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Functional genomics of the human HDL receptor scavenger receptor BI: An old dog with new tricks

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Abstract

Purpose of review—The athero-protective role of scavenger receptor BI (SR-BI) is primarily attributed to its ability to selectively transfer cholesteryl esters from high density lipoproteins (HDL) to the liver during reverse cholesterol transport (RCT). In this review, we highlight recent findings that reveal the impact of SR-BI on lipid levels and cardiovascular disease in humans. Moreover, additional responsibilities of SR-BI in modulating adrenal and platelet function, as well as female fertility in humans, are discussed.

Recent findings—Heterozygote carriers of P297S-, S112F- and T175A- mutant SR-BI receptors were identified in patients with high HDL-cholesterol levels. HDL from P297S-SR-BI carriers was unable to mediate macrophage cholesterol efflux, while hepatocytes expressing P297S-SR-BI were unable to mediate the selective uptake of HDL-cholesteryl esters. S112F- and T175A-mutant receptors exhibited similar impaired cholesterol transport functions in vitro. Reduced SR-BI function in P297S carriers was also associated with decreased steroidogenesis and altered platelet function. Further, human population studies identified *SCARB1* variants associated with female infertility.

Summary—Identification of SR-BI variants confirms the key role of this receptor in influencing lipid levels and RCT in humans. Deeper understanding of the contributions of SR-BI to steroidogenesis, platelet function and fertility is required in light of exploration of HDL-raising therapies aimed at reducing cardiovascular risk.

Keywords

Scavenger receptor BI; platelets; fertility; HDL-cholesterol; steroidogenesis

INTRODUCTION

Scavenger receptor BI (SR-BI) is an integral membrane glycoprotein that binds numerous ligands [reviewed in [1]]. However, its most well-characterized role remains its ability to mediate high affinity binding to high density lipoproteins (HDL) [2, 3] for delivery of HDL-cholesteryl esters (CE) to the liver for bile acid formation via a process termed reverse cholesterol transport (RCT) (reviewed in [4]). SR-BI is the primary molecule responsible for

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CONFLICTS OF INTEREST

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the selective transfer of HDL lipids to cells [5, 6] without holoparticle uptake [2]. Its role in mediating HDL-CE delivery has been confirmed in genetic murine models. Transgenic overexpression [7–9] or adenoviral infection [10, 11] of SR-BI decreased HDL-cholesterol (HDL-C) levels and increased cholesterol catabolism and excretion. In contrast, SR-BI deficiency in mice increased plasma HDL-C levels and reduced neutral lipid stores in the adrenal gland and ovary [12–14].

While the role of SR-BI as a physiologically relevant HDL receptor is firmly established in rodents, its role in humans is less defined. The human homologue of SR-BI, also known as CLA-1 (CD36 and LIMPII analogous-1), was cloned based on sequence similarity with CD36 and LIMPII, two other members of the class B scavenger receptor family [15]. The *SCARB1* gene is located on chromosome 12 (Cytogenetic Location 12q24.31) and encompasses 13 exons [16, 17]. Like rodents, human SR-BI was expressed in tissues that exhibit high rates of cholesterol catabolism [18, 19] and was also confirmed to be a high affinity HDL receptor that mediates HDL-CE selective uptake [20]. While HDL serves as the major cholesterol-carrying lipoprotein in mouse plasma, adult humans carry the bulk of plasma cholesterol in apoB-containing particles, bringing into question the relevance of SR-BI in human physiology. In addition, mice lack cholesteryl ester transfer protein (CETP), a protein critical for RCT in humans that mediates the transfer of CE from HDL to the apoB-containing lipoproteins (i.e. very low density lipoprotein (VLDL) and low density lipoprotein (LDL)) in exchange for triglycerides (TG) [21]. Therefore, while hepatic SR-BI deficiency in mice prevents clearance of plasma HDL-C by blocking the last step of RCT [13, 14], one might assume that the consequences of SR-BI deficiency in humans would be less severe as HDL-CE can be returned to the liver via apoB-containing lipoproteins via CETP. In this review, we will summarize recent findings from studies that provide new information about human SR-BI variants that are associated with changes in HDL-C and protein levels, as well as cardiovascular disease (CVD). Most importantly, we will discuss how the recent identification of novel SR-BI mutant receptors in humans has generated a renewed interest in the role of SR-BI in human physiology. Specifically, we will describe findings that support the critical need for SR-BI in hepatic clearance of HDL-CE and regulation of circulating plasma HDL levels. Moreover, we will describe additional physiological roles of SR-BI in human steroidogenesis, platelet activation and female infertility.

