprotein cholesterol in biliary steroid secretion. Studies with *in vivo* experimental models. Prog Lipid Res 34:71–97
37. **Leitersdorf E, Stein O, Eisenberg S, Stein Y** 1984 Uptake of rat plasma HDL subfractions labeled with [^{3}H]cholesteryl linoleyl ether or with ^{125}I by cultured rat hepatocytes and adrenal cells. Biochim Biophys Acta 796:72–82
38. **Reaven E, Chen YD, Spicher M, Azhar S** 1984 Morphological evidence that high density lipoproteins are not internalized by steroid producing cells during *in situ* organ perfusion. J Clin Invest 74:1384–1397
39. **Reaven E, Zhan L, Nomoto A, Leers-Sucheta S, Azhar S** 2000 Expression and microvillar localization of scavenger receptor class B, type I (SR-BI) and selective cholesteryl ester uptake in Leydig cells from rat testis. J Lipid Res 41:343–356
40. **Gwynne JT, Mahaffee DD** 1989 Rat adrenal uptake and metabolism of high density lipoprotein cholesteryl ester. J Biol Chem 264:8141–8150
41. **Glomset JA** 1968 The plasma lecithin:cholesterol acyltransferase reaction. J Lipid Res 9:155–167
42. **Brown MS, Goldstein JL** 1986 A receptor-mediated pathway for cholesterol homeostasis. Science 232:33–47
43. **Krieger M, Herz J** 1994 Structures and functions of multiligand lipoprotein receptors: macrophage scavenger receptors and LDL receptor-related protein (LRP). Annu Rev Biochem 63:601–637
44. **Herz J, Gotthardt M, Willnow TE** 2000 Cellular signalling by lipoprotein receptors. Curr Opin Lipidol 11:161–166
45. **Willnow TE, Nykjaer A, Herz J** 1999 Lipoprotein receptors: new roles for ancient proteins. Nat Cell Biol 1:E157–E162
46. **Garcia CK, Wilund K, Arca M, Zuliani G, Fellin R, Maioli M, Calandra S, Bertolini S, Cossu F, Grishin N, Barnes R, Cohen JC, Hobbs HH** 2001 Autosomal recessive hypercholesterolemia caused by mutations in a putative LDL receptor adaptor protein. Science 292:1394–1398
47. **Brown MS, Goldstein JL** 1999 A proteolytic pathway that controls the cholesterol content of membranes, cells, and blood. Proc Natl Acad Sci USA 96:11041–11048
48. **Gwynne JT, Strauss III JF** 1982 The role of lipoproteins in steroidogenesis and cholesterol metabolism in steroidogenic glands. Endocr Rev 3:299–329
49. **Illingworth DR, Kenny TA, Connor WE, Orwoll E, S** 1982 Corticosteroid production in abetalipoproteinemia: evidence for an impaired response ACTH. J Lab Clin Med 100:115–126
50. **Illingworth DR, Kenny TA, Orwoll ES** 1982 Adrenal function in heterozygous and homozygous hypobetalipoproteinemia. J Clin Endocrinol Metab 54:27–33
51. **Illingworth DR, Corbin DK, Kemp ED, Keenan EJ** 1982 Hormone changes during the menstrual cycle in abetalipoproteinemia: reduced luteal phase progesterone in a patient with homozygous hypobetalipoproteinemia. Proc Natl Acad Sci USA 79:6685–6689
52. **Illingworth DR, Lees AM, Lees RS** 1983 Adrenal cortical function in homozygous familial hypercholesterolemia. Metabolism 32:1045–1052
53. **Laue L, Hoeg JM, Barnes K, Loriaux DL, Chrousos GP** 1987 The effect of mevinolin on steroidogenesis in patients with defects in the low density lipoprotein receptor pathway. J Clin Endocrinol Metab 64:531–535
54. **Illingworth DR, Alam NA, Lindsey S** 1984 Adrenocortical response to adrenocorticotropin in heterozygous familial hypercholesterolemia. J Clin Endocrinol Metab 58:206–211
55. **Allen JM, Thompson GR, Myant NB** 1983 Normal adrenocortical response to adrenocorticotrophic hormone in patients with homozygous familial hypercholesterolaemia. Clin Sci (Lond) 65:99–101
56. **Hoeg JM, Loriaux L, Gregg RE, Green WR, Brewer HBJ** 1985 Impaired adrenal reserve in the Watanabe Heritable Hyperlipidemic rabbit: implications for LDL-receptor function in steroidogenesis. Metabolism 34:194–197
57. **Robins ED, Nelson LM, Hoeg JM** 1994 Aberrant hypothalamic-pituitary-ovarian axis in the Watanabe heritable hyperlipidemic rabbit. J Lipid Res 35:52–59
58. **Mortensen A, Frandsen H** 1996 Reproductive performance and changes in blood lipids in breeding females and in growing Watanabe heritable hyperlipidaemic and New Zealand White rabbits. Lab Anim 30:252–259
59. **Sturley RH, Stirling C, McGarrigle HH, Katz M, Reckless JP, Betteridge DJ** 1991 Effects of pravastatin and cholestyramine on gonadal and adrenal steroid production in familial hypercholesterolaemia. Br J Clin Pharmacol 32:417–422
60. **Purvis K, Tollefsrud A, Rui H, Haug E, Norseth J, Viksmoen L, Ose L, Lund H** 1992 Short-term effects of treatment with simvastatin on testicular function in patients with heterozygous familial hypercholesterolaemia. Eur J Clin Pharmacol 42:61–64
61. **Krieger M** 1992 Molecular flypaper and atherosclerosis: structure of the macrophage scavenger receptor. Trends Biochem Sci 17:141–146
62. **Krieger M, Acton S, Ashkenas J, Pearson A, Penman M, Resnick D** 1993 Molecular flypaper, host defense, and atherosclerosis. Structure, binding properties, and functions of macrophage scavenger receptors. J Biol Chem 268:4569–4572
63. **Krieger M, Stern DM** 2001 Series introduction: multiligand receptors and human disease. J Clin Invest 108:645–647
64. **Kodama T, Doi T, Suzuki H, Takahashi K, Wada Y, Gordon S** 1996 Collagenous macrophage scavenger receptors. Curr Opin Lipidol 7:287–291
65. **Krieger M** 1997 The other side of scavenger receptors: pattern recognition for host defense. Curr Opin Lipidol 8:275–280
66. **Greaves DR, Gough PJ, Gordon S** 1998 Recent progress in defining the role of scavenger receptors in lipid transport, atherosclerosis and host defence. Curr Opin Lipidol 9:425–432
67. **Steinberg D, Dhaliwal BS, Steinbrecher UP** 1999 Scavenger receptors and oxidized low density lipoproteins. Clin Chim Acta 286:191–205
68. **Johnson WJ, Mahlberg FH, Rothblat GH, Phillips MC** 1991 Cholesterol transport between cells and high-density lipoproteins. Biochem Biophys Acta 1085:273–298
69. **Assmann G, Schmitz G, Brewer HBJ** 1995 Familial HDL deficiency: Tangier disease. In: Scriver CR, Beaudet AS, Sly WS, Valle D, eds. The metabolic and molecular bases of inherited diseases. 6th ed. New York: McGraw-Hill; 2053–2072
70. **Acton SL, Scherer PE, Lodish HF, Krieger M** 1994 Expression cloning of SR-BI, a CD36-related class B scavenger receptor. J Biol Chem 269:21003–21009
71. **Acton S, Rigotti A, Landschulz KT, Xu S, Hobbs HH, Krieger M** 1996 Identification of scavenger receptor SR-BI as a high density lipoprotein receptor. Science 271:518–520
72. **Webb NR, de Villiers WJ, Connell PM, de Beer FC, van der Westhuyzen DR** 1997 Alternative forms of the scavenger receptor BI (SR-BI). J Lipid Res 38:1490–1495
73. **Calvo D, Dopazo J, Vega MA** 1995 The CD36, CLA-1 (CD36L1), and LIMPII (CD36L2) gene family: cellular distribution, chromosomal location, and genetic evolution. Genomics 25:100–106
74. **Oquendo P, Hundt E, Lawler J, Seed B** 1989 CD36 directly me-

diates cytoadherence of *Plasmodium falciparum* parasitized erythrocytes. Cell 58:95–101
75. **Vega MA, Segui-Real B, Garcia JA, Cales C, Rodriguez F, Vanderkerckhove J, Sandoval IV** 1991 Cloning, sequencing, and expression of a cDNA encoding rat LIMP II, a novel 74-kDa lysosomal membrane protein related to the surface adhesion protein CD36. J Biol Chem 266:16818–16824
76. **Hart K, Wilcox M** 1993 A Drosophila gene encoding an epithelial membrane protein with homology to CD36/LIMP II. J Mol Biol 234:249–253
77. **Franc NC, Dimarcq JL, Lagueux M, Hoffmann J, Ezekowitz RA** 1996 Croquemort, a novel Drosophila hemocyte/macrophage receptor that recognizes apoptotic cells. Immunity 4:431–443
78. **Franc NC, Heitzler P, Ezekowitz RA, White K** 1999 Requirement for croquemort in phagocytosis of apoptotic cells in *Drosophila*. Science 284:1991–1994
79. **Rogers ME, Sun M, Lerner MR, Vogt RG** 1997 Snmp-1, a novel membrane protein of olfactory neurons of the silk moth *Antheraea polyphemus* with homology to the CD36 family of membrane proteins. J Biol Chem 272:14792–14799
80. **Cao G, Garcia CK, Wyne KL, Schultz RA, Parker KL, Hobbs HH** 1997 Structure and localization of the human gene encoding SR-BI/CLA-1. Evidence for transcriptional control by steroidogenic factor 1. J Biol Chem 272:33068–33076
81. **Armesilla AL, Vega MA** 1994 Structural organization of the gene for human CD36 glycoprotein. J Biol Chem 269:18985–18991
82. **Calvo D, Vega MA** 1993 Identification, primary structure, and distribution of CLA-1, a novel member of the CD36/LIMPII gene family. J Biol Chem 268:18929–18935
83. **Hirano K, Tsukamoto K, Zhongyan Z, Matsuyama A, Tsujji K, Shishio N, Yamashita S, Matsuzawa Y** 2000 Macrophage-specific variant of human scavenger receptor class B type I (SR-BI), SR-BIII, has possible function to regulate direction of SR-BI-mediated cholesterol flux as an accessory protein. Circulation 102:II86
84. **Babitt J, Trigatti B, Rigotti A, Smart EJ, Anderson RG, Xu S, Krieger M** 1997 Murine SR-BI, a high density lipoprotein receptor that mediates selective lipid uptake, is N-glycosylated and fatty acylated and colocalizes with plasma membrane caveolae. J Biol Chem 272:13242–13249
85. **Vinals M, Xu S, Vasile E, Krieger M** 2003 Identification of the N-linked glycosylation sites on the high density lipoprotein (HDL) receptor SR-BI and assessment of their effects on HDL binding and selective lipid uptake. J Biol Chem 278:5325–5332
