Hepatic Medicine: Evidence and Research

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REVIEW

Scavenger receptor class B member 1 protein: hepatic regulation and its effects on lipids, reverse cholesterol transport, and atherosclerosis

This article was published in the following Dove Press journal:
Hepatic Medicine: Evidence and Research
7 April 2011
Number of times this article has been viewed

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Abstract: Scavenger receptor class B member 1 (SR-BI, also known as *SCARB1*) is the primary receptor for the selective uptake of cholesterol from high-density lipoprotein (HDL). SR-BI is present in several key tissues; however, its presence and function in the liver is deemed the most relevant for protection against atherosclerosis. Cholesterol is transferred from HDL via SR-BI to the liver, which ultimately results in the excretion of cholesterol via bile and feces in what is known as the reverse cholesterol transport pathway. Much of our knowledge of SR-BI hepatic function and regulation is derived from mouse models and in vitro characterization. Multiple independent regulatory mechanisms of SR-BI have been discovered that operate at the transcriptional and post-transcriptional levels. In this review we summarize the critical discoveries relating to hepatic SR-BI cholesterol metabolism, atherosclerosis, and regulation of SR-BI, as well as alternative functions that may indirectly affect atherosclerosis.

Keywords: SR-BI, SCARB1, lipids, atherosclerosis, CAD, mouse models

Function and structure of SR-BI and other class B scavenger receptors

Scavenger receptor class B member 1 (SR-BI, gene name *SCARB1*) belongs to the CD36 superfamily of membrane-bound, cell-surface glycoproteins, which include mammalian scavenger receptor CD36 and the lysosomal membrane protein 2 (gene name *SCARB2*, formerly LIMPII).[1] These receptors can bind to modified forms of low-density lipoprotein (LDL) as well as native high-density lipoprotein (HDL) and very low density lipoprotein (VLDL).[2,3] However, SR-BI is distinguished from other class B scavengers by its high affinity to facilitating selective cholesterol uptake from HDL, without the internationalization and degradation of the apolipoprotein-AI (APOA1)-containing whole particle.[2] There are several common structural features shared among this family of proteins. These include membrane-associated hydrophobic regions near the N- and C-termini, a large extracellular loop comprising the portion of the peptide sequence between the two membrane-bound end regions, and several sites of N-linked glycosylation.[4]

SR-BI and CD36 share considerable sequence homology throughout much of their extracellular loop, with several conserved cysteine and asparagine residues, as well as canonical sites of fatty acylation and N-linked glycosylation. Interestingly, SR-BI and CD36 bear little sequence homology in their transmembrane and N- and C-terminal membrane-associated domains.[5] SR-BI is considered the HDL cholesteryl ester (HDL-CE) selective uptake receptor, CD36 is often ignored or described as not having HDL-CE selective uptake activity. While it has been known for some time

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that CD36 knockout (KO) (*Cd36*$^{-/-}$) mice exhibit increased plasma HDL, and recently HDL-CE selective uptake activity was shown to be impaired in *Cd36*$^{-/-}$ mice compared to control mice.[6] In vitro studies comparing CD36 and SR-BI showed that both bound to HDL and both mediated HDL-CE selective uptake; however, CD36 mediates selective uptake at a slower rate than SR-BI.[5,7,8] CD36 and SR-BI also have similar binding capabilities to a variety of particles and ligands other than HDL, including acetylated LDL and oxidized LDL (oxLDL), although CD36 is considerably better at binding and internalizing oxLDL than SR-BI.[9] CD36 can also mediate binding and uptake of carbamylated LDL in endothelial cells, although the impact in the liver and that of SR-BI have not been reported,[10] and CD36 has significant fatty acid translocase activity, which may be the primary metabolic function of CD36.[11]

The primary structure of murine SR-BI is a 509 amino acid sequence, with a predicted mass of ~57 kDa.[12,13] However, Western blot analysis of tissues and cultured cells indicates that SR-BI is an 80–84 kDa protein due to significant post-translational processing.[12] Site-directed mutagenesis experiments have confirmed that mouse SR-BI is fatty acylated at two cysteine residues in the cytoplasmic domain of the C-terminus at the junction of the transmembrane region (Cys462 and Cys470).[5] In addition, SR-BI undergoes homo-oligomerization to form dimers and tetramers[14–18] that are dependent on C-to-C-transmembrane and/or C-C-terminal interactions (Figure 1).[14] It is likely that these oligomers form a hydrophobic channel whereby water is excluded[15,19,20] and HDL-CE molecules move toward the plasma membrane, which has a low concentration of CE.[19]

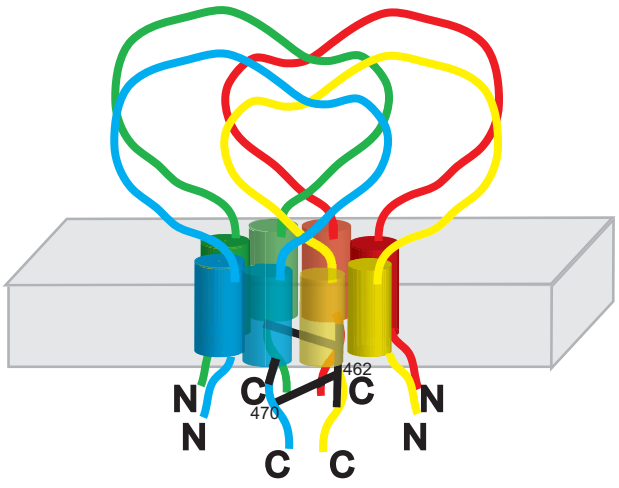

Figure 1 Hyphothetical structure of scavenger receptor class B member 1 membrane-bound tetramer with potential cysteine-to-cysteine (Cys462 and Cys470) interactions interconnecting the four C-termini.

There are four known alternatively coding SR-BI splice variants. In mouse liver, SR-BI and SR-BI.2 (also described as SR-BII) are the most common. There is no detailed characterization of the other two variants described in genome databases. SR-BI.2 differs from SR-BI by having a different cytoplasmic C-terminus, specifically the terminal 42 amino acids.[21] SR-BI.2 mRNA levels are comparable with SR-BI in all tissues examined, although protein levels are lower. In liver, SR-BI.2 accounts for only 10%–15% of the SR-BI/SR-BI.2 total protein.[22] Experiments in Chinese hamster ovary (CHO) cells indicate that SR-BI.2 is mostly intracellular rather than membrane bound and may be involved in within-cell cholesterol trafficking and HDL endocytosis.[23,24] However, liver-specific effects and the in vivo relevance of SR-BI.2 have not been fully elucidated.