SR-BI INFLUENCES LIPID LEVELS AND CARDIOVASCULAR DISEASE

Numerous studies in humans have identified genetic variants or polymorphisms in the human *SCARB1* gene locus that are linked to human lipid metabolism. The less common allele of an exon 1 single nucleotide polymorphism (SNP) (rs4238001; G>A at base pair 4 that encodes a glycine-to-serine (G2S) mutation at amino acid 2), was significantly associated with higher HDL-C and lower LDL-cholesterol (LDL-C) levels in men, but not in women [16]. In contrast, the G2S variant, which is found in all populations except for East Asia [16, 22, 23], was associated with lower HDL-C and LDL-C levels in type 2 diabetics of the Framingham Heart Study [24], and suggests that SR-BI variants in this population may contribute to the decrease in HDL-C found in metabolic syndrome. The G2S polymorphism, along with an intron 3 variant (rs2278986; T>C), were more recently identified as an independent predictors of SR-BI protein levels in subjects with hyperalphalipoproteinemia [25]. Moreover, stable expression of the G2S mutant receptor in murine macrophages demonstrated that an increased rate of turnover of the G2S variant decreased SR-BI protein levels, which in turn, resulted in significantly lower levels of cell association of HDL in macrophages as compared to wild-type SR-BI [25]. While the association of HDL-C and LDL-C levels with a separate, yet common, synonymous exon 8 polymorphism (rs5888; C>T; no resulting amino acid change) is population-dependent [16, 24, 26, 27], detailed

investigations revealed that this SNP resulted in lower SR-BI protein expression as a direct consequence of altered SR-BI RNA secondary structure and inefficient protein translation [28].

Interestingly, many of these studies show different effects of the polymorphisms in men and women, suggesting a possible mediating role of sex hormones [16, 22, 26, 29, 30]. Indeed, estrogen down-regulates SR-BI expression in human HepG2 cells and rodent models [31, 32] and estrogen therapy can modulate HDL-C and TG levels in humans [27, 33–35]. Indeed, genetic variants in intron 11 of *SCARB1* were found to influence TG and HDL-C levels in an endogenous estrogen-dependent manner in post-menopausal women [36]. Moreover, one would expect pre-menopausal women to have higher levels of estrogen, and only livers from female subjects expressed significantly lower levels of *SCARB1*.

The strongest evidence for the physiological importance of SR-BI in atherosclerosis has been obtained from studies of genetically-modified mice. With the exception of a few reports [37–40], the majority of murine studies that include genetic deletion of *Scarb1* [14, 41], liver-specific [42] or adenovirus-mediated overexpression of SR-BI [43], as well as bone marrow transplantation studies [38, 44, 45], clearly highlights the role of SR-BI in promoting RCT and thus preventing atherogenesis. In humans, however, the influence of SR-BI on CVD remains under-studied. In an extensive genome-wide association study involving over 100,000 individuals, the rs838880 *SCARB1* SNP was associated with HDL-C levels, but not with coronary artery disease (CAD) [46]. However, polymorphisms in exon 8 and/or intron 5 of *SCARB1* have been associated with CAD in a variety of populations [16, 22, 29, 47–49], while the rs4238001 exon 1 SNP was associated with internal carotid intimal-medial thickness [50]. Most recently, the rs10846744 variant was significantly associated with common carotid intimal thickening across different ethnic/racial groups of the Multi-Ethnic Study of Atherosclerosis (MESA) cohort [51, 52], with a particularly strong association in women [52]. A novel association of rs10846744 with incident myocardial infarction and CVD was also reported [51–53]. Traditional atherosclerosis risk factors such as lipid levels did not influence this association. This is not surprising as SR-BI has been shown to mediate effects on CVD independent of lipid effects (reviewed in [54]). Taken together, the majority of studies support the influence of *SCARB1* on human cardiovascular health. Certainly, identifying the mechanisms by which these SNPs affect cardiovascular events, and whether these effects are lipid-dependent or –independent, warrants further investigation.