86. **Tao N, Wagner SJ, Lublin DM** 1996 CD36 is palmitoylated on both N- and C-terminal cytoplasmic tails. J Biol Chem 271:22315–22320
87. **Gu X, Trigatti B, Xu S, Acton S, Babitt J, Krieger M** 1998 The efficient cellular uptake of high density lipoprotein lipids via scavenger receptor class B type I requires not only receptor-mediated surface binding but also receptor-specific lipid transfer mediated by its extracellular domain. J Biol Chem 273:26338–26348
88. **Webb NR, Connell PM, Graf GA, Smart EJ, de Villiers WJ, de Beer FC, van der Westhuyzen DR** 1998 SR-BII, an isoform of the scavenger receptor BI containing an alternate cytoplasmic tail, mediates lipid transfer between high density lipoprotein and cells. J Biol Chem 273:15241–15248
89. **Kozarsky KF, Donahee MH, Rigotti A, Iqbal SN, Edelman ER, Krieger M** 1997 Overexpression of the HDL receptor SR-BI alters plasma HDL and bile cholesterol levels. Nature 387:414–417
90. **Stangl H, Graf GA, Yu L, Cao G, Wyne K** 2002 Effect of estrogen on scavenger receptor BI expression in the rat. J Endocrinol 175: 663–672
91. **Mardones P, Pilon A, Bouly M, Duran D, Nishimoto T, Arai H, Kozarsky KF, Altayo M, Miquel JF, Luc GV, Staels B, Rigotti A** 2003 Fibrates down-regulate hepatic scavenger receptor class B type I (SR-BI) protein expression in mice. J Biol Chem 278:7884–7890
92. **Burgos P, Klattenhoff C, Rigotti A, González A** 1999 Polarized basolateral distribution of HDL receptor SR-BI is disrupted by cholesterol depletion. Mol Biol Cell 10S:A1763
93. **Silver DL, Wang N, Xiao X, Tall AR** 2001 High density lipoprotein (HDL) particle uptake mediated by scavenger receptor class B type 1 results in selective sorting of HDL cholesterol from protein and polarized cholesterol secretion. J Biol Chem 276:25287–25293
94. **Cai SF, Kirby RJ, Howles PN, Hui DY** 2001 Differentiation-dependent expression and localization of the class B type I scavenger receptor in intestine. J Lipid Res 42:902–909
95. **Voshol PJ, Schwarz M, Rigotti A, Krieger M, Groen AK, Kuipers F** 2001 Down-regulation of intestinal scavenger receptor class B, type I (SR-BI) expression in rodents under conditions of deficient bile delivery to the intestine. Biochem J 356:317–325
96. **Miquel JF, Moreno M, Santibañez E, Amigo L, Wistuba I, Acton S, Rigotti A** 2000 Expression and regulation of scavenger receptor class B type I (SR-BI) in human and murine gallbladder epithelial cells. Gastroenterology 188:A134
97. **Ikemoto M, Arai H, Feng D, Tanaka K, Aoki J, Dohmae N, Takio K, Adachi H, Tsujimoto M, Inoue K** 2000 Identification of a PDZ-domain-containing protein that interacts with the scavenger receptor class B type I. Proc Natl Acad Sci USA 97:6538–6543
98. **Silver DL** 2002 A carboxyl-terminal PDZ-interacting domain of scavenger receptor B, type I is essential for cell surface expression in liver. J Biol Chem 277:34042–34047
99. **Gillotte-Taylor K, Boullier A, Witztum JL, Steinberg D, Quehenberger O** 2001 Scavenger receptor class B type I as a receptor for oxidized low density lipoprotein. J Lipid Res 42:1474–1482
100. **Marsche G, Hammer A, Oskolkova O, Kozarsky KF, Sattler W, Malle E** 2002 Hypochlorite-modified high density lipoprotein, a high affinity ligand to scavenger receptor class B, type I impairs high density lipoprotein-dependent selective lipid uptake and reverse cholesterol transport. J Biol Chem 277:32172–32179
101. **Ohgami N, Nagai R, Miyazaki A, Ikemoto M, Arai H, Horiuchi S, Nakayama H** 2001 Scavenger receptor class B type I-mediated reverse cholesterol transport is inhibited by advanced glycation end products. J Biol Chem 276:13348–13355
102. **Rigotti A, Acton SL, Krieger M** 1995 The class B scavenger receptors SR-BI and CD36 are receptors for anionic phospholipids. J Biol Chem 270:16221–16224
103. **Fukasawa M, Adachi H, Hirota K, Tsujimoto M, Arai H, Inoue K** 1996 SRB1, a class B scavenger receptor, recognizes both negatively charged liposomes and apoptotic cells. Exp Cell Res 222:246–250
104. **Murao K, Terpstra V, Green SR, Kondratenko N, Steinberg D, Quehenberger O** 1997 Characterization of CLA-1, a human homologue of rodent scavenger receptor BI, as a receptor for high density lipoprotein and apoptotic thymocytes. J Biol Chem 272: 17551–17557
105. **Shiratsuchi A, Kawasaki Y, Ikemoto M, Arai H, Nakanishi Y** 1999 Role of class B scavenger receptor type I in phagocytosis of apoptotic rat spermatogenic cells by Sertoli cells. J Biol Chem 274: 5901–5908
106. **Svensson PA, Johnson MS, Ling C, Carlsson LM, Billig H, Carlsson B** 1999 Scavenger receptor class B type I in the rat ovary: possible role in high density lipoprotein cholesterol uptake and in the recognition of apoptotic granulosa cells. Endocrinology 140: 2494–2500
107. **Imachi H, Murao K, Hiramine C, Sayo Y, Sato M, Hosokawa H, Ishida T, Kodama T, Quehenberger O, Steinberg D, Takahara J** 2000 Human scavenger receptor B1 is involved in recognition of apoptotic thymocytes by thymic nurse cells. Lab Invest 80:263–270
108. **Paresce DM, Ghosh RN, Maxfield FR** 1996 Microglial cells internalize aggregates of the Alzheimer's disease amyloid β-protein via a scavenger receptor. Neuron 17:553–565
109. **Husemann J, Loike JD, Kodama T, Silverstein SC** 2001 Scavenger receptor class B type I (SR-BI) mediates adhesion of neonatal murine microglia to fibrillar β-amyloid. J Neuroimmunol 114:142–150
110. **Husemann J, Silverstein SC** 2001 Expression of scavenger receptor class B, type I, by astrocytes and vascular smooth muscle cells in normal adult mouse and human brain and in Alzheimer's disease brain. Am J Pathol 158:825–832
111. **Scarselli E, Ansuini H, Cerino R, Roccasecca RM, Acali S, Filocamo G, Traboni C, Nicosia A, Cortese R, Vitelli A** 2002 The human scavenger receptor class B type I is a novel candidate receptor for the hepatitis C virus. EMBO J 21:5017–5025
112. **Gu X, Lawrence R, Krieger M** 2000 Dissociation of the high density lipoprotein and low density lipoprotein binding activities of murine scavenger receptor class B type I (mSR-BI) using retrovirus library-based activity dissection. J Biol Chem 275:9120–9130
113. **Calvo D, Gomez-Coronado D, Lasuncion MA, Vega MA** 1997

CLA-1 is an 85-kD plasma membrane glycoprotein that acts as a high-affinity receptor for both native (HDL, LDL, and VLDL) and modified (OxLDL and AcLDL) lipoproteins. Arterioscler Thromb Vasc Biol 17:2341–2349

114. **Brissette L, Noel SP** 1986 The effects of human low and high density lipoproteins on the binding of rat intermediate density lipoproteins to rat liver membranes. J Biol Chem 261:6847–6852
115. **Ashkenas J, Penman M, Vasile E, Acton S, Freeman M, Krieger M** 1993 Structures and high and low affinity ligand binding properties of murine type I and type II macrophage scavenger receptors. J Lipid Res 34:983–1000
116. **Gu X, Kozarsky K, Krieger M** 2000 Scavenger receptor, class B, type I-mediated [^{3}H]cholesterol efflux to high density and low density lipoproteins is dependent on lipoprotein binding to the receptor. J Biol Chem 275:29993–30001
117. **Liadaki KN, Liu T, Xu S, Ishida BY, Duchateaux PN, Krieger JP, Kane J, Krieger M, Zannis VI** 2000 Binding of high density lipoprotein (HDL) and discoidal reconstituted HDL to the HDL receptor scavenger receptor class B type I. Effect of lipid association and APOA-I mutations on receptor binding. J Biol Chem 275: 21262–21271
118. **de Beer MC, Durbin DM, Cai L, Jonas A, de Beer FC, van der Westhuyzen DR** 2001 Apolipoprotein A-I conformation markedly influences HDL interaction with scavenger receptor BI. J Lipid Res 42:309–313
119. **Xu S, Laccotripe M, Huang X, Rigotti A, Zannis VI, Krieger M** 1997 Apolipoproteins of HDL can directly mediate binding to the scavenger receptor SR-BI, an HDL receptor that mediates selective lipid uptake. J Lipid Res 38:1289–1298
120. **Williams DL, de La Llera-Moya M, Thuahnai ST, Lund-Katz S, Connelly MA, Azhar S, Anantharamaiah GM, Phillips MC** 2000 Binding and cross-linking studies show that scavenger receptor BI interacts with multiple sites in apolipoprotein A-I and identify the class A amphipathic α-helix as a recognition motif. J Biol Chem 275:18897–18904
121. **Li X, Kan HY, Lavrentiadou SN, Krieger M, Zannis VI** 2002 Reconstituted discoidal ApoE-phospholipid particles are ligands for the scavenger receptor BI. The amino terminal 1–165 domain of ApoE suffices for receptor binding. J Biol Chem 277:21149–21157
122. **Bultel-Brienne S, Lestavel S, Pilon A, Laffont I, Tailleux A, Fruchart JC, Siest G, Clavey V** 2002 Lipid free apolipoprotein E binds to the class B type I scavenger receptor I (SR-BI) and enhances cholesteryl ester uptake from lipoproteins. J Biol Chem 277:36092–36099
123. **Pilon A, Briand O, Lestavel S, Copin C, Majd Z, Fruchart JC, Castro G, Clavey V** 2000 Apolipoprotein AII enrichment of HDL enhances their affinity for class B type I scavenger receptor but inhibits specific cholesteryl ester uptake. Arterioscler Thromb Vasc Biol 20:1074–1081
124. **de Beer MC, Durbin DM, Cai L, Mirocha N, Jonas A, Webb NR, de Beer FC, van Der Westhuyzen DR** 2001 Apolipoprotein A-II modulates the binding and selective lipid uptake of reconstituted high density lipoprotein by scavenger receptor BI. J Biol Chem 276:15832–15839