Tissue expression and cellular location of SR-BI

SR-BI is expressed in multiple tissues, including the adrenals, gonads, macrophages, endothelial cells, and liver.[2,18,25] The liver, by total mass, is the primary location of SR-BI protein, and given our knowledge of HDL-CE selective uptake in the liver, determining the hepatic-specific in vivo function of SR-BI is a critical goal. Early immunohistochemical analysis of hepatocytes indicated that SR-BI is localized to the surface of hepatocytes, both at the sinusoidal and bile canalicular domains.[26] This has been confirmed by others using immunohistochemistry and Western blot-based studies.[27–29] In addition, it has been shown in purified membrane fractions that SR-BI is present in both canalicular membranes and basolateral membranes,[30] and, when stimulated by cholesterol, SR-BI undergoes transcytosis to the bile canaliculus.[31]

In CHO cells, SR-BI colocalizes with caveolae[12,32] and preferentially, but not exclusively, colocalizes and copurifies with the major caveolae protein component caveolin-1 (CAV-1).[12] Caveolae are low-density, 50–100 nm invaginated plasma membrane microdomains enriched in cholesterol as well as glycolipids relative to the remainder of the plasma membrane in general.[33] As these membrane microdomains have been shown to be important in mediating many transport and signaling events, including the subcellular transport of cholesterol and cholesterol efflux from cells, the colocalization of SR-BI with membrane caveolae may substantially modulate its selective lipid uptake activity in various tissues and cell types.[12,34]

However, later studies examining rat adrenal[35] and ovary tissue[36] in vivo showed that caveolae are less significant

for the localization of SR-BI and that SR-BI is localized to plasma membrane microvillar channel-like structures. Indeed, in adrenocortical cells, it appears that SR-BI is a prerequisite for the formation of these structures.[37] It was also demonstrated in vitro using adrenocortical cells that SR-BI does not colocalize with caveolae but rather it non-uniformly clusters on microvillar extensions that lack CAV-1 expression.[38] Furthermore, in kidney and thyroid cell lines, CAV-1 expression does not affect SR-BI-mediated selective uptake of CE.[39] It is noteworthy that there is comparatively very little CAV-1 in mouse liver, and the homologs CAV-2 and CAV-3 are completely absent.[40,41] There have been very few studies examining the relationship of SR-BI and caveolae in the liver.

In humans, immunohistochemisty of samples from autopsied cadavers has revealed that human SR-BI is present in both hepatocytes and Kupffer cells, which are liver-specific macrophages. In addition, SR-BI is present in human atherosclerotic aortas and coronary arteries, which are essentially all the key tissues for reverse cholesterol transport (RCT).[25] Despite this basic characterization of human SR-BI in vitro, almost all of our functional in vivo knowledge of SR-BI is derived from animal models.

In vivo SR-BI characterization

Functional in vivo characterization of SR-BI, and hepatic SR-BI function in particular, has been elucidated using animal models, including rats,[18] rabbits,[42] and hamsters,[43] but particularly mice. The primary mouse model is the whole-body *Sr-bI*$^{-/-}$.[44] However, there are additional mouse models with reduced as well as increased *Sr-bI* expression that have proven useful in characterizing SR-BI.

Liver-specific overexpression of SR-BI

Isolating the hepatic-specific effects of SR-BI versus the extrahepatic specific effects of SR-BI has not been a trivial endeavor, and indeed some of the earlier studies to examine liver-specific SR-BI function utilized overexpression of SR-BI (Table 1).[26,45–48] Overexpression of SR-BI by adenovirus in mouse liver results in decreased plasma HDL and APOAI levels, increased hepatic uptake of DiI-label from HDL, and increased biliary cholesterol.[26] Stable transgenic mice with hepatic SR-BI overexpression (*Sr-bI.Tg*) show similar results along with decreased APOAII, increased CE-selective uptake in liver, increased uptake of HDL protein in both liver and kidney, and decreased VLDL and LDL-CE and APOB levels by up to 97%. These results demonstrate that the effects on APOB levels are not trivial and could influence the outcome of atherosclerosis beyond the effects of HDL.[46] Additional studies in various overexpression models also show the non-HDL cholesterol decrease presented as decreased APOB, LDL, and VLDL.[45,47,48] A study examining SR-BI overexpression in the background of human APOB transgenic mice revealed some complex diet-dependent responses and showed that with two-fold SR-BI overexpression, mice have reduced atherosclerosis, but with higher levels of SR-BI protein expression (10-fold), there was no decrease in lesion size compared with controls (Table 1).[49]

Whole-body *Sr-bI*$^{-/-}$ mice

The whole-body KO displays increased total plasma cholesterol, and on a standard chow diet, that increased cholesterol is distributed wholly in the HDL fractions.[44] Other lipid changes that are common in the *Sr-bI*$^{-/-}$ mice include increased plasma-free cholesterol, HDL-CE, and a decrease in biliary cholesterol. Interestingly, there are no changes in hepatic lipids, triglycerides, free cholesterol, and CE, or in plasma triglycerides.[44,50] Mice placed on a high-fat Western diet for 20 weeks show a significant increase in aortic lesions, proving that SR-BI deficiency in mice is proatherogenic.[50] In the absence of APOE (*Sr-bI*$^{-/-}$ *Apoe*$^{-/-}$ double knockout [dKO] mice), lesion size and plasma cholesterol are raised even higher than in either single KO strains.[51] The dKO mice suffer severe cardiac dysfunction, resulting in premature death.[52] However, HDL and HDL cholesterol in the dKO mice is significantly reduced, with almost no normal-sized HDL particles. Total APOAI levels are reduced only slightly in the dKO mice; however, the distribution of APOAI is more in the intermediate-density lipoprotein/LDL and VLDL fractions (Table 2).

Liver-specific knockdown of SR-BI

Knockdown mouse models beyond the whole-body *Sr-bI*$^{-/-}$ have also been developed to study SR-BI function. A knockdown model targeting the promoter region (*Sr-bI.att*) was generated, resulting in approximately 50% reduction of SR-BI protein levels in all tissues examined, including liver, adrenals, and testis. These mice show increased HDL and total cholesterol with decreased HDL-CE selective uptake, as expected. However, in contrast to the overexpression models, there are no changes in VLDL, LDL, and APOB.[53] This strain was examined for atherosclerosis susceptibility by crossing it on to the *Ldlr*$^{-/-}$ background.[54] The authors observed a 50%–70% increase in plasma cholesterol that was attributed mostly