Excitingly, within the past two years, the HDL receptor has returned to the spotlight, as the identification of three novel SR-BI mutations in humans now provides strong evidence that impaired SR-BI function affects human physiology. Vergeer *et al.* were the first to discover a missense nucleotide mutation (c.889C→T) that resulted in a proline-to-serine point mutation at amino acid 297 (P297S) in a patient with an HDL-C level above the 95th percentile [55]. An additional 18 family members were carriers of the P297S mutation, with HDL-C levels that were 32% higher than non-carriers. However, no significant differences in other plasma lipid levels were noted, which contrasts previous associations of *SCARB1* polymorphisms with serum levels of TG [16, 29, 30, 56], LDL-C [16, 56, 57] and VLDL-C [56]. Paralleling observations in SR-BI knock-out mice [13, 14, 58], carriers of P297S-SR-BI had larger-sized HDL particles [55].

Adenoviral expression of P297S-SR-BI in SR-BI knock-out mice revealed a statistically significant inability to reduce plasma total cholesterol levels as compared to wild-type SR-BI, despite similar levels of hepatic SR-BI mRNA expression and protein levels [55]. Furthermore, HDL-CE uptake was markedly reduced in primary hepatocytes expressing P297S-SR-BI [55]. SR-BI also mediates the bidirectional transfer of cholesterol between

cells and HDL acceptors [59–61], and although controversial [39, 62], cholesterol efflux from monocyte-macrophages obtained from carriers and non-carriers to HDL was significantly lower in carriers of the P297S variant [55].

Soon after the discovery of the P297S-SR-BI variant, Burnham *et al.* discovered two additional novel missense mutations at serine 112 (nucleotide C588T) or threonine 175 (nucleotide A776T) to generate the S112F or T175A point mutations, respectively [63]. These two mutations were identified in two separate individuals with HDL-C levels 90th percentile. Family members heterozygous for these mutations had a 37% increase in HDL-C, without affecting LDL-C levels or body mass index [63], resembling previous findings [55]. Chadwick & Sahoo further characterized the S112F- and T175A-SR-BI mutations in vitro, and found that both mutant receptors were associated with reductions in HDL binding and selective uptake of HDL-CE uptake, as well as an impaired ability to mediate cholesterol efflux from cells to HDL [64].

These three newly-discovered mutations in *SCARB1* that underlie elevated HDL-C levels in humans occur at evolutionarily-conserved amino acid residues. Moreover, they are all located in the extracellular domain of SR-BI that is critical for mediating the selective uptake of HDL-CE [65–68]. Indeed, all three mutant receptors displayed impaired cholesterol transport functions that are thought to be key in mediating their athero-protective effects in murine models [37–41, 69–71]. In the case of T175A-SR-BI, mutation at residue 175 appears to disrupt N-linked glycosylation [64] and may explain, in part, the decreased cell surface expression and defective functions of this mutant receptor. Both the S112F and T175A point mutations occur in conserved regions of hydrophobicity in the N-terminal half of the extracellular domain that have been shown to influence SR-BI-mediated cholesterol transport [72]. Future investigations will determine whether these amino acid substitutions prevent conformational changes that may be required to support SR-BI function. Interestingly, while it has been hypothesized that SR-BI oligomerization [73–75] may facilitate the selective uptake efficiency of HDL-CE [75–77], the impaired function of the S112F-, T175A- and P297S-SR-BI receptors were independent of the oligomeric status of the receptors ([64]; unpublished observations by A.C. Chadwick and D. Sahoo).

Although strong evidence supports the notion that increases in HDL-C levels in humans may be due to the inefficient clearance of HDL-C from circulation [55, 64], the bigger question as to whether these mutations impact CVD remains unanswered. Despite compromised SR-BI function, carotid intima-media thickness and the number of cardiovascular events in carriers and non-carriers of the P297S variant did not differ [55]. Similarly, carriers of the S112F- and T175A-SR-BI mutations did not report any history of CAD, cerebro- or peripheral vascular disease [63]. It is possible that SR-BI mutations may affect the progression of atherosclerosis only when combined with another atherogenic factor, as has been described for accelerated atherosclerosis upon deletion of *Scarb1* in an apoE-deficient background [78], or in an individual with a combined S112F-SR-BI/ABCA1 mutation [63]. Certainly, due to the age and limited number of carriers, establishing an association between CVD and these novel SR-BI mutations warrants further investigation.