125. **Liu T, Krieger M, Kan HY, Zannis VI** 2002 The effects of mutations in helices 4 and 6 of apoA-I on SR-BI-mediated cholesterol efflux suggest that formation of a productive complex between reconstituted HDL and SR-BI is required for efficient lipid transport. J Biol Chem 277:21576–21584
126. **Ji Y, Jian B, Wang N, Sun Y, Moya ML, Phillips MC, Rothblat GH, Swaney JB, Tall AR** 1997 Scavenger receptor BI promotes high density lipoprotein-mediated cellular cholesterol efflux. J Biol Chem 272:20982–20985
127. **Jian B, de la Llera-Moya M, Ji Y, Wang N, Phillips MC, Swaney JB, Tall AR, Rothblat GH** 1998 Scavenger receptor class B type I as a mediator of cellular cholesterol efflux to lipoproteins and phospholipid acceptors. J Biol Chem 273:5599–5606
128. **Stangl H, Hyatt M, Hobbs HH** 1999 Transport of lipids from high and low density lipoproteins via scavenger receptor-BI. J Biol Chem 274:32692–32698
129. **Ji Y, Wang N, Ramakrishnan R, Sehayek E, Huszar D, Breslow JL, Tall AR** 1999 Hepatic scavenger receptor BI promotes rapid clearance of high density lipoprotein free cholesterol and its transport into bile. J Biol Chem 274:33398–33402
130. **Urban S, Zieseniss S, Werder M, Hauser H, Budzinski R, Engelmann B** 2000 Scavenger receptor BI transfers major lipoprotein associated phospholipids into the cells. J Biol Chem 275:33409–33341
131. **Greene DJ, Skeggs JW, Morton RE** 2001 Elevated triglyceride content diminishes the capacity of high density lipoprotein to deliver cholesteryl esters via the scavenger receptor class B type I (SR-BI). J Biol Chem 276:4804–4811
132. **Goti D, Hrzenjak A, Levak-Frank S, Frank S, van Der Westhuyzen DR, Malle E, Sattler W** 2001 Scavenger receptor class B, type I is expressed in porcine brain capillary endothelial cells and contributes to selective uptake of HDL-associated vitamin E. J Neurochem 76:498–508
133. **Mardones P, Strobel P, Miranda S, Leighton F, Quinones V, Amigo L, Rozowski J, Krieger M, Rigotti A** 2002 α-Tocopherol metabolism is abnormal in scavenger receptor class B type I (SR-BI)-deficient mice. J Nutr 132:443–449
134. **Reaven E, Leers-Sucheta S, Nomoto A, Azhar S** 2001 Expression of scavenger receptor class B type 1 (SR-BI) promotes microvillar channel formation and selective cholesteryl ester transport in a heterologous reconstituted system. Proc Natl Acad Sci USA 98: 1613–1618
135. **Thuahnai ST, Lund-Katz S, Williams DL, Phillips MC** 2001 Scavenger receptor class B, type I-mediated uptake of various lipids into cells. Influence of the nature of the donor particle interaction with the receptor. J Biol Chem 276:43801–43808
136. **Temel RE, Trigatti B, DeMattos RB, Azhar S, Krieger M, Williams DL** 1997 Scavenger receptor class B, type I (SR-BI) is the major route for the delivery of high density lipoprotein cholesterol to the steroidogenic pathway in cultured mouse adrenocortical cells. Proc Natl Acad Sci USA 94:13600–13605
137. **Reaven E, Nomoto A, Leers-Sucheta S, Temel R, Williams DL, Azhar S** 1998 Expression and microvillar localization of scavenger receptor, class B, type I (a high density lipoprotein receptor) in luteinized and hormone-desensitized rat ovarian models. Endocrinology 139:2847–2856
138. **Mackinnon M, Savage J, Wishart R, Barter P** 1986 Metabolism of high density lipoproteins by the perfused rabbit liver. J Biol Chem 261:2548–2552
139. **Arbeeny CM, Rifici VA, Eder HA** 1987 The uptake of the apoprotein and cholesteryl ester of high-density lipoproteins by the perfused rat liver. Biochim Biophys Acta 917:9–17
140. **Brissette, L, Charest MC, Falstrault L, Lafond J, Rhainds D, Tremblay C, Truong TQ** 1999 Selective uptake of cholesteryl esters from various classes of lipoproteins by HepG2 cells. Biochem Cell Biol 77:157–163
141. **Pittman RC, Glass CK, Atkinson D, Small DM** 1987 Synthetic high density lipoprotein particles. Application to studies of the apoprotein specificity for selective uptake of cholesterol esters. J Biol Chem 262:2435–2442
142. **Brissette L, Falstrault L** 1994 Analysis of the selective uptake of the cholesteryl ester of human intermediate density lipoproteins by HepG2 cells. Biochim Biophys Acta 1213:5–13
143. **Brissette L, Falstrault L, Lafond J, Izem L** 1996 The selective uptake of the cholesteryl esters of low density lipoproteins parallels the activity of protein kinase C. Biochim Biophys Acta 1301:133–140
144. **Green SR, Pittman RC** 1991 Selective uptake of cholesteryl esters from low density lipoproteins *in vitro* and *in vivo*. J Lipid Res 32:667–678
145. **Rinninger F, Brundert M, Jackle S, Kaiser T, Greten H** 1995 Selective uptake of low-density lipoprotein-associated cholesteryl esters by human fibroblasts, human HepG2 hepatoma cells and J774 macrophages in culture. Biochim Biophys Acta 1255:141–153
146. **Swarnakar S, Temel RE, Connelly MA, Azhar S, Williams DL** 1999 Scavenger receptor class B, type I, mediates selective uptake of low density lipoprotein cholesteryl ester. J Biol Chem 274:29733–29739
147. **Stangl H, Cao G, Wyne KL, Hobbs HH** 1998 Scavenger receptor, class B, type I-dependent stimulation of cholesterol esterification by high density lipoproteins, low density lipoproteins, and nonlipoprotein cholesterol. J Biol Chem 273:31002–31008

148. **Connelly MA, Klein SM, Azhar S, Abumrad NA, Williams DL** 1999 Comparison of class B scavenger receptors, CD36 and scavenger receptor BI (SR-BI), shows that both receptors mediate high density lipoprotein-cholesteryl ester selective uptake but SR-BI exhibits a unique enhancement of cholesteryl ester uptake. J Biol Chem 274:41–47
149. **Webb NR, de Beer MC, Yu J, Kindy MS, Daugherty A, van der Westhuyzen DR, de Beer FC** 2002 Overexpression of SR-BI by adenoviral vector promotes clearance of apoA-I, but not apoB, in human apoB transgenic mice. J Lipid Res 43:1421–1428
150. **Rinninger F, Brundert M, Budzinski RM, Fruchart JC, Greten H, Castro GR** 2003 Scavenger receptor BI (SR-BI) mediates a higher selective cholesteryl ester uptake from LpA-I compared with LpA-I:A-II lipoprotein particles. Atherosclerosis 166:31–40
151. **Rinninger F, Kaiser T, Mann WA, Meyer N, Greten H, Beisiegel U** 1998 Lipoprotein lipase mediates an increase in the selective uptake of high density lipoprotein-associated cholesteryl esters by hepatic cells in culture. J Lipid Res 39:1335–1348
152. **Rinninger F, Mann WA, Kaiser T, Ahle S, Meyer N, Greten H** 1998 Hepatic lipase mediates an increase in selective uptake of high-density lipoprotein-associated cholesteryl esters by human Hep 3B hepatoma cells in culture. Atherosclerosis 141:273–285
153. **Buton X, Mamdouh Z, Ghosh R, Du H, Kuriakose G, Beatini N, Grabowski GA, Maxfield FR, Tabas I** 1999 Unique cellular events occurring during the initial interaction of macrophages with matrix-retained or methylated aggregated low density lipoprotein (LDL). Prolonged cell-surface contact during which LDL-cholesteryl ester hydrolysis exceeds LDL protein degradation. J Biol Chem 274:32112–32121
154. **Swarnakar S, Beers J, Strickland DK, Azhar S, Williams DL** 2001 The apolipoprotein E-dependent low density lipoprotein cholesteryl ester selective uptake pathway in murine adrenocortical cells involves chondroitin sulfate proteoglycans and an α2-macroglobulin receptor. J Biol Chem 276:21121–21128
155. **Seo T, Al-Haideri M, Treskova E, Worgall TS, Kako J, Goldberg IJ, Deckelbaum RJ** 2000 Lipoprotein lipase-mediated selective uptake from low density lipoprotein requires cell surface proteoglycans and is independent of scavenger receptor class B type 1. J Biol Chem 275:30355–30362
156. **Calvo D, Gomez-Coronado D, Suarez Y, Lasuncion MA, Vega MA** 1998 Human CD36 is a high affinity receptor for the native lipoproteins HDL, LDL, and VLDL. J Lipid Res 39:777–788
157. **Nieland TJ, Penman M, Dori L, Krieger M, Kirchhausen T** 2002 Discovery of chemical inhibitors of the selective transfer of lipids mediated by the HDL receptor SR-BI. Proc Natl Acad Sci USA 99:15422–15427
158. **Temel RE, Walzem RL, Banka CL, Williams DL** 2002 Apolipoprotein A-I is necessary for the *in vivo* formation of HDL competent for scavenger receptor-mediated cholesteryl ester selective uptake. J Biol Chem 277:26565–26572
159. **Frank PG, Marcel YL, Connelly MA, Lublin DM, Franklin V, Williams DL, Lisanti MP** 2002 Stabilization of caveolin-1 by cellular cholesterol and scavenger receptor class B type I. Biochemistry 41:11931–11940
160. **Graf GA, Connell PM, van der Westhuyzen DR, Smart EJ** 1999 The class B, type I scavenger receptor promotes the selective uptake of high density lipoprotein cholesterol ethers into caveolae. J Biol Chem 274:12043–12048
161. **Matveev S, van der Westhuyzen DR, Smart EJ** 1999 Co-expression of scavenger receptor-BI and caveolin-1 is associated with enhanced selective cholesteryl ester uptake in THP-1 macrophages. J Lipid Res 40:1647–1654
162. **Murata M, Peranen J, Schreiner R, Wieland F, Kurzchalia TV, Simons K** 1995 VIP21/caveolin is a cholesterol-binding protein. Proc Natl Acad Sci USA 92:10339–10343
163. **Graf GA, Matveev SV, Smart EJ** 1999 Class B scavenger receptors, caveolae and cholesterol homeostasis. Trends Cardiovasc Med 9:221–225