Table 1 Hepatic overexpression of SR-BI in mice

Strain (background)	Diet	Phenotype	Direction	Ref
Ad.m*Sr-bI* (C57BL/6J)	Chow	HDL-C	↓	26
		Biliary cholesterol	↑	
Sr-bI.Tg (C57BL/6J)	Chow	HDL-C	↓	46
		APOAI, APOAII	↓	
		VLDL, LDL, APOB	↓	
	HF HC	APOB	↔	
Sr-bI.Tg Ldlr–/– (C57BL/6J)	HF HC	HDL-C, LDL	↓	48
		VLDL	↑	
		Lesion size	↔	
Sr-bI.Tg Ldlr–/+ (C57BL/6J)	HF HC + CA	HDL-C	↓	
		VLDL, LDL	↓	
		Lesion size	↓	
Combined analysis				
Sr-bI (FVB Bac transgenics)	Chow (6 weeks of age)	HDL-C	↓	47
		HDL, LDL, VLDL particle size	↓	
		APOB, non-HDL-C	↓	
		Increased LDL clearance	↑	
	HF HC + CA (+4 weeks)	HDL-C	↓	
		APOB	↓	
Sr-bI (FVB Bac transgenics with hAPOB.Tg)	Chow (6 weeks of age)	HDL, TC, non-HDL	↓	49
		mAPOB	↔	
		hAPOB	↓	
	HF HC + CA (+18 weeks)	HDL	↓	
		Lesion size (low SR-BI exp)	↓	
		TC, non-HDL m/hAPOB	↔	
		Lesion size (high SR-BI exp)	↔	
Ad.m*Sr-bI Ldlr–/–* (C57BL/6J)	HF HC (no CA)	HDL-C, APOAI	↓	45
		LDL-C (FPLC)	↓	
		Lesion size	↓	
Ad.m*Sr-bI* hAPOB.Tg	Chow	HDL-C (24–72 h)	↓	137
		TC (72 hours)	↓	
		HDL-C (FPLC at 72 hours)	↓	
		APOB	↔	
Ad.m*Sr-bI* (C57BL/6J)	Chow	HDL	↓	58
		TC, FC	↓	
		TG, phospholipids	↓	
		APOB, VLDL	↓	
Ad.hSR-BI hAPOA1.Tg (C57BL/6J)	Chow	RCT to liver and feces	↑	79
Ad.m*Sr-bI* (C57BL/6J)	Chow	TC, day 3, 7, and 14	↓	65
		TG day 3	↓	
		TG day 7, 14	↑	
		VLDL-C (FPLC) day 7 and 14	↑	
		LDL-C (FPLC) day 3, 7, and 14	↑	
		Hepatic VLDL-TG production	↑	
		Hepatic VLDL-APOB production	↑	
		Liver weight as % bodyweight	↑	
		HDL-C resecreted by liver in VLDL	↑	

Abbreviations: APO, apolipoprotein; CA, cholic acid; FPLC, fast protein liquid chromatography; HC, high cholesterol; HDL-C, high-density lipoprotein cholesterol; HF, high fat; LDL, low-density lipoprotein; RCT, reverse cholesterol transport; SR-BI, scavenger receptor class B member 1; TG, triglycerides; TC, total cholesterol; VLDL, very low-density lipoprotein.

to non-HDL cholesterol, accompanied by significantly elevated atherosclerosis, with only a slight but significant increase in HDL. The authors also showed that SR-BI in vivo did not mediate selective uptake of CE from LDL, nor did it affect LDL catabolism or plasma LDL clearance. The authors point toward the increased LDL production as the cause of the observed atherosclerosis, probably arising from increased conversion of VLDL-CE to LDL-CE, which, in turn, may be caused by the "backup function" of SR-BI to take up VLDL remnants.[54]

Table 2 Key *Sr-bI*$^{-/-}$ mouse models and studies

Strain	Control strain	Diet	Phenotype	Direction	Ref
Sr-bI–/–	*Sr-bI+/+*	Chow	TC, HDL	↑	44
			Total APOAI	↔	
			Adrenal cholesterol	↓	
Sr-bI–/–	*Sr-bI+/+*	Chow	TC	↑	51
Apoe–/–	*Apoe–/–*		VLDL cholesterol (FPLC)	↑	
			Lesion size	↑	
			HDL, APOAI	↓	
			Biliary cholesterol	↓	
Sr-bI–/–	*Sr-bI+/+*	Chow	Increased premature death	↑	52
Apoe–/–	*Apoe–/–*		Occlusive athero CAD	↑	
			Body size	↓	
Sr-bI–/–	*Sr-bI+/+*	Chow followed by WTD (20 weeks)	TC, FC	↑	50
			HDL-CE	↑	
			TG	↔	
			Lesion size	↑	
			Hepatic TG, FC, CE	↔	
			Biliary cholesterol	↓	
Sr-bI–/–	*Ldlr–/–*	High-fat diet (12 weeks)	TC	↑	74
Ldlr–/–			HDL	↑	
			Lesion size	↑	
			VLDL cholesterol	↔	
Sr-bI–/–	*Sr-bI+/+*	Chow	RCT to liver and feces	↑	79
Sr-bI–/–	*Sr-bI+/+*	Chow	Hepatic VLDL-TG production	↓	65
			Hepatic VLDL-APOB production	↓	
			TC and FC	↑	
			HDL-C resecreted by liver in VLDL	↓	

Abbreviations: APO, apolipoprotein; CAD, coronary artery disease; CE, cholesteryl ester; FC, free cholesterol; FPLC, fast protein liquid chromatography; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RCT, reverse cholesterol transport; TC, total cholesterol; TG, triglycerides; VLDL, very low-density lipoprotein; WTD, Western type diet.

A second knockdown model was developed as a liver-specific SR-BI KO (hypom*Sr-bI*^{liver}). However, unexpectedly, SR-BI protein levels were reduced in all the tissues that were examined, not just in the liver. Phenotypically, as with the *Sr-bI.att* mice, the hypom*Sr-bI*^{liver} mice showed increased HDL and total cholesterol with decreased HDL-CE uptake and there were no changes in VLDL, LDL, and APOB levels. The hypom*Sr-bI*^{liver} mice showed increased atherosclerosis, although this was decreased compared with *Sr-bI*$^{-/-}$ (whole-body KO) mice. The authors hypothesized that this could be due to residual extrahepatic SR-BI providing atheroprotection in addition to the known liver lipoprotein function.[55] If this is true, the protection is unlikely to be from macrophage SR-BI function.[56] Although not explored by the authors, the observed differences in atherosclerosis of the hypom*Sr-bI*^{liver} mice compared with *Sr-bI*$^{-/-}$ mice could also be due to the significantly different genetic backgrounds of the two strains.

More recently, a third model for SR-BI knockdown was reported, having been identified through a mutagenesis screen: the *Sr-bI*^{I179N} mutant mice. This strain has 90% knockdown of SR-BI protein in the liver with no knockdown in adrenals or ovaries caused by a single nucleotide mutation in the 179th amino acid.[57] This strain differs from the other two knockdown strains, as well as the *Sr-bI*$^{-/-}$ strain, by being in a pure C57BL/6 background, allowing for a more direct comparison with the transgenic overexpression models *Sr-bI.Tg*,[46,48] as well as the somatic adenovirus liver transgenic studies.[26,45,58] HDL, total cholesterol, and free cholesterol in *Sr-bI*^{I179N} mice are significantly increased with an accompanying decrease in selective uptake, as expected, compared with wildtype controls. In addition, an increase in phospholipids is observed (also indicated in the *Sr-bI.att* mice), as well as, for the first time, a significant increase in triglycerides, noting that somatic liver adenovirus overexpression of SR-BI (Ad.m*Sr-bI*) leads to decreased phospholipids and triglycerides (Table 1).[58] The effects on atherosclerosis and APOB lipoproteins have not yet been reported for this strain (Table 3).