SR-BI IMPACTS ADRENAL STEROIDOGENESIS

SR-BI serves as the major route for the delivery of HDL-CE in cultured adrenal cells in vitro [68] and in mice [6] for steroid hormone synthesis [79, 80]. Genetic deletion of *Scarb1* impairs both basal and stress-induced adrenal glucocorticoid synthesis [81] and prevents glucocorticoid production in the adrenals in response to endotoxin [82]. Humans homozygous for familial hypercholesterolemia or those with abetalipoproteinemia have normal basal corticosteroid concentrations [83–85], suggesting that removal of the LDL-

receptor pathway has only a modest effect on the cholesterol utilized for steroid production in humans. Carriers of P297S-SR-BI had decreased urinary steroid secretion and a reduced response to corticotrophin stimulation, both symptoms indicative of reduced adrenal function [55]. Mimicking observations from mouse studies [81], carriers of P297S-SR-BI also had a higher cortisol-binding protein level [55], whose expression is inhibited by glucocorticoids [86, 87]. Therefore, this novel mutation provides the first direct evidence for a critical role of SR-BI in human adrenal gland function and brings us several steps closer to providing a better understanding of patients that present with adrenal insufficiency during a stress response, systemic bacterial infection or sepsis. A role for the S112F and T175A mutant SR-BI receptors [63, 64] in adrenal function remains to be determined.

SR-BI MODULATES PLATELET FUNCTION

Patients with diabetes and dyslipidemia have heightened platelet reactivity, an important risk factor for arterial thrombosis [88–91]. Hypercholesterolemic SR-BI knockout mice [6, 13, 41] have larger platelets with abnormal morphology, as well as a significantly greater level of free cholesterol [92]. These platelets exhibited a blunted aggregation response in response to ADP agonist. Interestingly, SR-BI knock-out mice are thrombocytopenic (i.e. reduced platelet count), most likely due to abnormally rapid platelet clearance that results from the high free cholesterol-to-total cholesterol ratio in the dysfunctional lipoproteins of these mice [14, 92]. Hypomorphic liver-specific SR-BI knockout mice with elevated HDL-C levels also exhibit a marked reduction in circulating platelets [93]. In support of these observations, an elegant series of bone marrow transplantation studies -- specifically where reduced platelet count and abnormal platelet morphology were still observed when SR-BI knock-out mice were transplanted with wild-type SR-BI positive bone marrow -- strongly supported the notion that the hyperlipidemia associated with non-bone marrow-derived SR-BI deficiency was the principal cause of thrombocytopenia and altered platelet morphology and not SR-BI deficiency in platelets themselves [94].

Increased platelet reactivity has been linked to high platelet cholesterol content [89, 95–97], and bone marrow transplantation studies further demonstrated that SR-BI deficiency-associated dyslipidemia leads to platelet hyperreactivity [94]. More recently, the ex-vivo binding of HDL₃ to SR-BI in platelets, which is inhibited by negatively-charged phospholipids, was shown to inhibit thrombin-induced platelet aggregation, fibrinogen binding, P-selectin expression and mobilization of Ca²⁺ that activates platelets [98].

Reduced platelet survival time and thrombocytopenia have been associated with hyperlipidemia in hypercholesterolemic individuals [99]. Patients with atherosclerosis show a strong correlation between SR-BI expression on platelets, the free cholesterol content of platelets and the ability of platelets to aggregate [100]. The first evidence for a direct role of SR-BI in influencing platelet physiology was demonstrated by identification of carriers of P297S-SR-BI [55]. Although platelet counts did not differ between P297S carriers and non-carriers, platelets from carriers contained more free cholesterol. In addition to increased P-selectin expression, these platelets displayed an increased ability to adhere to and spread on immobilized fibrinogen and a reduced ability to aggregate upon agonist stimulation [55]. We eagerly await future studies that will help define how alterations in SR-BI expression in humans may modulate the contribution of platelets to atherosclerosis [88, 90, 101–103].

SR-BI INFLUENCES FERTILITY

Due to its role in steroid hormone synthesis [79, 80], it is not surprising that SR-BI influences reproduction [104, 105]. Homozygous SR-BI knockout female, but not male, mice are infertile [13, 14, 58] and displayed abnormalities in oocyte development and viability [14], despite normal estrus cycles, ovulation and progesterone levels. However, the

amounts of steroid hormones required for female fertility are not dependent on normal lipid stores in steroidogenic tissues, as evidenced by other genetically-modified fertile murine models that lack steroidogenic tissue cholesterol stores [80, 106, 107].