164. **Ikonen E, Parton RG** 2000 Caveolins and cellular cholesterol balance. Traffic 1:212–217
165. **Uittenbogaard A, Everson WV, Matveev SV, Smart EJ** 2002 Cholesteryl ester is transported from caveolae to internal membranes as part of a caveolin-annexin II lipid-protein complex. J Biol Chem 277:4925–4931
166. **Matveev S, Uittenbogaard A, van Der Westhuyzen D, Smart EJ** 2001 Caveolin-1 negatively regulates SR-BI mediated selective uptake of high-density lipoprotein-derived cholesteryl ester. Eur J Biochem 268:5609–5616
167. **Wang L, Connelly MA, Ostermeyer AG, Chen HH, Williams DL, Brown DA** 2003 Caveolin-1 does not affect SR-BI-mediated cholesterol efflux or selective uptake of cholesteryl ester in two cell lines. J Lipid Res 44:807–815
168. **Briand O, Lestavel S, Pilon A, Torpier G, Fruchart JC, Clavey V** 2003 SR-BI does not require raft/caveola localisation for cholesteryl ester selective uptake in the human adrenal cell line NCI-H295R. Biochim Biophys Acta 1631:42–50
169. **Rigotti A, Edelman ER, Seifert P, Iqbal SN, DeMattos RB, Temel RE, Krieger M, Williams DL** 1996 Regulation by adrenocorticotropic hormone of the *in vivo* expression of scavenger receptor class B type I (SR-BI), a high density lipoprotein receptor, in steroidogenic cells of the murine adrenal gland. J Biol Chem 271:33545–33549
170. **Reaven E, Spicher M, Azhar S** 1989 Microvillar channels: a unique plasma membrane compartment for concentrating lipoproteins on the surface of rat adrenal cortical cells. J Lipid Res 30:1551–1560
171. **Reaven E, Shi XY, Azhar S** 1990 Interaction of lipoproteins with isolated ovary plasma membranes. J Biol Chem 265:19100–19111
172. **Plump AS, Erickson SK, Weng W, Partin JS, Brewslow JL, Williams DL** 1996 Apolipoprotein A-I is required for cholesteryl ester accumulation in steroidogenic cells and for normal adrenal steroid production. J Clin Invest 97:2660–2671
173. **Williams DL, Wong JS, Hamilton RL** 2002 SR-BI is required for microvillar channel formation and the localization of HDL particles to the surface of adrenocortical cells *in vivo*. J Lipid Res 43:544–549
174. **Silver DL, Wang N, Tall AR** 2000 Defective HDL particle uptake in ob/ob hepatocytes causes decreased recycling, degradation, and selective lipid uptake. J Clin Invest 105:151–159
175. **Liu B, Krieger M** 2002 Highly purified scavenger receptor class B, type I reconstituted into phosphatidylcholine/cholesterol liposomes mediates high affinity HDL binding and selective lipid uptake. J Biol Chem 277:34125–34135
176. **Santamarina-Fojo S, Haudenschild C, Amar M** 1998 The role of hepatic lipase in lipoprotein metabolism and atherosclerosis. Curr Opin Lipidol 9:211–219
177. **Wang N, Weng W, Breslow JL, Tall AR** 1996 Scavenger receptor BI (SR-BI) is up-regulated in adrenal gland in apolipoprotein A-I and hepatic lipase knockout mice as a response to depletion of cholesterol stores. J Biol Chem 271:21001–21004
178. **Komaromy M, Azhar S, Cooper AD** 1996 Chinese hamster ovary cells expressing a cell surface-anchored form of hepatic lipase. Characterization of low density lipoprotein and chylomicron remnant uptake and selective uptake of high density lipoprotein-cholesteryl ester. J Biol Chem 271:16906–16914
179. **Bergeron N, Kotite L, Verges M, Blanche P, Hamilton RL, Krauss RM, Bensadoun A, Havel RJ** 1998 Lamellar lipoproteins uniquely contribute to hyperlipidemia in mice doubly deficient in apolipoprotein E and hepatic lipase. Proc Natl Acad Sci USA 95:15647–15652
180. **Lambert G, Chase MB, Dugi K, Bensadoun A, Brewer Jr HB, Santamarina-Fojo S** 1999 Hepatic lipase promotes the selective uptake of high density lipoprotein-cholesteryl esters via the scavenger receptor B1. J Lipid Res 40:1294–1303
181. **Collet X, Tall AR, Serajuddin H, Guendouzi K, Royer L, Oliveira H, Barbaras R, Jiang XC, Francone OL** 1999 Remodeling of HDL by CETP *in vivo* and by CETP and hepatic lipase *in vitro* results in enhanced uptake of HDL CE by cells expressing scavenger receptor B-I. J Lipid Res 40:1185–1193
182. **Landschulz K, Pathak R, Rigotti A, Krieger M, Hobbs H** 1996 Regulation of scavenger receptor, class B, type I, a high density lipoprotein receptor, in liver and steroidogenic tissues of the rat. J Clin Invest 98:984–995
183. **Verhoeven AJ, Carling D, Jansen H** 1994 Hepatic lipase gene is transcribed in rat adrenals into a truncated mRNA. J Lipid Res 35:966–975
184. **Verhoeven AJ, Jansen H** 1994 Hepatic lipase mRNA is expressed

in rat and human steroidogenic organs. Biochim Biophys Acta 1211:121–124
185. **Vieira-van Bruggen D, Kalkman I, van Gent T, van Tol A, Jansen H** 1998 Induction of adrenal scavenger receptor BI and increased high density lipoprotein-cholesteryl ether uptake by *in vivo* inhibition of hepatic lipase. J Biol Chem 273:32038–32041
186. **Foger B, Chase M, Amar MJ, Vaisman BL, Shamburek RD, Paigen B, Fruchart-Najib J, Paiz JA, Koch CA, Hoyt RF, Brewer Jr HB, Santamarina-Fojo S** 1999 Cholesteryl ester transfer protein corrects dysfunctional high density lipoproteins and reduces aortic atherosclerosis in lecithin cholesterol acyltransferase transgenic mice. J Biol Chem 274:36912–36920
187. **de Beer FC, Connell PM, Yu J, de Beer MC, Webb NR, van der Westhuyzen DR** 2000 HDL modification by secretory phospholipase A(2) promotes scavenger receptor class B type I interaction and accelerates HDL catabolism. J Lipid Res 41:1849–1857
188. **Yancey PG, de La Llera-Moya M, Swarnakar S, Monzo P, Klein SM, Connelly MA, Johnson WJ, Williams DL, Rothblat GH** 2000 HDL phospholipid composition is a major determinant of the bidirectional flux and net movement of cellular free cholesterol mediated by scavenger receptor-BI (SR-BI). J Biol Chem 275:36596–36604
189. **Temel RE, Parks JS, Williams DL** 2002 Enhancement of SR-BI-mediated selective cholesteryl ester uptake from ApoA-I$^{-/-}$ HDL by ApoA-I requires HDL reorganization by LCAT. J Biol Chem 278:4792–4799
190. **Holm C, Osterlund T** 1999 Hormone-sensitive lipase and neutral cholesteryl ester lipase. Methods Mol Biol 109:109–121
191. **Fielding PE, Fielding CJ** 1995 Plasma membrane caveolae mediate the efflux of cellular free cholesterol. Biochemistry 34:14288–14292
192. **Huang ZH, Mazzone T** 2002 ApoE-dependent sterol efflux from macrophages is modulated by scavenger receptor class B type I expression. J Lipid Res 43:375–382
193. **Connelly MA, de la Llera-Moya M, Monzo P, Yancey PG, Drazul D, Stoudt G, Fournier N, Klein SM, Rothblat GH, Williams DL** 2001 Analysis of chimeric receptors shows that multiple distinct functional activities of scavenger receptor, class B, type I (SR-BI), are localized to the extracellular receptor domain. Biochemistry 40:5249–5259
194. **de la Llera-Moya M, Rothblat GH, Connelly MA, Kellner-Weibel G, Sakr SW, Phillips MC, Williams DL** 1999 Scavenger receptor BI (SR-BI) mediates free cholesterol flux independently of HDL tethering to the cell surface. J Lipid Res 40:575–580
195. **Kellner-Weibel G, de La Llera-Moya M, Connelly MA, Stoudt G, Christian AE, Haynes MP, Williams DL, Rothblat GH** 2000 Expression of scavenger receptor BI in COS-7 cells alters cholesterol content and distribution. Biochemistry 39:221–229
196. **Rothblat GH, de la Llera-Moya M, Atger V, Kellner-Weibel G, Williams DL, Phillips MC** 1999 Cell cholesterol efflux: integration of old and new observations provides new insights. J Lipid Res 40:781–796
197. **Brooks-Wilson A, Marcil M, Clee SM, Zhang LH, Roomp K, van Dam M, Yu L, Brewer C, Collins JA, Molhuizen HO, Loubser O, Ouelette BF, Fichter K, Ashbourne-Excoffon KJ, Sensen CW, Scherer S, Mott S, Denis M, Martindale D, Frohlich J, Morgan K, Koop B, Pimstone S, Kastelein JJ, Genest JJ, Hayden MR** 1999 Mutations in ABC1 in Tangier disease and familial high-density lipoprotein deficiency. Nat Genet 22:336–345
198. **Bodzioch M, Orso E, Klucken J, Langmann T, Bottcher A, Diederich W, Drobnik W, Barlage S, Buchler C, Porsch-Ozcurumez M, Kaminski WE, Hahmann HW, Oette K, Rothe G, Aslanidis C, Lackner KJ, Schmitz G** 1999 The gene encoding ATP-binding cassette transporter 1 is mutated in Tangier disease. Nat Genet 22:347–351
199. **Rust S, Rosier M, Funke H, Real J, Amoura Z, Piette JC, Deleuze JF, Brewer HB, Duverger N, Denefle P, Assmann G** 1999 Tangier disease is caused by mutations in the gene encoding ATP-binding cassette transporter 1. Nat Genet 22:352–355
200. **Lawn RM, Wade DP, Garvin MR, Wang X, Schwartz K, Porter JG, Seilhamer JJ, Vaughan AM, Oram JF** 1999 The Tangier disease gene product ABC1 controls the cellular apolipoprotein-mediated lipid removal pathway. J Clin Invest 104:25–31
201. **Chen W, Silver DL, Smith JD, Tall AR** 2000 Scavenger receptor-BI inhibits ATP-binding cassette transporter 1-mediated cholesterol efflux in macrophages. J Biol Chem 275:30794–30800
202. **Fielding PE, Nagao K, Hakamata H, Chimini G, Fielding CJ** 2000 A two-step mechanism for free cholesterol and phospholipid efflux from human vascular cells to apolipoprotein A-1. Biochemistry 39:14113–14120
203. **Wang N, Silver DL, Costet P, Tall AR** 2000 Specific binding of apoA-I, enhanced cholesterol efflux and altered plasma membrane morphology in cells expressing ABC1. J Biol Chem 275:33053–33058