"Humanizing" SR-BI mouse models by introducing CETP

The mouse is not a perfect model for human lipid and atherosclerosis studies. A key missing component in mice is the

Table 3 Knockdown of SR-BI in mice

Strain (background)	Diet	Tissue specificity	Phenotype	Direction	Ref
Sr-blatt (BALB/cByJ) promoter mutation	Chow	Liver, adrenal, testis	HDL,TC	↑	53
			HDL particle size	↑	
			Phospholipids	↑	
			APOAI	↑	
			3H CE clearance	↓	
			Selective uptake	↓	
			TG	↔	
			VLDL, APOB, APOE	↔	
Sr-blatt Ldlr−/− (BALB, C57BL6 mix)	Chow or HF + HC	Liver, adrenal, testis	HDL, TC	↑	54
			LDL, APOB	↑	
			Lesion size	↑	
			Clearance: APOB, APOE	↔	
			TG	↔	
hypom*Sr-bI*-KO*liver* flox/cre liver conditional knockout (129, C57BL/6 mix)	Chow	Liver, kidney, adrenal, testis, ovary, aorta, BMM	HDL, TC, FC	↑	55
			FC/TC	↑	
			TG	↔	
	HF HC + CA		TC	↑	
			FC		
			FC/TC%	↑	
			TG	↑	
			Lesion size	↑	
Sr-bI^{I179N} (C57BL/6J)	Chow	Liver	HDL, APOAI	↑	57
			TC FC, FC/TC	↑	
			TG phospholipids		
			3H CE clearance	↑	
			Selective uptake	↓	
				↓	

Abbreviations: APO, apolipoprotein; BMM, bone marrow derived macrophages; CAD, coronary artery disease; CE, cholesteryl ester; FC, free cholesterol; HC, high cholesterol; HDL, high-density lipoprotein; HF, high fat; LDL, low-density lipoprotein; SR-BI, scavenger receptor class B member 1; TC, total cholesterol; TG, triglycerides; VLDL, very low-density lipoprotein.

absence of cholesteryl ester transfer protein (CETP), which accounts for the vast majority of human plasma HDL cholesterol heritability.[59] Consequently, an increasing component of determining the comparable human function of lipid genes is the use of more humanized mouse models. Several studies have examined the absence of SR-BI in the presence of CETP using CETP transgenic mouse models (CETP.Tg). One study that introduced CETP.Tg with a liver-specific hAPOA1-promoter into the *Sr-bI*$^{-/-}$ genetic background fed the mice a cholate-free atherogenic diet and showed that the CETP expression reduced atherosclerosis. This is likely due to the movement of cholesterol away from the enlarged dysfunctional HDL in *Sr-bI*$^{-/-}$ to APOB-containing lipoproteins, clearing the cholesterol via alternative reverse cholesterol pathways such as the LDL receptor[60] and other LDL-independent pathways.[61] Controversially, a more recent study using a similar approach but using CETP.Tg mice with the human endogenous CETP promoter (endoCETP.Tg), rather than a liver-specific promoter,[62] showed no reduction in atherosclerosis despite an increase in HDL-CE transfer to the liver.[63] In both of these studies of *Sr-bI*$^{-/-}$CETP.Tg and *Sr-bI*$^{-/-}$endoCETP.Tg, the mice involved have wildtype LDL receptor and APOE, which means they are not particularly prone to atherosclerosis. Further studies are required to delineate whether or not CETP is antiatherogenic in the absence of SR-BI (Table 4).

In vivo hepatic SR-BI: effects on APOB-containing lipoproteins and bidirectional flux of free cholesterol

Clearly, a major function of SR-BI is the selective uptake of HDL-CE; however, as discussed previously for the overexpression studies, SR-BI has a distinct role in APOB-containing lipoprotein metabolism, especially with regard to VLDL and chylomicrons.[46,47,49,58,64–67] In almost all mouse liver overexpression studies (Table 2), combinations of VLDL, APOB, total cholesterol, and triglycerides were all affected. The resulting changes in atherosclerosis susceptibility could therefore be due to changes in atherogenic APOB lipoproteins. Studies using radiolabeled VLDL have shown that SR-BI has a major role in VLDL remnant uptake in vivo (as well as in vitro) that does not involve selective

Table 4 "Humanized" SR-BI mouse models

Strain	Diet	Control	Phenotype	Direction	Ref
Sr-bI–/– CETP.Tg	Chow (6–8 weeks) followed by Western diet for 22 weeks	*Sr-bI–/–*	Lesion size	↓	60
			TC	↓	
			Hepatic CE	↓	
			Hepatic FC, esterified cholesterol	↔	
Sr-bI–/– endo CETP.Tg	Chow	WT mice and *Sr-bI–/–*	HDL, TC, FC	↓	63
			FC/TC %	↓	
			VLDL	↓	
			LDL	↔	
		WT mice only	LDL	↓	
	Western diet	WT mice and *Sr-bI–/–*	HDL, TC, FC	↓	
			FC/TC %	↓	
			VLDL, LDL	↔	
		WT mice only	VLDL, LDL	↓	
		Sr-bI–/–	Lesion size	↔	

Abbreviations: CE, cholesteryl ester; CETP, cholesteryl ester transfer protein; FC, free cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SR-B1, scavenger receptor class B member 1; TC, total cholesterol; Tg, transgenic; VLDL, very low-density lipoprotein.

uptake.[65,67] It is also believed that reduced hepatic SR-BI leads to reduced VLDL-triglyceride and VLDL-APOB in vivo production, indicating that hepatic SR-BI HDL-derived cholesterol is affected by SR-BI in hepatocytes in the form of VLDL particles (Figure 2, red arrows).[65]

Reverse cholesterol transport

The complete RCT pathway[68] involves many proteins, including enzymes, apolipoproteins, receptors, and transporters. These function to return cholesterol from lipid-laden macrophages and peripheral tissues to the liver for secretion via the bile and feces. However, the individual steps of the RCT pathway can be assessed separately to determine the effects due to individual proteins. These include the removal of cholesterol from macrophages to lipoproteins, considered the governing and first step of RCT; the removal of HDL-CE from lipoproteins to the liver, governed in large part by SR-BI;[69] and the removal of cholesterol from bile to the feces.[70] The purpose of examining individual aspects of the RCT pathway allows the assessment of individual, specific proteins