Fertility can be restored either by treatment of SR-BI knock-out mice with probucol, a cholesterol-lowering drug, by inactivation of the apoA-I gene in a *Scarb1*-deficient background [58] or via adenovirus-mediated or stable transgenic expression of SR-BI in the liver [108]. Further, ovaries from SR-BI knockout mice functioned normally when transplanted into SR-BI positive mice [58]. As SR-BI knockout mice have abnormally large HDL particles [13, 14], it is likely that fertility could be restored by methods that normalize HDL particle composition and lipoprotein metabolism.

Recent findings from human subjects now reveal the potential clinical importance of SR-BI in human fertility. Lower baseline and peak estradiol levels in infertile women correlated with lower levels of SR-BI expression in granulosa cells, as well as lower number of retrieved and fertilized oocytes [109]. Markedly lower progesterone secretion was associated with SR-BI protein deficiency in granulosa cells, independent of lipoproteins in the culture media [110]. In a very recent study of women undergoing in vitro fertilization, the *SCARB1* SNP rs4238001 (G2S mutation) was significantly associated with decreased follicular progesterone levels and poor fetal viability, with no restoration of fertility upon progesterone replacement treatment [111]. The intron 1 rs10846744 SNP, shown to be associated with subclinical atherosclerosis in participants of the MESA study [52], was also associated with poor fetal viability [111]. Subjects with hyperalphalipoproteinemia carrying the rs4238001 SNP had lower SR-BI receptor expression [25], yet a possible link between hyperalphalipoproteinemia and human female infertility remains undefined. Taken together, these clinical data nicely complement previous studies [109, 110, 112] and demonstrate the importance of SR-BI for ovarian function and human female reproduction.

CONCLUSIONS

Since its discovery in 1994 [3], the physiological relevance of SR-BI in humans has been debatable. In addition to the identification of genetic variants of *SCARB1* that influence fertility, the ground-breaking discovery of patients harboring functional mutations in *SCARB1* now proves a critical role for the HDL receptor, not only in RCT, but also in adrenal steroidogenesis and platelet function. Undoubtedly, the relationship between SR-BI and HDL-C levels is complex. A strong inverse association exists between plasma HDL-C levels and the incidence of CAD [113], yet paradoxically, elevated HDL-C levels are associated with increased atherosclerosis in SR-BI knockout mice [13, 78, 114]. As such, investigation of additional patients with the same or new SR-BI mutations will be invaluable as we address the on-going debate as to whether higher HDL-C levels are truly athero-protective [115–117], especially in light of a recent Mendelian randomization study that revealed a lack of association between lowered risk of myocardial infarction and genetic mechanisms that raise plasma HDL-C levels [118]. Further, restoration of HDL-C levels in SR-BI knockout mice by expression of human CETP did not change the susceptibility to atherosclerosis, nor did it normalize female infertility, thrombocytopenia and impaired platelet aggregation [116, 117], suggesting that SR-BI deficiency may mediate pathophysiology independent of lipid effects [54, 119, 120]. Therefore, in light of current efforts directed at developing HDL-raising therapeutics to lower cardiovascular risk [121, 122], an improved understanding of the mechanisms that modulate the new roles ascribed to SR-BI in human physiology are now more relevant than ever.

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ABBREVIATIONS

CAD	coronary artery disease
CVD	cardiovascular disease
CE	cholesteryl ester
CETP	cholesteryl ester transfer protein
HDL	high density lipoprotein
HDL-C	HDL-cholesterol
LDL	low density lipoprotein
LDL-C	LDL-cholesterol
MESA	Multi-ethnic Atherosclerosis Study
RCT	reverse cholesterol transport
SNP	single nucleotide polymorphism
SR-BI	scavenger receptor class B type I
TG	triglyceride
VLDL	very low density lipoprotein

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KEY POINTS

- Genetic variants of *SCARB1* influence lipid levels and cardiovascular disease in humans.
- Mutations at amino acids 112, 175 or 297 in SR-BI are associated with high HDL-C in carriers of these mutant receptors, and confirm a critical role of SR-BI in mediating selective uptake of HDL-CE, as well as the release of cholesterol from cells to HDL.
- SR-BI-mediated uptake of HDL-CE is required for adrenal steroidogenesis in humans.
- Platelet function is altered, to some extent, as a result of the dyslipidemia that results from reduced SR-BI function in humans.
- The importance of SR-BI for ovarian function and human female reproduction is demonstrated by genetic variants of *SCARB1*.