204. **Oram JF, Lawn RM, Garvin MR, Wade DP** 2000 ABCA1 is the cAMP-inducible apolipoprotein receptor that mediates cholesterol secretion from macrophages. J Biol Chem 275:34508–34511
205. **Chambenoit O, Hamon Y, Marguet D, Rigneault H, Rosseneu M, Chimini G** 2001 Specific docking of apolipoprotein A-I at the cell surface requires a functional ABCA1 transporter. J Biol Chem 276:9955–9960
206. **Wang N, Silver DL, Thiele C, Tall AR** 2001 ATP-binding cassette transporter a1 (abca1) functions as a cholesterol efflux regulatory protein. J Biol Chem 276:23742–23747
207. **Hauser H, Dyer JH, Nandy A, Vega MA, Werder M, Bieliauskaite E, Weber FE, Compassi S, Gemperli A, Boffelli D, Wehrli E, Schulthess G, Phillips MC** 1998 Identification of a receptor mediating absorption of dietary cholesterol in the intestine. Biochemistry 37:17843–17850
208. **Hatzopoulos AK, Rigotti A, Rosenberg RD, Krieger M** 1998 Temporal and spatial pattern of expression of the HDL receptor SR-BI during murine embryogenesis. J Lipid Res 39:495–508
209. **Wyne KL, Woollett LA** 1998 Transport of maternal LDL and HDL to the fetal membranes and placenta of the Golden Syrian hamster is mediated by receptor-dependent and receptor-independent processes. J Lipid Res 39:518–530
210. **Ramachandran S, Song M, Murphy AA, Parthasarathy S** 2001 Expression of scavenger receptor class B1 in endometrium and endometriosis. J Clin Endocrinol Metab 86:3924–3928
211. **Kolleck I, Schlame M, Fechner H, Looman AC, Wissel H, Rustow B** 1999 HDL is the major source of vitamin E for type II pneumocytes. Free Radic Biol Med 27:882–890
212. **Fluiter K, van der Westhuijzen DR, van Berkel TJ** 1998 *In vivo* regulation of scavenger receptor BI and the selective uptake of high density lipoprotein cholesteryl esters in rat liver parenchymal and Kupffer cells. J Biol Chem 273:8434–8438
213. **Hirano K, Yamashita S, Nakagawa Y, Ohya T, Matsuura F, Tsukamoto K, Okamoto Y, Matsuyama A, Matsumoto K, Miyagawa J, Matsuzawa Y** 1999 Expression of human scavenger receptor class B type I in cultured human monocyte-derived macrophages and atherosclerotic lesions. Circ Res 85:108–116
214. **Chinetti G, Gbaguidi FG, Griglio S, Mallat Z, Antonucci M, Poulain P, Chapman J, Fruchart JC, Tedgui A, Najib-Fruchart J, Staels B** 2000 CLA-1/SR-BI is expressed in atherosclerotic lesion macrophages and regulated by activators of peroxisome proliferator-activated receptors. Circulation 101:2411–2417
215. **Uittenbogaard A, Shaul PW, Yuhanna IS, Blair A, Smart EJ** 2000 High density lipoprotein prevents oxidized low density lipoprotein-induced inhibition of endothelial nitric-oxide synthase localization and activation in caveolae. J Biol Chem 275:11278–11283
216. **Marsche G, Levak-Frank S, Quehenberger O, Heller R, Sattler W, Malle E** 2001 Identification of the human analog of SR-BI and LOX-1 as receptors for hypochlorite-modified high density lipoprotein on human umbilical venous endothelial cells. FASEB J 15:1095–1097
217. **Yeh YC, Hwang GY, Liu IP, Yang VC** 2002 Identification and expression of scavenger receptor SR-BI in endothelial cells and smooth muscle cells of rat aorta *in vitro* and *in vivo*. Atherosclerosis 161:95–103
218. **Nakagawa-Toyama Y, Hirano K, Okamoto Y, Nishida M, Miyagawa J, Fujimura H, Yamashita S, Matsuzawa Y** 2000 Expression on high density lipoprotein receptor scavenger receptor class B type I in human central nervous system. Atherosclerosis 151:295
219. **Duncan KG, Bailey KR, Kane JP, Schwartz DM** 2002 Human retinal pigment epithelial cells express scavenger receptors BI and BII. Biochem Biophys Res Commun 292:1017–1022
220. **Tsuruoka H, Khovidhunkit W, Brown BE, Fluhr JW, Elias PM, Feingold KR** 2002 Scavenger receptor class B type I is expressed in

cultured keratinocytes and epidermis. Regulation in response to changes in cholesterol homeostasis and barrier requirements. J Biol Chem 277:2916–2922
221. **Buechler C, Ritter M, Quoc CD, Agildere A, Schmitz G** 1999 Lipopolysaccharide inhibits the expression of the scavenger receptor Cla-1 in human monocytes and macrophages. Biochem Biophys Res Commun 262:251–254
222. **Arai T, Rinninger F, Varban L, Fairchild-Huntress V, Liang CP, Chen W, Seo T, Deckelbaum R, Huszar D, Tall AR** 2055 1999 Decreased selective uptake of high density lipoprotein cholesteryl esters in apolipoprotein E knock-out mice. Proc Natl Acad Sci USA 96:12050–12051
223. **Witt W, Kolleck I, Fechner H, Sinha P, Rustow B** 2000 Regulation by vitamin E of the scavenger receptor BI in rat liver and HepG2 cells. J Lipid Res 41:2009–2016
224. **Goldberg DI, Beltz WF, Pittman RC** 1991 Evaluation of pathways for the cellular uptake of high density lipoprotein cholesterol esters in rabbits. J Clin Invest 87:331–346
225. **Bachorik PS, Kwiterovich P, Cooke JC** 1978 Isolation of a porcine liver plasma membrane fraction that binds low density lipoproteins. Biochemistry 17:5287–5299
226. **Truong TQ, Auger A, Denizeau F, Brissette L** 2000 Analysis of low-density lipoprotein catabolism by primary cultures of hepatic cells from normal and low-density lipoprotein receptor knockout mice. Biochim Biophys Acta 1484:307–315
227. **Malerod L, Juvet K, Gjoen T, Berg T** 2002 The expression of scavenger receptor class B, type I (SR-BI) and caveolin-1 in parenchymal and nonparenchymal liver cells. Cell Tissue Res 307:173–180
228. **Spady DK, Kearney DM, Hobbs HH** 1999 Polyunsaturated fatty acids up-regulate hepatic scavenger receptor B1 (SR-BI) expression and HDL cholesteryl ester uptake in the hamster. J Lipid Res 40:1384–1394
229. **Loison C, Mendy F, Serougne C, Lutton C** 2002 Dietary myristic acid modifies the HDL-cholesterol concentration and liver scavenger receptor BI expression in the hamster. Br J Nutr 87:199–210
230. **Milliat F, Ferezou J, Delhon A, Lutton C** 2001 Overexpression of SR-BI in hamsters treated with a novel ACAT inhibitor (F12511). C R Acad Sci III 324:229–234
231. **Khovidhunkit W, Moser AH, Shigenaga JK, Grunfeld C, Feingold KR** 2001 Regulation of scavenger receptor class B type I in hamster liver and Hep3B cells by endotoxin and cytokines. J Lipid Res 42:1636–1644
232. **Milliat F, Gripois D, Blouquit M-E, Ferezou J, Serougne C, Fidge NH, Lutton C** 2000 Short and long-term effects of streptozotocin on dietary cholesterol absorption, plasma lipoproteins and liver lipoprotein receptors in RICO rats. Exp Clin Endocrinol Diabetes 108:436–446
233. **Dubrac S, Parquet M, Gripois D, Blouquit MF, Serougne C, Loison C, Lutton C** 2001 Diet-dependent effects of insulin infusion on the hepatic lipoprotein receptors and the key enzymes of bile acid synthesis in the hamster. Life Sci 69:2517–2532
234. **Serougne C, Feurgard C, Hajri T, Champarnaud G, Ferezou J, Mathe D, Lutton C** 1999 Catabolism of HDL1 cholesteryl ester in the rat. Effect of ethinyl estradiol treatment. C R Acad Sci III 322:591–596
235. **Graf GA, Roswell KL, Smart EJ** 2001 17β-Estradiol promotes the up-regulation of SR-BII in HepG2 cells and in rat livers. J Lipid Res 42:1444–1449
236. **Pieters MN, Schouten D, Bakkeren HF, Esbach B, Brouwer A, Knook DL, van Berkel TJ** 1991 Selective uptake of cholesteryl esters from apolipoprotein-E-free high-density lipoproteins by rat parenchymal cells *in vivo* is efficiently coupled to bile acid synthesis. Biochem J 280:359–365
237. **Woollett LA, Kearney DM, Spady DK** 1997 Diet modification alters plasma HDL cholesterol concentrations but not the transport of HDL cholesteryl esters to the liver in the hamster. J Lipid Res 38:2289–2302
238. **Mardones P, Quinone V, Amigo L, Moreno M, Miquel JF, Schwarz M, Miettinen HE, Trigatti B, Krieger M, VanPatten S, Cohen DE, Rigotti A** 2001 Hepatic cholesterol and bile acid metabolism and intestinal cholesterol absorption in scavenger receptor class B type I-deficient mice. J Lipid Res 42:170–180
239. **Souidi M, Combettes-Souverain M, Milliat F, Eckhardt ER, Audas O, Dubrac S, Parquet M, Ferezou J, Lutton C** 2001 Hamsters predisposed to sucrose-induced cholesterol gallstones (LPN strain) are more resistant to excess dietary cholesterol than hamsters that are not sensitive to cholelithiasis induction. J Nutr 13:1803–1811
240. **Spady DK, Woollett LA, Meidell RS, Hobbs HH** 1998 Kinetic characteristics and regulation of HDL cholesteryl ester and apolipoprotein transport in the apoA-I$^{-/-}$ mouse. J Lipid Res 39:1483–1492
241. **Galman C, Angelin B, Rudling M** 2002 Prolonged stimulation of the adrenals by corticotropin suppresses hepatic low-density lipoprotein and high-density lipoprotein receptors and increases plasma cholesterol. Endocrinology 143:1809–1816
242. **Smith JL, Lear SR, Forte TM, Ko W, Massimi M, Erickson SK** 1998 Effect of pregnancy and lactation on lipoprotein and cholesterol metabolism in the rat. J Lipid Res 39:2237–2249
243. **Malerod L, Juvet LK, Hanssen-Bauer A, Eskild W, Berg T** 2002 Oxysterol-activated LXRα/RXR induces hSR-BI-promoter activity in hepatoma cells and preadipocytes. Biochem Biophys Res Commun 299:916–923
244. **Schoonjans K, Annicotte JS, Huby T, Botrugno OA, Fayard E, Ueda Y, Chapman J, Auwerx J** 2002 Liver receptor homolog 1 controls the expression of the scavenger receptor class B type I. EMBO Rep 3:1181–1187