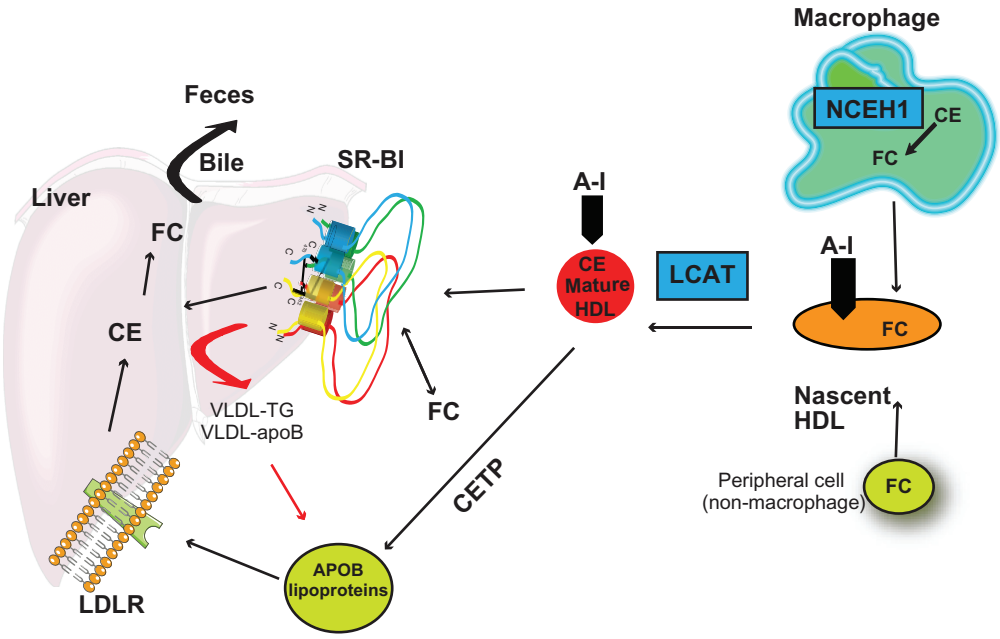

Figure 2 Reverse cholesterol transport. SR-BI selective HDL-CE uptake is crucial in the clearance of cholesterol from macrophages and peripheral tissue, reducing the incidence of atherosclerosis.

Abbreviations: CE, cholesteryl ester; CEH, cholesteryl ester hydrolase; CETP, cholesteryl ester transfer protein; FC, free cholesterol; HDL, high-density lipoprotein; LCAT, lecithin cholesterol acyltransferase; LDL, low-density lipoprotein; LDLR, low-density lipoprotein receptor; NCEH, neutral cholesteryl ester hydrolase; SR-BI, scavenger receptor class B member 1; VLDL, very low-density lipoprotein.

to be characterized without necessarily following the cholesterol all the way to the feces, where it is difficult and tedious to measure. Figure 2 provides an overview of RCT.

RCT: SR-BI in macrophages

SR-BI is critical for the uptake of CE to the liver; however, SR-BI is also present in the macrophages,[1] and the removal of cholesterol from macrophages is a critical component of reducing atherosclerosis. RCT can be examined in vivo by using macrophage foam cells that are loaded with radiolabeled cholesterol.[71] The cells are injected intraperitoneally, and the cholesterol is effluxed by lipoproteins to different tissues. Interestingly, murine macrophages also seem to exhibit HDL-CE selective uptake that is independent of SR-BI.[72] In vivo studies have examined the potential of macrophage SR-BI to promote RCT.[56] However, primary bone marrow-derived macrophages (BMMs), as well as mouse peritoneal macrophages (MPMs) from *Sr-bI*$^{-/-}$ mice, showed no net effect on RCT compared with wildtype mice. Furthermore, MPMs show very little SR-BI-dependent efflux capacity.[73] This indicates that the impact on atherosclerosis attributable to SR-BI is primarily due to its liver function, rather than to function in the macrophages. However, studies using BMM transplants have shown that macrophage SR-BI may yet play a role in atherosclerosis development (Table 5). When BMMs derived from *Sr-bI*$^{-/-}$ mice are transplanted into *Ldlr*$^{-/-}$ or *Apoe*$^{-/-}$ mice, atherosclerosis increases.[74–76] This may be due to changes in cholesterol efflux capacity and/or inflammation. Interestingly, VLDL and LDL cholesterol strangely increases in mice transplanted with BMMs derived from *Sr-bI*$^{-/-}$ mice, whereas HDL cholesterol is unchanged when compared with *Ldlr*$^{-/-}$ mice transplanted with wildtype BMMs.

RCT: SR-BI in hepatocytes

Although SR-BI in liver acts as an acceptor for HDL-CE, it has also been shown in vitro to efflux cholesterol, ie, to move cholesterol out of cells on to HDL. This cholesterol efflux function of SR-BI has been observed only in nonmacrophage cell lines.[2,77,78] Studies performed to specifically observe the same function in macrophages have shown that SR-BI is not involved in cholesterol efflux[72] or that efflux is minimal, with bidirectional flux favoring influx.[73] In vivo overexpression of SR-BI in mouse hepatocytes results in increased RCT from radiolabeled cholesterol-loaded macrophages, leading

Table 5 Bone marrow transplant studies examining SR-BI

Strain			Diet	Phenotype	Direction	Ref
BMM donor	**Control**	**BMM recipient**				
Sr-bI–/–	*Sr-bI+/+*	*Ldlr–/–*	Western diet 4 weeks after transplant for 16 weeks	VLDL and IDL/LDL Cholesterol (FPLC)	↑	74
				Lesion size	↑	
				HDL cholesterol (FPLC)	↔	
Sr-bI–/–	*Sr-bI+/+*	*Apoe–/–*	Baseline, 4, 8, and 12 weeks post-transplant	Lesion size	↑	138
Apoe–/–	*Apoe–/–*			TC, TG	↔	
				VLDL and IDL/LDL Cholesterol (FPLC)	↔	
Sr-bI–/–	*Sr-bI+/+*	*Ldlr–/–*	Chow, Western diet	Lesion size	↑	75
			Western diet 9–12 wks	HDL, FC, CE	↔	
		C57BL/6J	Chow	HDL, FC, CE	↔	
			Paigen diet	Lesion size	↑	
Sr-bI–/–	*Sr-bI+/+*	C57BL/6J	Chow	Reverse cholesterol Transport	↔	56
Sr-bI–/– and Sr-bI–/– Abca1–/–	*Sr-bI+/+*	*Ldlr–/–*	Chow, 8 weeks post transplant	TC	↔	76
				VLDL, LDL, HDL cholesterol (FPLC)	↔	
			Western diet for 10 weeks, 18 weeks post-transplant	Lesions in aortic root	↑	
				Lesions in aortic arch, Coronary artery	↔	
				HDL cholesterol (FPLC)	↔	
				Lesions in thoracic root	↓	
				TC	↓	
				VLDL, LDL cholesterol (FPLC)	↓	

Abbreviations: BMM, bone marrow-derived macrophage; CE, cholesteryl ester; FC, free cholesterol; FPLC, fast protein liquid chromatography; HDL, high-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; SR-B1, scavenger receptor class B member 1; TC, total cholesterol; TG, triglycerides; VLDL, very low-density lipoprotein.

to increased clearance to the liver and ultimately the feces. This has been observed in wildtype C57BL/6J mice as well as in hAPOAI.Tg mice. Conversely, in *Sr-bI*$^{-/-}$ mice, RCT is reduced, resulting in decreased clearance from macrophages to the liver and feces.[79] Although the exact mechanism as to how hepatic SR-BI affects RCT from macrophages is not clear, the authors suggest that SR-BI may act on HDL to generate remnant HDL particles or lipid-poor APOAI, which may be better acceptors of cholesterol efflux from macrophages.[79]

Hepatic regulation of SR-BI

Given our knowledge of how hepatic SR-BI can influence RCT through HDL-CE selective uptake (and possibly through proatherogenic APOB-containing lipoproteins), it is important that we understand how hepatic SR-BI protein levels are regulated. Indeed, multiple regulatory pathways have been identified to act at the protein level, as well as through multiple independent transcriptional pathways (Figure 3).