245. **Lambert G, Amar MJ, Guo G, Brewer HBJ, Gonzalez FJ, Sinal CJ** 2003 The Farnesoid X-receptor is an essential regulator of cholesterol homeostasis. J Biol Chem 278:2563–2570
246. **Azhar S, Nomoto A, Reaven E** 2002 Hormonal regulation of adrenal microvillar channel formation. J Lipid Res 43:861–871
247. **Gwynne JT, Hess B, Hughes T, Rountree R, Mahaffee D** 1984 The role of serum high density lipoproteins in adrenal steroidogenesis. Endocr Res 10:411–430
248. **Sun Y, Wang N, Tall AR** 1999 Regulation of adrenal scavenger receptor-BI expression by ACTH and cellular cholesterol pools. J Lipid Res 40:1799–1805
249. **Liu J, Voutilainen R, Heikkila P, Kahri AI** 1997 Ribonucleic acid expression of the CLA-1 gene, a human homolog to mouse high density lipoprotein receptor SR-BI, in human adrenal tumors and cultured adrenal cells. J Clin Endocrinol Metab 82:2522–2527
250. **Martin G, Pilon A, Albert C, Valle M, Hum DW, Fruchart JC, Najib J, Clavey V, Staels B** 1999 Comparison of expression and regulation of the high-density lipoprotein receptor SR-BI and the low-density lipoprotein receptor in human adrenocortical carcinoma NCI-H295 cells. Eur J Biochem 261:481–491
251. **Ng DS, Francone OL, Forte TM, Zhang J, Haghpassand M, Rubin EM** 1997 Disruption of the murine lecithin:cholesterol acyltransferase gene causes impairment of adrenal lipid delivery and up-regulation of scavenger receptor class B type I. J Biol Chem 272: 15777–15781
252. **Rinninger F, Pittmann RC** 1987 Regulation of the selective uptake of high density lipoprotein-associated cholesteryl esters. J Lipid Res 28:1313–1325
253. **Burgess LH, Handa RJ** 1992 Chronic estrogen-induced alterations in adrenocorticotropin and corticosterone secretion, and glucocorticoid receptor-mediated functions in female rats. Endocrinology 131:1261–1269
254. **Imachi H, Murao K, Sayo Y, Hosokawa H, Sato M, Niimi M, Kobayashi S, Miyauchi A, Ishida T, Takahara J** 1999 Evidence for a potential role for HDL as an important source of cholesterol in human adrenocortical tumors via the CLA-1 pathway. Endocr J 46:27–34
255. **Rigotti A, Trigatti BL, Penman M, Rayburn H, Herz J, Krieger M** 1997 A targeted mutation in the murine gene encoding the high density lipoprotein (HDL) receptor scavenger receptor class B type I reveals its key role in HDL metabolism. Proc Natl Acad Sci USA 94:12610–12615
256. **Baumberger C, Ulevitch RJ, Dayer JM** 1991 Modulation of endotoxic activity of lipopolysaccharide by high-density lipoprotein. Pathobiology 59:378–383
257. **Levine DM, Parker TS, Donnelly TM, Walsh A, Rubin AL** 1993 *In vivo* protection against endotoxin by plasma high density lipoprotein. Proc Natl Acad Sci USA 90:12040–12044
258. **Parker TS, Levine DM, Chang JC, Laxer J, Coffin CC, Rubin AL** 1995 Reconstituted high-density lipoprotein neutralizes gram-negative bacterial lipopolysaccharides in human whole blood. Infect Immun 63:253–258

259. **Ulevitch RJ, Johnston AR, Weinstein DB** 1981 New function for high density lipoproteins. Isolation and characterization of a bacterial lipopolysaccharide-high density lipoprotein complex formed in rabbit plasma. J Clin Invest 67:827–837
260. **Munford RS, Andersen JM, Dietschy JM** 1981 Sites of tissue binding and uptake *in vivo* of bacterial lipopolysaccharide-high density lipoprotein complexes: studies in the rat and squirrel monkey. J Clin Invest 68:1503–1513
261. **Munford RS, Dietschy JM** 1985 Effects of specific antibodies, hormones, and lipoproteins on bacterial lipopolysaccharides injected into the rat. J Infect Dis 152:177–184
262. **Zaloga GP** 2001 Sepsis-induced adrenal deficiency syndrome. Crit Care Med 29:688–690
263. **Mizutani T, Sonoda Y, Minegishi T, Wakabayashi K, Miyamoto K** 1997 Cloning, characterization, and cellular distribution of rat scavenger receptor class B type I (SRBI) in the ovary. Biochem Biophys Res Commun 234:499–505
264. **Li X, Peegel H, Menon K** 1998 *In situ* hybridization of high density lipoprotein (scavenger, type 1) receptor messenger ribonucleic acid (mRNA) during folliculogenesis and luteinization: evidence for mRNA expression and induction by human chorionic gonadotropin specifically in cell types that use cholesterol for steroidogenesis. Endocrinology 139:3043–3049
265. **Rajapaksha WR, McBride M, Robertson L, O'Shaughnessy PJ** 1997 Sequence of the bovine HDL-receptor (SR-BI) cDNA and changes in receptor mRNA expression during granulosa cell luteinization *in vivo* and *in vitro*. Mol Cell Endocrinol 134:59–67
266. **McLean MP, Sandhoff TW** 1998 Expression and hormonal regulation of the high-density lipoprotein (HDL) receptor scavenger receptor class B type I messenger ribonucleic acid in the rat ovary. Endocrine 9:243–252
267. **Azhar S, Nomoto A, Leers-Sucheta S, Reaven E** 1998 Simultaneous induction of an HDL receptor protein (SR-BI) and the selective uptake of HDL-cholesteryl esters in a physiologically relevant steroidogenic cell model. J Lipid Res 39:1616–1628
268. **Reaven E, Lua Y, Temel R, Williams D, van der Westhuyzen D, Azhar S** 1999 The selective pathway and a high-density lipoprotein receptor (SR-BI) in ovarian granulosa cells of the mouse. Biochim Biophys Acta 1436:565–576
269. **Azhar S, Luo Y, Medicherla S, Reaven E** 1999 Upregulation of selective cholesteryl ester uptake pathway in mice with deletion of low-density lipoprotein receptor function. J Cell Physiol 180:190–202
270. **Repa JJ, Turley SD, Lobaccaro JA, Medina J, Li L, Lustig K, Shan B, Heyman RA, Dietschy JM, Mangelsdorf DJ** 2000 Regulation of absorption and ABC1-mediated efflux of cholesterol by RXR heterodimers. Science 289:1524–1529
271. **Altmann SW, Davis HR, Yao X, Laverty M, Compton DS, Zhu L, Crona JH, Caplen MA, Hoos LM, Tetzloff G, Priestley T, Burnett DA, Strader CD, Graziano MP** 2002 The identification of intestinal scavenger receptor class B, type I (SR-BI) by expression cloning and its role in cholesterol absorption. Biochim Biophys Acta 1580:77–93
272. **Johnson MS, Svensson PA, Boren J, Billig H, Carlsson LM, Carlsson B** 2002 Expression of scavenger receptor class B type I in gallbladder columnar epithelium. J Gastroenterol Hepatol 17:713–720
273. **Kolleck I, Witt W, Wissel H, Sinha P, Rustow B** 2000 HDL and vitamin E in plasma and the expression of SR-BI on lung cells during rat perinatal development. Lung 178:191–200
274. **Koch S, Donarski N, Goetze K, Kreckel M, Stuerenburg H-J, Buhmann C, Beisiegel U** 2001 Characterization of four lipoprotein classes in human cerebrospinal fluid. J Lipid Res 42:1143–1151
275. **Srivastava RA, Jain JC** 2002 Scavenger receptor class B type I expression and elemental analysis in cerebellum and parietal cortex regions of the Alzheimer's disease brain. J Neurol Sci 196:45–52
276. **Posse De Chaves EI, Vance DE, Campenot RB, Kiss RS, Vance JE** 2000 Uptake of lipoproteins for axonal growth of sympathetic neurons. J Biol Chem 275:19883–19890
277. **Pussinen PJ, Karten B, Wintersperger A, Reicher H, McLean M, Malle E, Sattler W** 2000 The human breast carcinoma cell line HBL-100 acquires exogenous cholesterol from high-density lipoprotein via CLA-1 (CD-36 and LIMPII analogous 1)-mediated selective cholesteryl ester uptake. Biochem J 349:559–566
278. **Monks J, Uelmen Huey P, Hanson L, Eckel RH, Neville MC, Gavigan S** 2001 A lipoprotein-containing particle is transferred from the serum across the mammary epithelium into the milk of lactating mice. J Lipid Res 42:686–696
279. **Miettinen HE, Rayburn H, Krieger M** 2001 Abnormal lipoprotein metabolism in HDL receptor (SR-BI)-deficient mice and reversible female infertility. J Clin Invest 108:1717–1722
280. **Yuhanna IS, Zhu Y, Cox BE, Hahner LD, Osborne-Lawrence S, Lu P, Marcel YL, Anderson RG, Mendelsohn ME, Hobbs HH, Shaul PW** 2001 High-density lipoprotein binding to scavenger receptor-BI activates endothelial nitric oxide synthase. Nat Med 7:853–857
281. **Zuckerman SH, Panousis C, Mizrahi J, Evans G** 2000 The effect of γ-interferon to inhibit macrophage-high density lipoprotein interactions is reversed by 15-deoxy-δ12,14-prostaglandin J2. Lipids 35:1239–1247
282. **Langer C, Gansz B, Goepfert C, Engel T, Uehara Y, von Dehn G, Jansen H, Assmann G, von Eckardstein A** 2002 Testosterone upregulates scavenger receptor BI and stimulates cholesterol efflux from macrophages. Biochem Biophys Res Commun 296:1051–1057
283. **Iwashima Y, Eto M, Hata A, Kaku K, Horiuchi S, Ushikubi F, Sano H** 2000 Advanced glycation end products-induced gene expression of scavenger receptors in cultured human monocyte-derived macrophages. Biochem Biophys Res Commun 277:368–380
284. **Zuckerman SH, Panousis C, Evans G** 2001 TGF-β reduced binding of high-density lipoproteins in murine macrophages and macrophage-derived foam cells. Atherosclerosis 155:79–85
285. **Hullinger TG, Panek RL, Xu X, Karathanasis SK** 2001 p21-activated kinase-1 (PAK1) inhibition of the human scavenger receptor class B, type I promoter in macrophages is independent of PAK1 kinase activity, but requires the GTPase-binding domain. J Biol Chem 276:46807–46814
286. **Baranova I, Vishnyakova T, Bocharov A, Chen Z, Remaley AT, Stonik J, Eggerman TL, Patterson AP** 2002 Lipopolysaccharide down regulates both scavenger receptor B1 and ATP binding cassette transporter A1 in RAW cells. Infect Immun 70:2995–3003
287. **Han J, Nicholson AC, Zhou X, Feng J, Gotto AMJ, Hajjar DP** 2001 Oxidized low density lipoprotein decreases macrophage expression of scavenger receptor B-I. J Biol Chem 276:16567–16572
288. **Farese RVJ, Herz J** 1998 Cholesterol metabolism and embryogenesis. Trends Genet 14:115–120
289. **Jurevics HA, Kidwai FZ, Morell P** 1997 Sources of cholesterol during development of the rat fetus and fetal organs. J Lipid Res 38:723–733
290. **Woollett LA** 1996 Origin of cholesterol in the fetal Golden Syrian hamster: contribution of *de novo* sterol synthesis and maternal-derived lipoprotein cholesterol. J Lipid Res 37:1246–1257
291. **Cummings SW, Hatley W, Simpson ER, Ohashi M** 1982 The binding of high and low density lipoproteins to human placental membrane fractions. J Clin Endocrinol Metab 54:903–908
292. **Alsat E, Bouali Y, Goldstein S, Malassine A, Berthelier M, Mondon F, Gedard L** 1984 Low-density lipoprotein binding sites in the microvillus membranes of human placenta at different stages of gestation. Mol Cell Endocrinol 38:197–203
293. **Furuhashi M, Seo S, Mizutani O, Narita Y, Tomoda Y, Matsui N** 1989 Expression of low density lipoprotein receptor gene in human placenta during pregnancy. Mol Endocrinol 3:1252–1256
294. **Wittmaack FM, Gafvels ME, Bronner M, Matsuo H, McCrae KR, Tomaszewski JE, Robinson SL, Strickland DK, Strauss JF** 1995 Localization and regulation of the human very low density lipoprotein/apolipoprotein-E receptor: trophoblast expression predicts a role for the receptor in placental lipid transport. Endocrinology 136:340–348
295. **Gafvels ME, Coukos G, Sayegh R, Coutifaris C, Strickland DK, Strauss JF** 1992 Regulated expression of the trophoblast α 2-macroglobulin receptor/low density lipoprotein receptor-related protein. Differentiation and cAMP modulate protein and mRNA levels. J Biol Chem 267:21230–21234
296. **Alsat E, Malassine A** 1991 High density lipoprotein interaction with human placenta: biochemical and ultrastructural characterization of binding to microvillous receptor and lack of internalization. Mol Cell Endocrinol 77:97–108
297. **Lafond J, Charest MC, Alain JF, Brissette L, Masse A, Robidoux J, Simoneau L** 1999 Presence of CLA-1 and HDL binding sites on syncytiotrophoblast brush border and basal plasma membranes of human placenta. Placenta 20:583–590

298. **Cao G, Zhao L, Stangl H, Hasegawa T, Richardson JA, Parker KL, Hobbs HH** 1999 Developmental and hormonal regulation of murine scavenger receptor, class B, type 1. Mol Endocrinol 13:1460–1473
299. **Lopez D, McLean MP** 1999 Sterol regulatory element-binding protein-1a binds to *cis* elements in the promoter of the rat high density lipoprotein receptor SR-BI gene. Endocrinology 140:5669–5681
300. **Parker KL** 1998 The roles of steroidogenic factor 1 in endocrine development and function. Mol Cell Endocrinol 140:59–63
301. **Lekstrom-Himes J, Xanthopoulos KG** 1998 Biological role of the CCAAT/enhancer binding protein family of transcription factors. J Biol Chem 273:28545–28548
302. **McConihay JA, Horn PS, Woollett LA** 2001 Effect of maternal hypercholesterolemia on fetal sterol metabolism in the Golden Syrian hamster. J Lipid Res 42:1111–1119
303. **Lopez D, Sanchez MD, Shea-Eaton W, McLean MP** 2002 Estrogen activates the high-density lipoprotein receptor gene via binding to estrogen response elements and interaction with sterol regulatory element binding protein-1A. Endocrinology 143:2155–2168
304. **Peet DJ, Turley SD, Ma W, Janowski BA, Lobaccaro JM, Hammer RE, Mangelsdorf DJ** 1998 Cholesterol and bile acid metabolism are impaired in mice lacking the nuclear oxysterol receptor LXRa. Cell 93:693–704
305. **Trigatti B, Rayburn H, Vinals M, Braun A, Miettinen H, Penman M, Hertz M, Schrenzel M, Amigo L, Rigotti A, Krieger M** 1999 Influence of the high density lipoprotein receptor SR-BI on reproductive and cardiovascular pathophysiology. Proc Natl Acad Sci USA 96:9322–9327
306. **Krieger M, Kozarsky K** 1999 Influence of the HDL receptor SR-BI on atherosclerosis. Curr Opin Lipidol 10:491–497
307. **Acton SL, Kozarsky KF, Rigotti A** 1999 The HDL receptor SR-BI: a new therapeutic target for atherosclerosis? Mol Med Today 5:518–524
308. **Wang N, Arai T, Ji Y, Rinninger F, Tall AR** 1998 Liver-specific overexpression of scavenger receptor BI decreases levels of very low density lipoprotein ApoB, low density lipoprotein ApoB, and high density lipoprotein in transgenic mice. J Biol Chem 273:32920–32926
309. **Ueda Y, Royer L, Gong E, Zhang J, Cooper PN, Francone O, Rubin EM** 1999 Lower plasma levels and accelerated clearance of high density lipoprotein (HDL) and non-HDL cholesterol in scavenger receptor class B type I transgenic mice. J Biol Chem 274:7165–7171
310. **Varban ML, Rinninger F, Wang N, Fairchild-Huntress V, Dunmore JH, Fang Q, Gosselin ML, Dixon KL, Deeds JD, Acton SL, Tall AR, Huszar D** 1998 Targeted mutation reveals a central role for SR-BI in hepatic selective uptake of high density lipoprotein cholesterol. Proc Natl Acad Sci USA 95:4619–4624
311. **Webb NR, Cai L, Ziemba KS, Yu J, Kindy MS, Van Der Westhuyzen DR, De Beer FC** 2002 The fate of HDL particles in vivo after SR-BI-mediated selective lipid uptake. J Lipid Res 43:1890–1898
312. **Sehayek E, Ono JG, Shefer S, Nguyen LB, Wang N, Batta AK, Salen G, Smith JD, Tall AR, Breslow JL** 1998 Biliary cholesterol excretion: a novel mechanism that regulates dietary cholesterol absorption. Proc Natl Acad Sci USA 95:10194–10199
313. **Alam K, Meidell RS, Spady DK** 2001 Effect of up-regulating individual steps in the reverse cholesterol transport pathway on reverse cholesterol transport in normolipidemic mice. J Biol Chem 276:15641–15649
314. **Paigen B, Morrow A, Brandon C, Mitchell D, Holmes P** 1985 Variation in susceptibility to atherosclerosis among inbred strains of mice. Atherosclerosis 57:65–73
315. **Ishibashi S, Brown MS, Goldstein JL, Gerard RD, Hammer RE, Herz J** 1993 Hypercholesterolemia in low density lipoprotein receptor knockout mice and its reversal by adenovirus-mediated gene delivery. J Clin Invest 92:883–893
316. **Piedrahita JA, Zhang SH, Hagaman JR, Oliver PM, Maeda N** 1992 Generation of mice carrying a mutant apolipoprotein E gene inactivated by gene targeting in embryonic stem cells. Proc Natl Acad Sci USA 89:4471–4475
317. **Plump AS, Smith JD, Hayek T, Aalto-Setala K, Walsh A, Verstuyft JG, Rubin EM, Breslow JL** 1992 Severe hypercholesterolemia and atherosclerosis in apolipoprotein E-deficient mice created by homologous recombination in ES cells. Cell 71:343–353
318. **Arai T, Wang N, Bezouevski M, Welch C, Tall AR** 1999 Decreased atherosclerosis in heterozygous low density lipoprotein receptor-deficient mice expressing the scavenger receptor BI transgene. J Biol Chem 274:2366–2371
319. **Huszar D, Varban ML, Rinninger F, Feeley R, Arai T, Fairchild-Huntress V, Donovan MJ, Tall AR** 2000 Increased LDL cholesterol and atherosclerosis in LDL receptor-deficient mice with attenuated expression of scavenger receptor B1. Arterioscler Thromb Vasc Biol 20:1068–1073
320. **Sakai N, Vaisman BL, Koch CA, Hoyt RFJ, Meyn SM, Talley GD, Paiz JA, Brewer HBJ, Santamarina-Fojo S** 1997 Targeted disruption of the mouse lecithin:cholesterol acyltransferase (LCAT) gene. Generation of a new animal model for human LCAT deficiency. J Biol Chem 272:7506–7510
321. **Shalgi R, Kraicer P, Rimon A, Pinto M, Soferman N** 1973 Proteins of human follicular fluid: the blood-follicle barrier. Fertil Steril 24:429–434
322. **Perret B-P, Parinaud J, Ribbes H, Moatti J-P, Pontonnier G, Chap H, Douste-Blazy L** 1985 Lipoprotein and phospholipid distribution in human follicular fluids. Fertil Steril 43:405–409
323. **Le Geoff D** 1994 Follicular fluid lipoproteins in the mare: evaluation of HDL transfer from plasma to follicular fluid. Biochim Biophys Acta 1210:226–232
324. **Jaspard B, Fournier N, Vieitez G, Atger V, Barbaras R, Vieue C, Manent J, Chap H, Perret B, Collet X** 1997 Structural and functional comparison of HDL from homologous human plasma and follicular fluid. A model for extravascular fluid. Arterioscler Thromb Vasc Biol 17:1605–1613
325. **Schmitz G, Kaminski WE, Orso E** 2000 ABC transporters in cellular lipid trafficking. Curr Opin Lipidol 11:493–501
326. **Christiansen-Weber TA, Voland JR, Wu Y, Ngo K, Roland BL, Nguyen S, Peterson PA, Fung-Leung WP** 2000 Functional loss of ABCA1 in mice causes severe placental malformation, aberrant lipid distribution, and kidney glomerulonephritis as well as high-density lipoprotein cholesterol deficiency. Am J Pathol 157:1017–1029
327. **McNeish J, Aiello RJ, Guyot D, Turi T, Gabel C, Aldinger C, Hopper KL, Roach ML, Royer LJ, de Wet J, Broccardo C, Chimini G, Francone OL** 2000 High density lipoprotein deficiency and foam cell accumulation in mice with targeted disruption of ATP-binding cassette transporter-1. Proc Natl Acad Sci USA 97:4245–4250
328. **Orso E, Broccardo C, Kaminski WE, Bottcher A, Liebisch G, Drobnik W, Gotz A, Chambenoit O, Diederich W, Langmann T, Spruss T, Luciani MF, Rothe G, Lackner KJ, Chimini G, Schmitz G** 2000 Transport of lipids from golgi to plasma membrane is defective in tangier disease patients and Abc1-deficient mice. Nat Genet 24:192–196