Protein regulation through PDZK1

A significant mechanism by which hepatic SR-BI protein levels are regulated is by the adaptor protein PDZ domain containing 1 (PDZK1, also known as C-terminal linking and modulating protein [CLAMP]). PDZK1 was the only protein identified to interact with SR-BI in a yeast two-hybrid screen.[27] Several studies have shown that the first of the four PDZ domains in PDZK1 (N-terminal) is critical for its binding to SR-BI and possibly promotes SR-BI translocation to the sinusoid.[27] The binding occurs at SR-BI's C-terminus, with the terminal amino acid (509) being especially critical, not only for the interaction but also for the cell surface expression of SR-BI in vivo.[27,80] PDZK1 does not interact with SR-BI.2, which has an alternative C-terminus. PDZK1 itself is regulated by a small PDZK1-associated protein (SPAP, also known as DD96/MAP17). Overexpression of SPAP in mice by adenovirus leads to decreased PDZK1 and decreased SR-BI liver protein levels.[81] In vitro evidence suggests that PDZK1 expression is upregulated by peroxisome proliferator-activated receptor (PPAR)α.[82]

Whole-body KO mice for PDZK1 (*Pdzk1*$^{-/-}$) have elucidated further effects and mechanisms of this interaction.[83] *Pdzk1*$^{-/-}$ mice have a 95% reduction of hepatic SR-BI protein levels and a 50% reduction in the proximal intestine, but in the steroidogenic tissues, adrenals, testis, and ovaries, SR-BI levels are unchanged. Due to the 95% hepatic SR-BI reduction, many of the resulting lipid phenotypes are unsurprising, such as the increased total cholesterol and free cholesterol. Phospholipids are also significantly increased, and triglycerides are increased in females. In the absence of PDZK1 and APOE (*Pdzk1*$^{-/-}$*Apoe*$^{-/-}$ dKO mice), aortic atherosclerotic lesions[84] and occlusive coronary artery disease (CAD) are

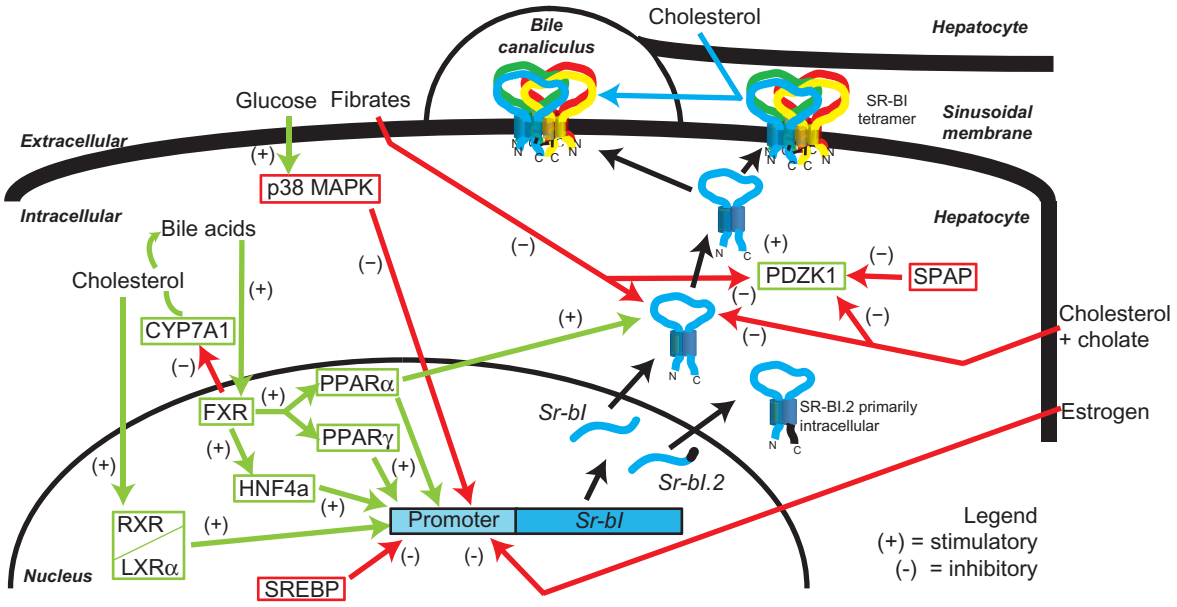

Figure 3 Mechanisms affecting SR-BI member 1 regulation. Green arrows and positive signs indicate that interaction increases the activity or abundance of the downstream element, and red arrows and negative signs indicate decreased function and abundance. The blue arrow indicates possible transcytosis to the bile canaliculus activated by cholesterol. Black arrows show the normal path of SR-BI to the membrane. Note that although fibrates increase PPARs, this does not translate to increased SR-BI, because the net effect is reduced hepatic SR-BI protein levels.

Abbreviations: CYP7A1, cholesterol 7-anhydroxylase; FXR, farnesoid X receptor; HNF4a, hepatic nuclear factor 4, alpha; LXR, liver X receptor; MAPK, mitogen-activated protein kinase; PPAR, proliferator-activated receptor; RXR, retinoid X receptor; SPAP, small PDZK1-associated protein; SR-BI, scavenger receptor class B member 1; SREBP, sterol regulatory element binding protein.

significantly increased.[85] Interestingly, in the dKO mice maintained on a Western atherogenic diet for 5 months, hepatic SR-BI protein remained significantly down (~93%), but there was no difference in total cholesterol. In addition, fast protein liquid chromatography analysis showed that VLDL cholesterol was slightly reduced, as opposed to increased in *Sr-bI*$^{-/-}$*Apoe*$^{-/-}$ dKO mice, and no occlusive atherogenic CAD was observed. Many reasons could explain the lack of occlusive atherogenic CAD, including differences in the genetic backgrounds of *Sr-bI*$^{-/-}$*Apoe*$^{-/-}$ vs *Pdzk1*$^{-/-}$*Apoe*$^{-/-}$, the protective effects of extrahepatic SR-BI in the *Pdzk1*$^{-/-}$ mice, or even the protective effect of the residual hepatic SR-BI (7%) in *Pdzk1*$^{-/-}$ mice (Table 6).