329. **Bujo H, Hermann M, Lindstedt KA, Nimpf J, Schneider WJ** 1997 Low density lipoprotein receptor gene family members mediate yolk deposition. J Nutr 127(5 Suppl):801S–804S
330. **Schneider WJ, Osanger A, Waclawek M, Nimpf J** 1998 Oocyte growth in the chicken: receptors and more. Biol Chem 379:965–971
331. **Bujo H, Yamamoto T, Hayashi K, Hermann M, Nimpf J, Schneider WJ** 1995 Mutant oocytic low density lipoprotein receptor gene family member causes atherosclerosis and female sterility. Proc Natl Acad Sci USA 92:9905–9909
332. **Gordon DJ, Rifkind BM** 1989 High-density lipoprotein: the clinical implications of recent studies. N Engl J Med 321:1311–1316
333. **Schaefer EJ, Genest JJ, Ordovas JM, Deeb NS, Wilson PWF** 1993 Familial lipoprotein disorders and premature coronary artery disease. Curr Opin Lipidol 4:288–298
334. **Fielding CJ, Fielding PE** 1995 Molecular physiology of reverse cholesterol transport. J Lipid Res 36:211–228
335. **Durrington PN, Mackness B, Mackness MI** 2001 Paraoxonase and atherosclerosis. Arterioscler Thromb Vasc Biol 21:473–480
336. **Mackness MI, Durrington PN** 1995 HDL, its enzymes and its potential to influence lipid peroxidation. Atherosclerosis 115:243–253
337. **Cockerill GW, Rye K-A, Gamble JR, Vadas MA, Barter PJ** 1995 High-density lipoproteins inhibit cytokine-induced expression of endothelial cell adhesion molecules. Arterioscler Thromb Vasc Biol 15:1987–1994

338. **Zilversmith DB** 1979 Atherogenesis: a postprandial phenomenon. Circulation 60:473–485
339. **Patch JR, Karlin JB, Scott LW, Smith LC, Gotto AMJ** 1983 Inverse relationship between blood levels of high density lipoprotein subfraction 2 and magnitude of postprandial lipemia. Proc Natl Acad Sci USA 80:1449–1453
340. **Ishibashi S, Goldstein JL, Brown MS, Herz J, Burns DK** 1994 Massive xanthomatosis and atherosclerosis in cholesterol-fed low density lipoprotein receptor-negative mice. J Clin Invest 93:1885–1893
341. **Linton MF, Farese RVJ, Chiesa G, Gras DS, Chin P, Hammer RE, Hobbs HH, Young SG** 1993 Transgenic mice expressing high plasma concentrations of human apolipoprotein B100 and lipoprotein(a). J Clin Invest 92:3029–3037
342. **Purcell-Huynh DA, Farese RVJ, Johnson DF, Flynn LM, Pierotti V, Newland DL, Linton MF, Sanan DA, Young SG** 1995 Transgenic mice expressing high levels of human apolipoprotein B develop severe atherosclerotic lesions in response to a high-fat diet. J Clin Invest 95:2246–2257
343. **Braun A, Trigatti BL, Post MJ, Sato K, Simons M, Edelberg JM, Rosenberg RD, Schrenzel M, Krieger M** 2002 Loss of SR-BI expression leads to the early onset of occlusive atherosclerotic coronary artery disease, spontaneous myocardial infarctions, severe cardiac dysfunction, and premature death in apolipoprotein E-deficient mice. Circ Res 90:270–276
344. **Kozarsky KF, Donahee MH, Glick JM, Krieger M, Rader DJ** 2000 Gene transfer and hepatic overexpression of the HDL receptor SR-BI reduces atherosclerosis in the cholesterol-fed LDL receptor-deficient mouse. Arterioscler Thromb Vasc Biol 20:721–727
345. **Ueda Y, Gong E, Royer L, Cooper PN, Francone OL, Rubin EM** 2000 Relationship between expression levels and atherogenesis in scavenger receptor class B, type I transgenics. J Biol Chem 275: 20368–20373
346. **Fuchs M, Ivandic B, Muller O, Schalla C, Scheibner J, Bartsch P, Stange EF** 2001 Biliary cholesterol hypersecretion in gallstone-susceptible mice is associated with hepatic up-regulation of the high-density lipoprotein receptor SR-BI. Hepatology 33:1451–1459
347. **Rigotti A, Zanlungo S, Miquel JF, Wang DQ** 2002 HDL receptor SR-BI and cholesterol gallstones. Hepatology 35:240–242
348. **Wang DQ, Carey MC** 2002 Murine cholesterol gallstone formation is not affected by partial disruption of the HDL receptor SR-BI. Biochim Biophys Acta 1583:141–150
349. **Berge KE, Tian H, Graf GA, Yu L, Grishin NV, Schultz J, Kwiterovich P, Shan B, Barnes R, Hobbs HH** 2000 Accumulation of dietary cholesterol in sitosterolemia caused by mutations in adjacent ABC transporters. Science 290:1771–1775
350. **Lee MH, Lu K, Hazard S, Yu H, Shulenin S, Hidaka H, Kojima H, Allikmets R, Sakuma N, Pegoraro R, Srivastava AK, Salen G, Dean M, Patel SB** 2001 Identification of a gene, ABCG5, important in the regulation of dietary cholesterol absorption. Nat Genet 27: 79–83
351. **Yu L, Li-Hawkins J, Hammer RE, Berge KE, Horton JD, Cohen JC, Hobbs HH** 2002 Overexpression of ABCG5 and ABCG8 promotes biliary cholesterol secretion and reduces fractional absorption of dietary cholesterol. J Clin Invest 110:671–680
352. **Yu L, Hammer RE, Li-Hawkins J, Von Bergmann K, Lutjohann D, Cohen JC, Hobbs HH** 2002 Disruption of Abcg5 and Abcg8 in mice reveals their crucial role in biliary cholesterol secretion. Proc Natl Acad Sci USA 99:16237–16242
353. **Arensburg J, Payne A, Orly J** 1999 Expression of steroidogenic genes in maternal and extraembryonic cells during early pregnancy in mice. Endocrinology 140:5220–5232
354. **Siiteri PK, Febres F, Clemens LE, Chang RJ, Gondos B, Stites D** 1977 Progesterone and maintenance of pregnancy: is progesterone nature's immunosuppressant? Ann NY Acad Sci 286:384–397
355. **Piccinni MP, Beloni L, Livi C, Maggi E, Scarselli G, Romagnani S** 1998 Defective production of both leukemia inhibitory factor and type 2 T-helper cytokines by decidual T cells in unexplained recurrent abortions. Nat Med 4:1020–1024
356. **Clark BJ, Soo S-C, Caron KM, Ikeda Y, Parker KL, Stocco DM** 1995 Hormonal and developmental regulation of the steroidogenic acute regulatory protein. Mol Endocrinol 9:1346–1355
357. **McConihay JA, Honkomp AM, Granholm NA, Woollett LA** 2000 Maternal high density lipoproteins affect fetal mass and extra-embryonic tissue sterol metabolism in the mouse. J Lipid Res 41: 424–432
358. **Kent G, Minick OT, Volini FI, Orfei E** 1966 Autophagic vacuoles in human red cells. Am J Pathol 48:831–857
359. **Holm TM, Braun A, Trigatti BL, Brugnara C, Sakamoto M, Krieger M, Andrews NC** 2002 Failure of red blood cell maturation in mice with defects in the high-density lipoprotein receptor SR-BI. Blood 99:1817–1824
360. **Coppinger RJ, Baum CL** 1999 Cholesterol-dependent regulation of nitric oxide production: potential role in atherosclerosis. Nutr Rev 57:279–282
361. **Li XA, Titlow WB, Jackson BA, Giltiay N, Nikolova-Karakashian M, Uittenbogaard A, Smart EJ** 2002 High density lipoprotein binding to scavenger receptor, class B, type I activates endothelial nitric-oxide synthase in a ceramide-dependent manner. J Biol Chem 277: 11058–11063
362. **Goti D, Reicher H, Malle E, Kostner GM, Panzenboeck U, Sattler W** 1998 High-density lipoprotein (HDL3)-associated α-tocopherol is taken up by HepG2 cells via the selective uptake pathway and resecreted with endogenously synthesized apo-lipoprotein B-rich lipoprotein particles. Biochem J 332:57–65
363. **Goti D, Hammer A, Galla HJ, Malle E, Sattler W** 2000 Uptake of lipoprotein-associated α-tocopherol by primary porcine brain capillary endothelial cells. J Neurochem 74:1374–1383
364. **Traber MG, Arai H** 1999 Molecular mechanisms of vitamin E transport. Ann Rev Nutr 19:343–355
365. **Goti D, Balazs Z, Panzenboeck U, Hrzenjak A, Reicher H, Wagner E, Zechner R, Malle E, Sattler W** 2002 Effects of lipoprotein lipase on uptake and transcytosis of low density lipoprotein (LDL) and LDL-associated α-tocopherol in a porcine *in vitro* blood-brain barrier model. J Biol Chem 277:28537–28544
366. **Kiefer C, Sumser E, Wernet MF, Von Lintig J** 2002 A class B scavenger receptor mediates the cellular uptake of carotenoids in *Drosophila*. Proc Natl Acad Sci USA 99:10581–10586
367. **Acton S, Osgood D, Donoghue M, Corella D, Pocovi M, Cenarro A, Mozas P, Keilty J, Squazzo S, Woolf EA, Ordovas JM** 1999 Association of polymorphisms at the SR-BI gene locus with plasma lipid levels and body mass index in a white population. Arterioscler Thromb Vasc Biol 19:1734–1743
368. **Plat J, Mensink RP** 2002 Relationship of genetic variation in genes encoding apolipoprotein A-IV, scavenger receptor BI, HMG-CoA reductase, CETP and apolipoprotein E with cholesterol metabolism and the response to plant stanol ester consumption. Eur J Clin Invest 32:242–250
369. **Yamada Y, Izawa H, Ichihara S, Takatsu F, Ishihara H, Hirayama H, Sone T, Tanaka M** 2002 Prediction of the risk of myocardial infarction from polymorphisms in candidate genes. N Engl J Med 347:1916–1923
370. **Hong SH, Kim YR, Yoon YM, Min WK, Chun SI, Kim JQ** 2002 Association between HaeIII polymorphism of scavenger receptor class B type I gene and plasma HDL-cholesterol concentration. Ann Clin Biochem 39:478–481
371. **Koumanis DJ, Christou NV, Wang XL, Gilfix BM** 2002 Pilot study examining the frequency of several gene polymorphisms in a morbidly obese population. Obes Surg 12:759–764
372. **Krieger M** 2001 Scavenger receptor class B type I is a multiligand HDL receptor that influences diverse physiologic systems. J Clin Invest 108:793–797
373. **Rigotti A, Krieger M** 1999 Getting a handle on "good" cholesterol with the high-density lipoprotein receptor. N Engl J Med 341:2011–2013