Transcriptional regulation by farnesoid X receptor

The farnesoid X receptor (FXR, gene name *Nr1h4*) is a member of the nuclear receptor super-family and is highly expressed in the liver. It was shown in vitro and in vivo that FXR activation upregulates SR-BI mRNA and protein expression in cultured hepatocytes[86] and that FXR-deficient mice (*Nr1h4*$^{-/-}$) have significantly reduced hepatic SR-BI mRNA and protein levels.[87] FXR plays an essential role in cholesterol metabolism, and genetic changes affecting FXR have proatherogenic risk.[87] FXR functions as a physiological sensor for bile acid (BA) and is part of a feedback loop, as it is activated by BA, which, in turn, causes the inhibition of cholesterol 7-anhydroxylase (CYP7A1), the rate-limiting enzyme in BA biosynthesis from cholesterol.[88] In terms of a pathway, FXR is known to upregulate PPARα[89] and PPARγ,[90] which, in turn, increases SR-BI expression.[91] *Nr1h4*$^{-/-}$ mice have increased plasma cholesterol, triglycerides, and CE, consistent with its effects on SR-BI.[92] However, in dKO mice with *Ldlr*$^{-/-}$, atherosclerosis was reduced in males (although not in females), even though plasma lipid levels were increased.[93] This likely reflects the complexity of the effects that FXR exerts on other lipid genes, and possibly in macrophages and atherosclerotic plaque development, beyond its direct liver effects.

Transcriptional regulation by LXR and RXR

Additional transcriptional regulators have been identified for hepatic SR-BI. These include the liver X receptor (LXR) and retinoid X receptor (RXR), which are members of the nuclear receptor family of transcription factors and are closely related to the PPARs and FXR.[94] LXR has two isoforms (α, gene name *Nr1h3*; and β, gene name *Nr1h2*), and these form heterodimers with RXR to maintain tissue cholesterol homeostasis, affecting multiple lipid genes.[95] It has also been shown that the LXRα/RXR heterodimer promotes both increased human SR-BI promoter activity and protein levels in hepatocytes as well as adipocytes in vitro and that this transcriptional activation is independent of sterol regulatory element binding protein (SREBP) transcriptional regulation.[96] Elimination of both LXRα (*Nr1h3*$^{-/-}$) and APOE leads to increased plasma cholesterol and atherosclerosis.[97] However, at least some of the effects on atherosclerosis are also due to the action of LXRs on lipid genes in macrophages.[98]

Transcriptional regulation by SREBPs

SREBP-1a-overexpressing transgenic (*Srebp1a Tg*) mice have elevated hepatic cholesterol and triglyceride concentrations because SREBP-1a transcriptionally activates lipid-synthesizing genes in the liver.[99] *Srebp1a Tg* mice have a 50% reduction in hepatic SR-BI protein and mRNA levels compared with wildtype mice, indicating that SREBPs mediate transcriptional downregulation of SR-BI.[100]

Table 6 Alternative mouse models for SR-BI

Strain	Control	Diet	Measure	Direction	Ref
Pdzk1–/– 129/SvEv	*Pdzk1*+/+	Chow	TC, FC	↑	83
			Triglycerides, phospholipids	↑	
			HDL particle size	↑	
Pdzk1–/– *Apoe*–/–	*Pdzk1*+/+ *Apoe*–/–	Chow	FC, FC/TC %	↑	84, 85
			TC, triglycerides	↔	
			Phospholipids	↔	
		Western diet (HF HC)	Lesion size	↑	
			FC, FC/TC %	↑	
			Phospholipids	↑	
			TC, triglycerides	↔	
			Occlusive athero CAD	↔	

Abbreviations: CAD, coronary artery disease; FC, free cholesterol; HC, high cholesterol; HDL, high-density lipoprotein; HF, high fat; SR-B1, scavenger receptor class B member 1; TC, total cholesterol.

Srebp1a Tg mice challenged with an atherogenic diet led to hepatic SR-BI protein being completely eliminated, indicating that FXR/diet SR-BI regulation pathways and the SREBP SR-BI pathways are, to some extent, mutually exclusive.

Transcriptional regulation by fibrates

Fibrate drugs benefit cardiovascular health by lowering plasma triglycerides, normalizing LDL levels, and raising HDL levels in patients with dyslipidemias,[101] as well as raising APOAI and APOAII.[102,103] Fibrates induce transcriptional activation of PPARs, particularly PPARa,[104,105] and many of the lipid effects of fibrates are likely due to this interaction. However, fibrates lower hepatic SR-BI protein levels, likely causing the net HDL increase.[106,107] This appears to be due to SR-BI protein degradation that at least is partially dependent on PPARa and PDZK1.[106] However, there is also evidence to suggest a PDZK1-independent mechanism that occurs in a postendoplasmic reticulum, postplasma membrane compartment and is independent of the proteasome, calpain protease, and lysosome.[107] It has also been shown that fenofibrate is a potent inhibitor of SR-BI HDL lipid uptake but does not affect surface expression or intracellular membrane transport of SR-BI protein.[108] There is little direct evidence of human hepatic SR-BI metabolism in patients taking fibrates; however, diabetic subjects taking fenofibrate have no difference in SR-BI protein levels in circulating monocytes.[109] This is likely to be because SR-BI protein levels are considerably lower in circulating monocytes compared with in hepatocytes and do not reflect hepatocyte metabolism.

Hyperglycemia

Diabetes and hyperglycemia pose a significant risk to cardiovascular health. In patients with type 2 diabetes, cardiovascular disease (CVD) is the major cause of morbidity and mortality, and CVD risk is two- to four-fold increased over nondiabetic subjects.[110,111] Administration of glucose to diabetic rats compared with to euglycemic control rats showed that hepatic expression of SR-BI is significantly decreased. This reduction appears to be under transcriptional control, as there is comparable knockdown of SR-BI mRNA and protein levels. In HepG2 cells, elevated glucose concentrations inhibit transcriptional activity of the human SR-BI promoter, possibly because high glucose induces the p38 mitogen-activated protein kinase (MAPK) signal transduction pathway. Expression of constitutively active MAPK in HepG2 cells inhibited SR-BI promoter activity in the presence or absence of glucose. Expression of a dominant-negative MAPK in HepG2 cells exposed to high glucose abolishes the inhibitory effect of glucose on SR-BI promoter activity.[112] In addition, deletion of a 266-bp human SR-BI promoter sequence fragment abolishes glucose suppression of the human SR-BI promoter activity in HepG2 cells.[112] SR-BI decrease due to high glucose levels has been confirmed in vitro for other cell lines. These studies also showed that PPARγ was upregulated, which is inconsistent with PPARγ effects on SR-BI and is therefore probably independent of the PPARγ pathway.[91,113]

Diet

It has been shown that an atherogenic diet comprising 2% cholesterol and 0.5% cholate can downregulate SR-BI in a post-translational manner that does not affect mRNA levels.[100] This regulation does not affect the localization of SR-BI on the hepatocyte surface. The mechanism likely involves regulation by PDZK1, which is also downregulated in parallel with SR-BI. Interestingly, only the combination of cholesterol and cholate, rather than cholesterol alone or cholate alone, resulted in significantly elevated liver cholesterol along with a decrease in hepatic SR-BI protein levels.

Estrogen

As discussed previously, SR-BI is present in steroidogenic tissues as well as in the liver. This has led to the hypothesis that estrogen may affect SR-BI regulation. In rats, high levels of synthetic estrogen can completely abolish liver SR-BI protein levels while simultaneously raising SR-BI in the adrenals and ovaries.[18] It has also been shown that although estrogen downregulates SR-BI, the common alternative splice variant SR-BI.2 is upregulated in both rat livers and human HepG2 cells.[114] The mechanism likely involves estrogen-binding elements in the promoter region of SR-BI.[115] In addition, recent human genetic studies have shown that SR-BI polymorphisms interact with estradiol levels to affect HDL and triglyceride levels.[116] The same study also showed liver SR-BI mRNA levels higher in males than in females for both SR-BI and SR-BI.2.

Overall, hepatic SR-BI is regulated by multiple independent metabolic pathways, and the majority of these pathways affect transcriptional regulation of SR-BI to control the abundance of the protein and alternative coding splice variants.

Human hepatic SR-BI

Obtaining human samples to examine hepatic SR-BI is obviously difficult and explains why there is very little direct evidence of human hepatic SR-BI function. An examination

of 91 human liver samples showed that males have higher SR-BI mRNA than females, although this was not confirmed by protein analysis.[116] Human genetic studies examining HDL cholesterol levels, and hence hepatic function of SR-BI, have examined polymorphisms in SR-BI for association in various lipid and metabolic traits. Initial analyses focused primarily on three single nucleotide polymorphism (SNPs) located in exon-1, intron-5, and exon-8. However, most of these studies showed weak association that could not be replicated. Advances in genomics have permitted significantly larger and more powerful studies to be performed, and genome-wide association studies (GWAS) have now proven that SNPs in and near SR-BI are significantly associated with human plasma levels of HDL cholesterol ($P < 3 \times 10^{-14}$).[117] Many of these SNPs are located downstream of the coding region, indicating that expression levels of SR-BI, likely in the liver, may be important for human HDL regulation. Interestingly, CD36 has not been associated at the genome wide level with any lipid trait, reflecting the importance of SR-BI in human HDL metabolism as the primary HDL-CE scavenger receptor.

More recently, a family with a functional mutation in SR-BI was identified through sequencing of SR-BI in a high HDL cholesterol cohort. Carriers show increased HDL cholesterol levels and reduced cholesterol efflux from macrophages but no significant increase in atherosclerosis.[118] Indeed, SR-BI associations with CAD have not yet been conclusively proven, not even with GWAS associations. However, this obviously does not rule out SR-BI as a critical CAD gene. The nature of loss of function mutations in SR-BI will lead to increased HDL cholesterol, which normally provides protection against atherosclerosis. Examining HDL cholesterol levels in humans, as a marker of SR-BI functional effects on CAD, may not necessarily be the best way to prove SR-BI's CAD impact. A more direct measure of challenging patients with safe radiolabeled CE, and determining its rate of clearance as a measure of RCT, may be a better way of determining SR-BI function.[119]

Noncholesterol roles and considerations for hepatic SR-BI

SR-BI is known to have functions beyond that of "HDL receptor", which may be under greater selection pressure. Indeed, the benefits of improved RCT and HDL may never have presented a selection pressure on humans, given that CAD acts after the lateral transmission of genes, and that CAD itself is a recent human disease. The evolutionary pressures that brought about and conserve SR-BI may be due to its less well-characterized functions that are beneficial for survival, such as supplying cholesterol to steroidogenic tissues for reproduction.[51] More likely, however, is the increasing role that SR-BI appears to have for protection from infectious disease. We now know that SR-BI has a role in endotoxemia and innate immunity and serves as a binding site for the uptake of bacteria and clearance of plasma lipopolysaccharide (LPS) via the liver, which is primarily carried by HDL.[120] SR-BI also protects against LPS-induced death and prevents nitric oxide cytotoxicity.[121] In addition, SR-BI supplies cholesterol to the adrenals for synthesis of glucocorticoids (anti-inflammatory compounds), providing protection from endotoxemia.[122] Serum opacity factor (SOF) is a virulence determinant protein of group A streptococci and induces opacity of mammalian serum[123] because it binds to APOAI on HDL, triggering the release of the HDL lipid cargo.[124] SOF converts HDL to lipid-free APOAI, neo-HDL (small HDL-like particles), and a large CE-rich microemulsion (CERM). Hepatocyte uptake of CERM-CE occurs faster than HDL-CE uptake, and CERM has a higher-affinity interaction with SR-BI compared with HDL.[125] Thus, the clearance of virulence factors may have been a driving force for SR-BI evolution.

Conversely, too much SR-BI can be detrimental, as human hepatic SR-BI serves as an entry receptor for hepatitis C virus (HCV).[126,127] HCV is a RNA virus that replicates in the liver, and HCV infection is the major cause of liver fibrosis, cirrhosis, and liver cancer in the Western world, as well as the leading cause for requiring liver transplantation.[128] HCV infection is characterized by alterations in lipids that reflect viral dependence on host lipid metabolism for replication and assembly.[129] PDZK1 can also enhance HCV entry via SR-BI.[130] Research into developing HCV entry inhibitors has become a novel approach to preventing infection, and studies have identified SR-BI antagonists with potent antiviral activity.[131] The antagonists are designed to target the extracellular loop of SR-BI or block SR-BI expression.[126,132–135] Consequently, studies on SR-BI-directed therapies in relation to HCV or CVD will require overlap. For example, HCV therapies that block SR-BI expression may have long-term cardiovascular consequences.

Conclusion

Inhibiting SR-BI in mouse models increases HDL, but this increase is not healthy and results in increased atherosclerosis, either due to reduced RCT or increased APOB-containing

lipoproteins. Overexpressing SR-BI in mouse models increases RCT, lowers APOB-containing lipoproteins, and reduces atherosclerosis, all of which serve as an optimal therapeutic package. However, increasing SR-BI without a clearer understanding of all the functions of SR-BI in humans, such as in the presence of endogenous CETP, particularly with regard to its effects on VLDL and LDL, could have detrimental effects. More research and better humanized mouse models may be required to distinguish the exact impact of human CETP, increased APOB-containing apolipoproteins and VLDL remnants, and free cholesterol flux versus reduced HDL-CE selective uptake. The consequence of raised SR-BI in the context of HCV, bacteria, LPS, and general infection and immunity could lead to an increase in bacterial infection and sepsis.[136] Indeed, if SR-BI is upregulated in all tissues, including macrophages, then LPS and other inflammatory markers may promote foam cell formation and atherosclerosis.

Although SR-BI has been extensively studied in vitro and in mouse models, there are clearly many questions concerning SR-BI that require investigation, especially regarding human relevance. Now that human genetics has finally proven beyond doubt that SR-BI is correlated with human HDL cholesterol levels, we can begin to address more confidently the question of whether SR-BI is relevant for CAD. However, a better assay to assess SR-BI hepatic function and RCT in humans, rather than simply measuring HDL cholesterol, should be developed to address the direct human genetic CAD associations more robustly.

Acknowledgment

Ioannis M Stylianou is supported by the AHA Scientists Development Award 09SDG2280011.

Disclosure

The authors report no conflicts of interest in this work.

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